Oxford Textbook of Oncology

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THIRD EDITION

Edited by
David J. Kerr
Daniel G. Haller
Cornelis J.H. van de Velde
Michael Baumann

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Preface

The opportunity to compile a third edition of the *Oxford Textbook of Oncology* (after a gap of over ten years) represented a chance to deliver a definitive and comprehensive text detailing the evolution, evidence base, and current best practice in multidisciplinary cancer care. The first half of the textbook opens with introductory chapters covering the basic science that underpins our understanding of how cancer cells grow and function. These are then followed by sections looking specifically at the aetiology of cancer and the general principles governing modern approaches to oncology treatments. The first half of the book ends with a look at the unique challenges presented by treatment of cancer on a larger scale within population groups, and conversely the importance of recognizing and supporting the needs of individual patients both during and after treatment.

Our aim for the second half of the textbook was to provide a series of disease-based chapters written by expert teams from across the globe. Each chapter takes a multidisciplinary approach to the diagnosis and management of cancer, with sections covering the epidemiology, biology and pathology, radiotherapy, medical and surgical management of specific disease types.

When looking at the contents list for the new edition, you may notice that we have not included a chapter on childhood cancers. We felt that any discussion of paediatric oncology that was limited to only one chapter would inevitably be too superficial to cover even the most central aspects of this important discipline. Instead, readers will find that the focus of this volume is on the treatment and management of adult patients. For special paediatric considerations, we refer readers to *Cancer in Children: Clinical Management* (eds Michael C.G. Stevens and Hubert N. Caron, Oxford University Press, 2011). Now in its sixth edition, this book provides an excellent guide to the management of common childhood cancers.

One of the most important innovations in the third edition of the *Oxford Textbook of Oncology* is that it is available both in print, ebook, and online formats. One of the negatives of preparing a major textbook is that it may be out of date by the time of publication. We seek to overcome this with regular online updates when change in knowledge demands. Purchasers of the print book will receive a free 12-month access to the online version of the book. The online version contains all the material from the printed book, as well as extensive reference linking via PubMed. Over the lifetime of the book, additional case studies, figures, and other reference material will be made available as part of a series of regular updates that will be made to the online edition.

We would like to thank Beth Womack, Nicola Wilson, Caroline Smith, and the rest of the OUP team and the many international experts who contributed time, knowledge, and wisdom in writing this book.

This is a time of extraordinary advancement in oncology, with improvements seen in each of the major therapeutic areas, underpinned by basic and translational science leading to an increasingly personalized approach for many cancer patients. Drawing on the combined experience of an extensive list of internationally renowned contributors, we believe that this updated and revitalized third edition provides an essential resource for oncologists in all fields.

David J. Kerr
Daniel G. Haller
Cornelis J.H. van de Velde
Michael Baumann

Contents

List of abbreviations

2D-CRT	two-dimensional conformal treatment
2GTKI	second generation TKI therapy
2-HG	2-hydroxyglutarate
3DCRT	3D conformal radiotherapy
5-FU	5-fluorouracil
5-FU/FA	5-fluorouracil and folinic acid (leucovorin)
5-HIAA	5-hydroxy-indole acetic acid
5-hmC	5-hydroxymethylcytosine
5-mC	5-methylcytosine
5'-TOP	5'-terminal oligopolypyrimidine
^{18}F-FDG	^{18}F-fluoro-deoxyglucose
AA	African American; anaplastic astrocytomas
AAH	atypical adenomatous hyperplasia
aaIPI	age-adjusted IPI
ABC	advanced biliary cancer; activated B-cell
ABVD	Adriamycin® (doxorubicin), bleomycin, vinblastine, and dacarbazine
AC	adrenal carcinoma
ACA	additional cytogenetic abnormalities
ACC	adenoid cystic carcinoma
ACF	aberrant crypt foci
ACS	American Cancer Society
ACTH	adrenocorticotrophic hormone
aCGH	array Comparative Genomic Hybridization
ADC	antibody drug conjugate; apparent diffusion coefficient
ADCC	antibody-dependent cellular cytotoxicity
ADH	antidiuretic hormone
ADME	absorption, distribution, metabolism, and excretion
ADOC	cyclophosphamide, Adriamycin® (doxorubicin), vincristine, and cisplatin
AF	accelerated radiotherapy
AFAP	attenuated FAP
AFP	alpha-feto protein
AfrOx	Africa Oxford Cancer Foundation
AFX	atypical fibroxanthoma
AICR	American Institute for Cancer Research
AIF	apoptosis inducing factor
AIS	adenocarcinoma in situ
AITL	angioimmunoblastic T-cell lymphoma
AJCC	American Joint Committee on Cancer
AK	actinic keratosis
ALA	aminolaevulinic acid
ALCL	anaplastic large-cell lymphoma
ALFA	Acute Leukemia French Association
ALK	activin-receptor-like kinases; anaplastic lymphoma receptor tyrosine kinase
ALL	acute lymphocytic leukaemia; acute lymphoblastic leukaemia
ALT	alternative lengthening of telomeres; atypical lipomatous tumour
allo-HSCT	allogeneic-haematopoietic stem cell transplantation
allo-SCT	allogeneic-stem cell transplantation
ALT	alternative lengthening of telomeres
AMC	Advanced Market Commitment
AML	acute myelogenous leukaemia; acute myeloid leukaemia
AMPK	adenosine monophosphate-activated protein kinase
AO	anaplastic oligoastrocytoma
AOA	anaplastic oligoastrocytoma
AP	accelerated phase
APA	aldosterone-producing adenoma
Apaf-1	apoptotic protease activating factor 1
APBD	anomalous pancreatic biliary duct
APC	adenomatous polyposis coli
APC	anaphase promoting complex
APL	acute promyelocytic leukaemia
array-CGH	array-based comparative genomic hybridization
ARF	alternative reading frame
ARHG	AP29 RHOA GTPase-activating protein 29
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
ASOC	advanced stage ovarian cancer
ASR	age standardized rates
Atg	autophagy-related gene
ATL	adult T-cell leukaemia
ATM	ataxia telangiectasia mutated
ATO	arsenic trioxide
ATP	adenosine triphosphate
ATRA	all-trans retinoic acid
Auto-SCT	autologous stem cell transplantation
AUC	area under the curve
AVC	angiogenic vascular cells
AYA	adolescents and young adults

β_2M β_2	microglobulin
β-TRCP	b-transducin repeat-containing protein
BAD	BCL-2 antagonist of cell death
BAFF	B-cell activating factor
B-ALL	B-cell acute lymphocytic leukaemia
BAO	basal acid output
BC	blast crisis
B-CLL	B-cell lymphocytic leukaemia
BBB	blood-brain barrier
BC	breast cancer; bladder cancer
BCC	basal cell carcinomas; breast cancer cells
BCG	Bacillus Calmette-Guérin
Bcl-2	B-cell lymphoma 2
BCLC	Barcelona Clinic for Liver Cancer
BCT	breast-conserving therapy
BDWG	Biomarkers Definitions Working Group
BEAM	BCNU, etoposide, cytarabine, and melphalan
BEP	cisplatin, etoposide, and bleomycin
BER	base excision repair
BH	Bcl-2 homology
BHDS	Birt-Hogg-Dube syndrome
BL	Burkitt's lymphoma
BM	bone marrow
BMD	bone mineral density
BMP	bone morphogenetic proteins
BOD	biologically optimal dose
BP	blastic phase
BRCP	breast cancer resistance protein
BRPC	borderline resectable pancreatic cancer
BRRM	bilateral risk reducing mastectomy
BRT	bioradiotherapy
BSC	best supportive care
BTK	Bruton's tyrosine kinase
CA	cryoablation
CAE	cyclophosphamide, Adriamycin® (doxorubicin), and etoposide
CAF	cancer-associated fibroblast
CAG	chronic atrophic gastritis
CAK	CDK activating kinase
CAIX	carbonic anhydrase IX
CALGB	Cancer and Leukemia Group B
CARES	Cancer Rehabilitation Evaluation System
CAT	computer-adaptive testing
CAV	cyclophosphamide, doxorubicin, and vincristine
CAVE	cyclophosphamide, doxorubicin, vincristine, and etoposide
CBE	complete blood count examination
CBR	clinical benefit rate
CBV	cyclophosphamide, BCNU, etoposide
cCR	clinical complete remission
CCRCC	clear cell renal cell carcinoma
CCRT	concurrent/concomitant chemoradiation therapy
CCS	cancer control strategy
CD	coeliac disease
CDC	complement-dependent cytotoxicity
CDK	cyclin-dependent kinase
CEA	carcino-embryonic antigen
CED	convection-enhanced delivery
CEP	circulating endothelial progenitors
CEUS	ultrasound contrast bubbles
CF	conventional fractionation
CGH	comparative genomic hybridization
CGIN	cervical glandular intraepithelial neoplasia
CHCC	combined hepatocellular and cholangiocarcinoma
CHD	carcinoid heart disease
CHF	congestive heart failure
CHL	classic Hodgkin lymphoma
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHR	complete haematological response
CI	confidence interval
CIN	cervical intraepithelial neoplasia; chromosome instability
CIMP	CpG island methylator phenotype
CIS	carcinoma in situ
CK	cytokeratin
CK-7	cytokeratin-7
CKI	CDK inhibitor
CLC	cardiotrophin-like cytokine
CLND	completion lymph node dissection
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
CMML	chronic myelomonocytic leukaemia
C-MIN	conjunctival melanocytic intraepithelial neoplasia
CMR	complete molecular response
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNA	copy number alterations
CNS	central nervous system
CNSL	central nervous system lymphoma
CNTF	ciliar neurotrophic factor
CoC	Commission on Cancer
COG	Children's Oncology Group
COO	cell-of-origin
COPD	chronic obstructive pulmonary disease
CP	chronic phase
CR	complete remission
CRAB	calcium, renal, anaemia, and bone abnormalities
CRC	colorectal carcinoma
CRKL	CRK-like protein
CRM	circumferential resection margin; continual reassessment method
CRPC	castrate-resistant prostate cancer
CRRM	contralateral risk-reducing mastectomy
CRS	cytoreductive surgery
CRT	chemoradiotherapy
(C)RT	radiotherapy alone or with chemotherapy
CS	carcinoid syndrome
CSA	cranio-spinal axis
CSC	cancer stem cell
CSF	cerebrospinal fluid
CSR	class switch recombination
CT	computed tomography
CT1	cardiotrophin
CTC	circulating tumour cell
CTL	cytotoxic T-lymphocyte
CTV	clinical target volume
CUP	cancer of unknown primary

CVA	cerebrovascular accidents
CVD	cyclophosphamide, vincristine, and dacarbazine
DAG	diacylglycerol
DAPK	death-associated protein kinase
DC	dendritic cell
DCC	deleted in colon cancer
DCE	dynamic contrast enhanced
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
DCIS	ductal carcinoma in situ
DD	death domain
DEB	drug-eluting beads
DEPTOR	DEP domain-containing mTOR-interacting protein
DEXA	dual-energy X-ray absorptiometry
DFCI	Dana Farber Cancer Institute
DFS	disease-free survival
DFSP	dermatofibrosarcoma protuberans
DHAP	dexamethasone/high-dose ara-C/cisplatin
DHFR	dihydrofolate reductase
DIC	disseminated intravascular coagulation
DFS	disease-free survival
DFSP	dermatofibrosarcoma protuberans
DIN	ductal intraepithelial neoplasia
DISC	death-inducing signalling complex
DKK	Dickkopfs
DLBCL	diffuse large B-cell lymphoma
DLL4	Delta-like ligand 4
DLT	dose-limiting toxicity
DM	distant metastases
DMPM	diffuse malignant peritoneal mesothelioma
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DRE	digital rectal examination
DSB	double strand break
DTC	direct-to-consumer; disseminated tumour cells
DTI	diffusion tensor tractography
Dvl	intracellular Dishevelled
DWI	diffusion-weighted imaging
EAP	Expanded Access Programs
EATL	enteropathy-associated T-cell lymphoma
EB	epidermolysis bullosa
EBMT	European Group for Blood and Marrow Transplantation
EBRT	external beam radiotherapy
EBUS	endobronchial ultrasound
EBUS-FNA	endobronchial ultrasound-guided fine needle aspiration
EBV	Epstein–Barr virus
EC	endometrial cancer
ECCO	European CanCer Organisation
ECF	epirubicin, cisplatin, and infusional 5-fluorouracil
ECM	extracellular matrix
ECOG	Eastern Cooperative Oncology Group
ECT	electrochemotherapy
EEA	extended endoscopic approaches
EFS	event-free survival rates
EGF	epidermal growth factor
EGRF	epidermal growth factor receptor
EGFR	epidermal growth factor receptor
EHCC	extrahepatocellular carcinoma
eIF4E	eukaryotic translation initiation factor 4E
ELND	elective lymph node dissection
EM	electron microscopy
EMA	endoscopic mucosal ablation
EMR	endoscopic mucosal resection
EMT	epithelial mesenchymal transformation/ transition
EMZL	extranodal marginal zone B-cell lymphomas
ENB	esthesioneuroblastomas
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core QoL Questionnaire
EPC	endothelial progenitor cells
EPO	erythropoietin
EPP	extrapleural pneumonectomy
EPT	electron-photon therapy
EPT	endocrine pancreatic tumour
EQ	erythroplasia of Queyrat
ER	endoplasmatic reticulum
ERAS	enhanced recovery after surgery
ERCP	endoscopic retrograde cholangio-pancreatography
ERR	excess relevant risk; oestrogen related receptors
ERUS	endorectal ultrasonography
ES	effect size
ESAS	Edmonton Symptom Assessment Scale
ESD	endoscopic submucosal dissection
ESMO	European Society of Medical Oncology
ESS	Edmonton Staging System
ESSO	European Society of Surgical Oncology
ET	essential thombocythaemia
ETP	early T-cell precursor
EUNICE	European Network for Indicators on Cancer
EURECCA	European Registration of Cancer Care
EUS	endoscopic ultrasound
EUS-FNA	endoscopic ultrasound-guided fine needle aspiration
EUSOMA	European Society of Mastology
FA	fluorescein angiography
FACS	fluorescence-activated cell sorting
FACT-G	Functional Assessment of Cancer Therapy
FADD	Fas-associated DD
FAMM	facial artery musculo-mucosal; familial atypical multiple mole/melanoma
FAMMM	familial atypical multiple mole/melanoma
FAP	familial adenomatous polyposis
FCTC	Framework Convention on Tobacco Control
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FDG-PET	18-fludeoxyglucose positron emission tomography
FFCD	Fédération Francophone de Cancérologie Digestive
FFPE	formalin-fixed and paraffin-embedded
FGF	fibroblast growth factor

FGFR	fibroblast growth factor receptor
FIT	faecal immunochemical testing
FISH	fluorescence in situ hybridization
FKHR	forkhead transcription factor
FLIC	Functional Living Index—Cancer
FN	fibronectin
FNA	fine needle aspiration
FNAC	fine needle aspiration cytology
FNR	false-negative rate
FL	follicular lymphoma
FLL	focal liver lesions
FLR	future liver remnant
FOB	fibreoptic bronchoscopy
FOLFOX	5-FU, leucovorin and oxaliplatin
FOXO	forkhead box O
FRO	familial renal oncocytoma
FRS2	FGFR substrate 2s
FS	flexible sigmoidoscopy
FTH	follicular T-helper
GAB1	GRB2-associated binding protein 1
GAP	GTPase activating protein
GARFT	glycinamide ribonucleotide formyltransferase
GASTRIC	Global Advanced/Adjuvant Stomach Tumour Research International Collaboration
GBC	gall bladder cancer; germinal centre B-cell
GBM	glioblastoma multiforme
GC	gemcitabine and carboplatin
GC	germinal centre
GCP	good clinical practice
GCSF	granulocyte colony stimulating factor
GDA	gastroduodenal artery
GDF	growth and differentiation factor
GDP	gemcitabine, dexamethasone, and cisplatin; guanosine diphosphate
GEF	guanine nucleotide exchange factor
GHRH	growth hormone-releasing hormone
GEJ	gastro-oesophageal junction
GEMM	genetically engineered mouse models
GEP	gastroenteropancreatic
GEP	gene expression profiling
GF	growth factor
GGR	global genome repair
GH	growth hormone
GINA	Genetic Information Nondiscrimination Act
GIST	gastrointestinal stromal tumour
GITSG	Gastrointestinal Tumour Study Group
GLUT4	glucose transporter type 4
GMALL	German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia
GMP	good manufacturing procedure; granulocyte/macrophage progenitor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GO	gemtuzumab ozogamicin
GPS	Glasgow Prognostic Score
GRA	glucocorticoid-remediable aldosteronism
GRB2	proteins growth-factor-receptor bound-2
GSK3	glycogen synthase kinase 3
GSK3-b	glycogen synthase kinase 3b
GTP	guanosine triphosphate
GTV	gross tumour volume
GvHD	graft-versus-host disease
GvL	graft-versus-leukaemia
GWAS	genome-wide association studies
HAART	highly active antiretroviral therapy
HAT	histone acetyl-transferase
HB	hepatobiliary
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBOC	hereditary breast-ovarian cancer
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCL	hairy cell leukaemia
HCL-v	hairy cell leukaemia-variant
HCT	haematopoietic cell transplantation
HCV	hepatitis C virus
HDAC	histone deacetylase
HDR	high dose rate
HDT	high-dose therapy
HDV	hepatitis delta virus
H&E	haematoxylin and eosin
Hep Par 1	hepatocyte paraffin 1 monoclonal antibody
HF	hyperfractionated radiotherapy
HGF	hepatocyte growth factor
HGFA	HGF activator
Hh	Hedgehog
HIDAC	high-doses cytarabine
HIF	hypoxia inducible factor; hypoxia inhibitory factor
HIFU	high intensity focused ultrasound
HICC	heated intracavity chemotherapy
HIPEC	hyperthermic perioperative chemotherapy
HLA	humoral leukocyte antigen
HNPCC	hereditary non-polyposis colorectal cancer
HNPGL	head and neck parasympathetic paraganglioma
HNSCC	head and neck squamous cell carcinoma
HPC	haemangiopericytoma
HPF	high power fields
HPRC	hereditary papillary renal carcinoma
HPV	human papilloma virus
HR	hazard ratio; homologous recombination
HRC	hereditary renal carcinoma
HRE	hypoxic response elements
HSC	haematopoietic stem cell
HSP90	heat shock protein 90
HT	hypertension
HTLV-1	Human T-cell leukaemia virus 1
IAP	inhibitor of apoptosis protein
IARC	International Agency for Research on Cancer
IASLC	International Association for the Study of Lung Cancer
IBI	International Breast Cancer Intervention Study
ICE	ifosfamide, carboplatin, etoposide
ICER	incremental cost-effectiveness ratio
ICL	interstrand cross-link
ICRP	International Commission on Radiation Protection

ICRU	International Commission on Radiation Units and Measurements
ICT	induction chemotherapy
IDC	NOS invasive ductal carcinoma not otherwise specified
IFFIm	International Finance Facility for Immunisation
IFL	irinotecan/bolus 5-FU, leucovorin
IFN	interferon
IFP	interstitial fluid pressure
IFRT	involved-field radiotherapy
IGABT	image-guided adaptive brachytherapy
IGF	insulin growth factor
IGF1	insulin growth factor 1
IGF2	insulin growth factor 2
IGFBP	IGF binding proteins
IGLC	International Gastric Cancer Linkage Consortium
IGRT	image-guided radiotherapy
IHA	idiopathic hyperaldosteronism
IHC	immunohistochemistry
IHCC	intrahepatic cholangiocarcinoma
IIC	infiltrating immune cell
IJCN	inflamed juvenile conjunctival naevi
IKK	IκB kinase
IKKB	IkB kinase b
IL	interleukin
IL1R	interleukin 1 receptor
IL6	Interleukin 6
ILC	invasive lobular carcinoma
ILND	inguinal lymph node dissection
ILP	isolated limb perfusion
iMR	intraoperative MR
IMRT	intensity-modulated radiation therapy
IMWG	International Myeloma Working Group
INCTR	International Network for Cancer Treatment
iNOS	inducible nitric oxide synthase
INRT	involved-node radiotherapy
Ins(1,4,5)P3	inositol-1,4,5- trisphosphate
IOM	Institute of Medicine
IORT	intraoperative radiotherapy
IOUS	intraoperative ultrasound
IP	intraperitoneal
IPAA	total proctocolectomy and ileoanal pouch
IPD	individual patient data
IPI	International Prognostic Index
IPMN	intraductal papillary mucinous neoplasms
iPS	induced pluripotent stem cells
IR	insulin receptor; ionizing radiation
IRA	ileorectal anastomosis
IRS	insulin receptor substrates
IRT	item response theory
ISGPF	International Study Group on Pancreatic Fistula Definition
ISGPS	International Study Group of Pancreatic Surgery
ITMIG	International Thymic Malignancy Interest Group
ITT	intention to treat
ITV	internal target volume
JAK	Janus kinase
JCOG	Japan Clinical Oncology Group
JGCA	Japanese Gastric Cancer Association
KA	keratoacanthoma
KPS	Karnofsky performance status
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma-associated herpesvirus
KSR	kinase suppressor of Ras
LAPC	locally advanced pancreatic cancer
LAR	long-acting repeatable
LCC	large cell carcinoma
LCIS	lobular carcinoma in situ
LCL	lymphoblastoid cell line
LCNEC	large cell neuroendocrine carcinoma
LDDST	low-dose dexamethasone suppression test
LDH	lactate dehydrogenase
LDHA	lactate dehydrogenase A
LDR	low dose rate
LEF	lymphoid enhancer factor
LEF1	lymphoid enhancer-binding factor 1
LFS	leukaemia-free survival
LETZ	loop excision of the transformation zone
LIF	leukaemia inhibitory factor
LIN	lobular intraepithelial neoplasia
LMICs	low- and middle-income countries
LMP-1	latent membrane protein-1
LOH	loss of heterozygosity
LP	lymphocyte predominant
LPL	lymphoplasmacytic lymphoma
LRR	local and/or regional recurrences
LS	Lynch syndrome
LSC	leukaemic stem cell
LUTS	lower urinary tract symptoms
LVSI	lymphovascular space invasion
MAA	macro-aggregated albumin
mAb	monoclonal antibodies
MACs	microsatellite and chromosome stable
MAC-NPC	meta-analysis of chemotherapy in NPC
MALT	lymphoma mucosa-associated lymphatic tissue lymphoma
MAP3K	MAP kinase kinase kinases
MAPK	mitogen-activated protein kinases
MAP	MUTYH-associated polyposis
MBL	monoclonal B-cell lymphocytosis
mBL	molecular BL
MC	mitotic count
MCC	Merkel cell carcinoma
MCD	Multicentric Castleman's Disease
MCL	mantle cell lymphoma
MCN	mucinous cystic neoplasm
MCP-1	monocyte chemotactic protein
MCPM	multicystic peritoneal mesothelioma
MCR	macroscopic complete resection; molecular complete response
MCRC	metastatic colorectal cancer
MCV	Merkel cell polyomavirus
MDCT	multidetector computed tomography
MDR	multidrug resistant

MDRT	moderate-dose radiation therapy
MDS	myelodysplastic syndromes
MDSC	myeloid derived suppressor cells
MDT	multidisciplinary team
MEC	mucoepidermoid carcinoma
MELD	model of end-stage liver disease
MelTUMP	melanocytic tumour of uncertain malignant potential
MEN	multiple endocrine neoplasia
MET	mesenchymal-to-epithelial transition
MFH	malignant fibrous histiocytoma
MGUS	monoclonal gammopathy of undetermined significance
MIBC	muscle invasive bladder carcinoma
MIC	metastasis-initiating cells; microinvasive carcinoma
MIE	minimally invasive oesophagectomy
MIF	Müllerian inhibitory factor
MIBG	metaiodobenzylguanidine
MiSG	minor salivary glands
MITF	micropthalmia transcription factor
Miz1	Myc interacting zinc-finger protein
MLC	multileaf collimators
MM	multiple myeloma
MMMT	Mixed malignant Müllerian tumours
MMP	matrix metalloproteinase
MMP-9	matrix metalloprotease-9
MMR	mismatch repair
MNGGCT	malignant non-germinoma germ cell tumour
MoAb	monoclonal antibody
MOMP	mitochondrial outer membrane permeabilization
MOPP	mechlorethamine, vincristine, procarbazine, prednisone
mOS	median overall survival
MPA	medroxyprogesterone acetate
MPD	myeloproliferative diseases
MPM	malignant peritoneal mesothelioma
MPN	myeloproliferative neoplasms
MR	minimal response
MRA	magnetic resonance angiography
MRC	Medical Research Council
MRCP	magnetic resonance cholangiopancreatography
MRD	minimal residual disease
MRF	mesorectal fascia
MRI	magnetic resonance imaging
MRP	multidrug resistance-associated protein
MSI	microsatellite instability
MSI-H	high microsatellite instability
MSI-L	low microsatellite instability
MSKCC	Memorial Sloan Kettering Cancer Center
MSS	microsatellite stable/stability
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
MZL	marginal zone lymphoma
NAC	nipple areolar complex
NAMPT	nicotinamide phosphoribosyltransferase
NASH	non-alcoholic steatohepatitis
NBCC	nodular BCC
NBOCAP	National Bowel Cancer Audit Programme
NCCN	National Comprehensive Cancer Network
NCCS	National Coalition for Cancer Survivorship
NCD	non-communicable disease
NCI	National Cancer Institute
NEC	neuroendocrine carcinoma
NEN	neuroendocrine neoplasia
NER	nucleotide excision repair
NET	neuroendocrine tumour
NETZ	needle excision of the transformation zone
NGS	next-generation sequencing
NHEJ	non-homologous end joining
NHL	Non-Hodgkin lymphoma
NHSCSP	National Health Service Cervical Screening Programme
NICD	Notch intracellular domain
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
NLR	neutrophil:lymphocyte ratio
NMIBC	non-muscle invasive bladder carcinoma
NMSC	non-melanoma skin cancer
NNK	N-nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N'-nitrosonornicenotine
NOS2	nitric oxide synthase-2
NOTES	natural orifice transluminal endoscopic surgery
NPC	nasopharyngeal carcinoma
NPM	nucleophosmin gene
NPV	negative predictive value
NRM	non-relapse mortality
NSABP	National Surgical Breast and Bowel Project
NSAID	non-steroidal anti-inflammatory drug
NSE	neuron-specific enolase
NSGCT	non-seminoma germ cell tumours
NSCLC	non-small-cell carcinoma; non-small-cell lung cancer
NTCP	normal tissue complication probability
OAR	organs at risk
OC	ovarian cancer
OCA	other chromosomal abnormality
ONB	olfactory neuroblastoma
OPC	oropharyngeal cancer
ORR	overall response rate
OS	overall survival
OSCC	oral cavity squamous cell carcinoma; oropharyngeal squamous cell carcinoma
OSM	oncostatin M
OSSN	ocular surface squamous neoplasia
P13K	phosphoinositide 3 kinase
PAC	cyclophosphamide, doxorubicin, and cisplatin
PAH	polycyclic aromatic hydrocarbon; primary adrenal hyperplasia
PAM	primary acquired melanosis
PanIN	pancreatic intraepithelial neoplasia
PAR3	partitioning defective 3
PARP	poly(ADP-ribose)polymerase
PBF	peripheral blood film

PBMNC	peripheral blood mononuclear cell
PBPC	peripheral blood progenitor cells
PBT	proton beam therapy
PCD	programmed cell death
PCI	prophylactic cranial irradiation; peritoneal cancer index
PCL	plasma cell leukaemia
PCM	plasma cell myeloma
pCR	pathological complete remission
P/D	pleurectomy/decortication
PDGF	platelet-derived growth factor
PDGFR-α	platelet-derived growth factor receptor α
PDGFR-β	platelet-derived growth factor receptor β
PDK1	phosphoinositide-dependent kinase 1
PDT	photodynamic therapy
PE	phosphatidylethanolamine
PET	positron emission tomography
PF	cisplatin and fluorouracil
PFE	platinum/5-FU/Erbitux® (cetuximab)
PFS	progression-free survival
PG	paraganglioma
PGP	P170 membrane glycoprotein
PH	pleckstrin homology
PHC	primary health care
PHD	prolyl hydroxylase domain protein
PI3K	phosphoinositide-3-kinase
PI3P	phosphatidylinositol g3-phosphate
PIAS	PIAS protein inhibitor of active STAT
PIKK	PI3K-related protein kinase
PIN	point mutation instability
PKB	protein kinase B
PKD1	protein kinase D1
PLC	phospholipase C
PLGA	polymorphous low-grade adenocarcinoma
PlGF	placental growth factor
Plk	polo-like kinases
PLL	prolymphocytic leukaemia
PMBL	primary mediastinal large B-cell lymphoma
PMF	primary myelofibrosis
PMLBCL	primary mediastinal large B-cell lymphomas
PNET	primitive neuro-ectodermal tumours
PODXL	podocalyxin
POPF	post-operative pancreatic fistula
PPH	postpancreatectomy haemorrhage
PPI	proton-pump inhibitor
PPPD	pylorus-preserving pancreaticoduodenectomy
PPT	pineal parenchymal tumours
PPV	positive predictive value
pre-RC	pre-replicative complex
pRb	retinoblastoma protein
PROCARisE	Project on Cancer of the Rectum
PROMIS	Patient-Reported Outcome Measurement Information System
PRP	platelet-rich plasma
PRRT	peptide receptor-mediated radionuclide therapy
PRV	planning organ-at-risk volume
PSA	prostate-specific antigen
PSC	pancreatic stem cells; primary sclerosing cholangitis
PSOGI	Peritoneal Surface Oncology Group International
PTC	percutaneous transhepatic cholangiography
PTCL	peripheral T-cell lymphomas
PTCL-NOS	peripheral T-cell lymphomas not otherwise specified
PTE	proportion of treatment effect
PTH-rp	parathyroid hormone-related protein
PTLD	post-transplant lymphoproliferative disorders
PTV	planning target volume
PUNLMP	papillary urothelial neoplasm of low malignant potential
PUVA	psoralens and UVA
PV	polycythaemia vera
PVC	primary vaginal cancer
QALY	quality-adjusted life years
RARECARE	Surveillance of Rare Cancers in Europe
RASIP1	RAS-interacting protein 1
Rb	retinoblastoma
RBE	relative biological effectiveness
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumours
rESS	revised Edmonton Staging System
RFA	radiofrequency ablation
RFR	relapse-free rate
RFS	relapse-free survival
RHEB	RAS homologue enriched in brain
RIC	reduced-intensity conditioning
RIC-allo-SCT	reduced-intensity conditioned allogeneic-stem cell transplantation
RILD	radiation induced lung disease
RIP	receptor-interacting protein
RIT	radioimmunotherapy
RKIP	RAF kinase inhibitor protein
R/M	recurrent/metastatic
ROLL	radio-guided occult lesion localization
ROS	reactive oxygen species
ROTI	myeloma-related organ and tissue impairment
RPE	retinal pigment epithelium
RPLS	reversible posterior leukoencephalopathy syndrome
RPS	retroperitoneal sarcomas
RR	response rate
RRSO	risk-reducing bilateral salpingo-oophorectomy
RS	recurrence score
RSCL	Rotterdam Symptom Checklist
RT	radiation therapy
RTK	receptor tyrosine kinase
RTOG	Radiation Therapy Oncology Group
RT-PCR	reverse transcriptase-polymerase chain reaction
RQ-PCR	real-time quantitative polymerase chain reaction
S1P	sphingosine-1-phosphate
SAP	serum amyloid P
SBCC	superficial BCC
SBRT	stereotactic body radiotherapy
SCC	squamous cell carcinoma
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small-cell lung carcinoma

sCR	stringent complete response
SDF-1	stromal derived factor-1
SDH	succinate dehydrogenase
SDPP	stroma-derived prognostic predictor
SEER	Surveillance, Epidemiology and End results
SEIC	serous endometrial intraepithelial carcinoma
SEMS	self-expanding metallic stents
SERM	selective estrogen receptor modulators
SET	sensitivity to endocrine therapy
SES	socio-economic status
SFLC	serum free light-chains
SFRP	secreted frizzled-related protein
SGC	salivary gland cancer
SGCT	seminoma germ cell tumour
SH2	Src homology 2
SH3	Src homology 3
SHIP	SH2-domain-containing inositol-5-phosphatase
SHM	somatic hypermutation
SHS	secondhand smoke
SIB	simultaneous integrated boost
SIGN	Scottish Intercollegiate Guidelines Network
SIL	squamous intraepithelial lesion; single incision laparoscopy
sIL-2R	soluble interleukin-2 receptor
SIN3	squamous intraepithelial neoplasia 3
SIRT	selective internal radiation treatment
SLAM	signalling lymphocytic activation molecule
SLNB	sentinel lymph node biopsy
SMA	superior mesenteric artery
SMAC	second mitochondria derived activator
smCC	small-cell cancer
SMM	smouldering myeloma
SMV	superior mesenteric vein
SN	sentinel node
SNP	single nuclear polymorphisms
SNEC	sinonasal neuroendocrine
SNUC	sinonasal undifferentiated carcinoma
SOCS	suppressor of cytokine signalling
SOS	Son of Sevenless
SPARC	secreted protein acidic and rich in cysteine
SPB	solitary plasmacytoma of bone
SPEP	serum electrophoresis
SPH	serine proteinase homology
SPT	secondary primary tumour
SRE	skeletal-related event
SREBP	sterol regulatory element binding proteins
SRM	standardized response mean
SRS	somatostatin-receptor scintigraphy
SRS	stereotaxic radiosurgery
SSA	single-strand annealing
SSA	somatostatin analogue
SSB	single-strand break
SSCP	single strand conformational polymorphism
SSRI	selective serotonin reuptake inhibitors
SSS	superior sagittal sinus
STAT3	transcription 3
STE	surrogate threshold effect
STS	soft tissue sarcomas
STAT5	signal transducer and activator of transcription-5
STIC	serous tubal intraepithelial carcinoma
SUV	standardized uptake value
SV40-T	simian virus large T antigen
SVCS	superior vena cava syndrome
SWETZ	straight wire excision of the transformation zone
TA	telomerase activity
TACE	transarterial chemoembolization
TAM	tumour-associated macrophages
TBI	total-body irradiation
TCD	T-cell depletion
TCF	docetaxel, cisplatin, infusional 5-fluorouracil; T-cell factor
TCP	tumor control probability
TCR	transcription-coupled repair
TEM	transanal endoscopic microsurgery
TG	total glansectomy
TGF	transforming growth factor
TGFβ, TGF-b	transforming growth factor beta
TGR	total glans resurfacing
TIEG1	TGFβ-inducible early-response gene
TIGAR	TP-53-induced glycolysis and apoptosis regulator
TIL	tumour-infiltrating lymphocytes
TK	tyrosine kinase
TKI	tyrosine kinase inhibitor
TLS	tumour lysis syndrome
TME	total mesorectal excision; tumour microenvironment
TNBC	triple-negative breast cancer
TNFR	tumour necrosis factor receptor
TNFR1	TNF receptor 1
TNM	tumour node metastasis
TORS	transoral robotic surgery
TOS	TOR signalling
T-PLL	T-cell prolymphocytic leukaemia
TPF	docetaxel, cisplatin, and 5-fluorouracil; Taxotere®, cisplatin, and fluorouracil
TPMT	thiopurine methyltransferase
TPS	treatment planning systems
TRADD	TNFR1-associated DD
TRAF	TNF receptor associated factor
TRAIL	TNF-related apoptosis inducing ligand
TRAIL-R1	TRAIL receptor 1
TRAIL-R2	TRAIL receptor2
TRM	treatment-related mortality
TRU	terminal respiratory unit
TRUS	transrectal ultrasonography
TS	thymidylate synthase; treatment score
TSC2	tuberous sclerosis 2
TSG	tumour suppressor gene
TSH	thyroid-stimulating hormone
TTF	time-to-treatment failure
TTF1	thyroid transcription factor 1
TTP	time-to-progression
TURT	transurethral resection of the tumour
UFC	urinary free cortisol
UFT	uracil/tegafur
UGT	UDP-glucuronosyltransferase

UICC	Union for International Cancer Control
UKELD	United Kingdom end-stage liver disease score
uPAR	urokinase plasminogen activator receptor
UPEP	urine electrophoresis
UPR	unfolded protein response
US	ultrasound
USPIO	ultrasmall superparamagnetic particles of iron oxide
UTUC	upper tract urothelial cancer
UV	ultraviolet
VAIN	vaginal intraepithelial neoplasia
VATS	video-assisted thoracic surgery
VC	vaginal cancer; verrucous carcinoma
VDA	vascular disrupting agent
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VEGF	MKI vascular endothelial growth factor multikinase inhibitors
VHL	von Hippel-Lindau
VIN	vulvar intraepithelial neoplasia
VIP	vasoactive intestinal polypeptide
WART	whole abdominal radiotherapy
WBC	white blood cell count
WBD	whole body dose
WBI	whole breast irradiation
WBRT	whole brain radiotherapy
WCRF	World Cancer Research Fund
WDLPS	well-differentiated liposarcoma
WDPPM	well-differentiated papillary peritoneal mesothelioma
WGS	Whole Genome Shotgun
WHEL	Women's Healthy Eating and Living
WIF1	Wnt inhibitory factor 1
WINS	Women's Intervention Nutrition Study
WLE	wide local excision
WM	Waldenström macroglobulinemia
XP	capecitabine plus cisplatin; xeroderma pigmentosum
ZES	Zollinger–Ellison syndrome
ZO1	zonula occludens 1

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SECTION 1

Hallmarks of cancer

CHAPTER 1

The hallmarks of cancer
Perspectives for cancer medicine

Douglas Hanahan and Robert A. Weinberg

Introduction: a conceptual organizing principle

This textbook elaborates the landscape of a disease characterized by extraordinary complexity across the spectrum of organ sites and cell types. The growths that are grouped together under the rubric of cancer exhibit scrambled and mutated cell genomes, diverse histopathologies, highly variable timelines of pathogenesis and progression to symptomatic and metastatic disease, and a plethora of pathological effects. The simple premise in proposing a generic set of cancer hallmarks came from our belief that the bewildering complexity of cancer could be rationalized in terms of an underlying principle.

We envisaged these hallmarks as a set of acquired functional capabilities that act in combination to produce most forms of cancer, despite genetic and pathologic differences that might otherwise suggest a lack of mechanistic commonality. We imagined that each of these capabilities could be acquired by developing cancers through several alternative means, representing different solutions to the common challenges facing all incipient neoplasias. This concept, first presented in 2000 [1] and refined in 2011 [2], has proven to be a useful heuristic tool for distilling the underlying foundations of this disease.

The following sections provide a concise synopsis of this scheme, with a brief perspective on clinical applications in the last section. The reader is referred to the primary publications [1, 2], as well as to another perspective that expands on the roles of stromal cells in enabling the hallmarks of cancer [3]. A textbook on the biology of cancer [4] may provide additional detail on many of the mechanisms of cancer pathogenesis described in outline in this chapter.

The hallmarks of cancer: necessary functional capabilities

In the current conceptualization, there are eight hallmarks—acquired capabilities—that are common to many forms of human cancer (Figure 1.1). Each capability serves a distinct role in supporting the development, progression, and persistence of tumours and their constituent cells, as briefly explained below.

Hallmark 1: sustaining proliferative signalling

The essence of the disease is a deregulated programme that instructs cancer cells to grow and divide, doing so at inappropriate times and places, chronically. Many so-called 'driver mutations' that convert normal cellular genes into oncogenes (by mutational alteration of gene function or amplification in expression) serve to stimulate and sustain progression of cells through their growth-and-division cycles. They act by perturbing multiple nodes in the signal transduction circuits that normally transmit growth signals from the extracellular milieu into the cell nucleus. Many of these mutations alter regulatory circuits involving secreted growth-stimulatory proteins that bind as ligands to activate their cognate cell-surface receptors. Signal transduction into the cell nucleus is accomplished by cascades of protein–protein associations and protein phosphorylations, the most prominent of these signalling channels being growth-promoting signals transmitted through the RAS-RAF-MEK-MAPK pathway. Signal-sustaining mutational alterations of genes in this pathway are commonly observed in a wide variety of human cancers, illustrating its importance in enabling acquisition of this hallmark capability. We note, however, that activation in cancer cells of this central mitogenic pathway does not invariably depend on genetic changes acquired during the course of tumour progression. In certain instances, epigenetic deregulation of autocrine (auto-stimulatory) and paracrine (cell-to-cell) signalling circuits can also provide cancer cells with chronic growth-promoting signals, doing so in the apparent absence of underlying somatic mutations.

Hallmark 2: evading growth suppressors

The essential complement to proliferative signals in normal cells are braking mechanisms that serve either to overrule the initiation of, or to subsequently turn off, cell division stimulated by such signals. These countervailing regulatory mechanisms often involve the tissue microenvironments in which normal cells reside, ensuring that cell proliferation is not an entirely cell-autonomous process. The most prominent brakes are the direct regulators of the cell division cycle, embodied in the retinoblastoma protein (pRb) and several 'cyclin-dependent' kinase inhibitors that block progression of an individual cell through its growth-and-division cycle. The activity of this molecular braking system is regulated in part by extracellular pro- and anti-growth signals transduced by receptors on the cell surface in order to permit transitory proliferation, thereby ensuring normal tissue homeostasis.

In addition to the brakes that respond to extracellular growth-modulatory signals, an intracellular monitoring system, centred upon the p53 protein, serves to ensure that cells advance only through their growth-and-division cycles when the

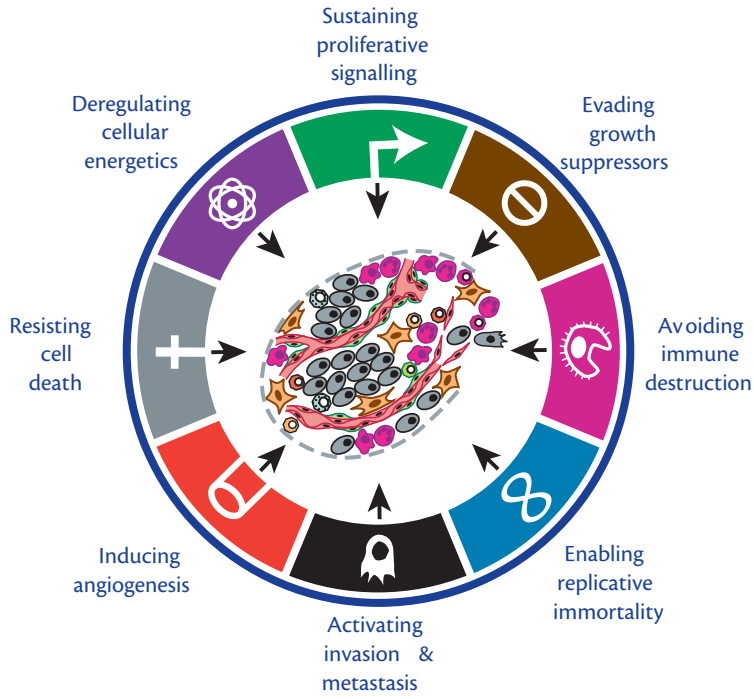

Fig. 1.1 The hallmarks of cancer. Eight distinctive functional capabilities—the hallmarks of cancer—are thought to be necessarily acquired during the multistep pathogenesis pathways leading to most forms of human cancer. Certain forms of cancer may be less dependent on one hallmark or another. Thus, adenomatous tumours evidently lack the capability for invasion and metastasis. Leukaemias may not require angiogenesis or invasive capabilities, although progression to lymphoma almost certainly requires both. And, the necessity for metabolic reprogramming or evading tumour immunity may be less pronounced in certain cancers.

physiologic state of the cell is appropriate. Thus, p53 serves to sense unrepaired damage to a cell's genome as well as other unresolved physiologic imbalances, and responds by shutting off the cell division cycle. In cases of severe genomic damage or physiological abnormalities, the p53 pathway can induce programmed cell death (see below), an extreme form of putting on the brakes to cell proliferation.

A number of component genes in both braking mechanisms—of the Rb and p53 pathways—are classified as tumour suppressors (TSGs) by virtue of their frequent loss-of-function via inactivating genetic mutations. Alternatively, the functions of TSGs can be lost by shutting down the expression of these genes through epigenetic mechanisms, notably those involving DNA and histone methylation. For example, while the p53 gene itself is mutated in ~40% of all human cancers, many other tumours carry genetic lesions that compromise p53 signalling in other ways. In sum, elimination or evasion of growth suppressors is clearly necessary to ensure that the chronic cell proliferation of cancer cells is not halted by braking mechanisms that, under normal conditions, would succeed in constraining cell proliferation.

Hallmark 3: resisting cell death

The second, qualitatively distinctive barrier to aberrant cell proliferation involves intrinsic mechanisms that can induce programmed cell death, a more drastic means to counteract inappropriate increases in cell number. The most prominent of these programmes is apoptosis, which helps to maintain tissue homoeostasis by inducing the suicide of aberrant cells, including ones that are inappropriately proliferating. The apoptotic programme can be triggered by cell-intrinsic as well as non-cell-autonomous signals that detect different forms of cellular abnormality.

The apoptotic cell death programme involves the directed degradation of critical cellular organelles, the shrivelling of the cell, and its engulfment, either by their neighbours or by tissue-monitoring phagocytes, notably macrophages. All this transpires in less than an hour in mammalian tissues, explaining why apoptotic cells are usually relatively rare, even in a population of cells that is actively undergoing apoptosis, such as the cancer cells in tumours being subjected to cytotoxic chemotherapy. The rapid engulfment of apoptotic cell bodies ensures that their death does not release subcellular components that could inadvertently provoke an immune response; the resulting absence of responding immune cells contrasts with the programme of necrosis, which may be activated by various conditions, including oxygen and energy deprivation. Cells that are dying by necrosis rupture, releasing their contents and leaving their carcasses as debris; the relicts of living cells incite an inflammatory response that, as discussed below, can have both tumour-promoting and tumour-antagonizing effects.

A third programme, termed autophagy, serves as a recycling system for cellular organelles that normally helps cells respond to conditions of nutrient deprivation; by degrading cellular organelles, autophagy generates the metabolites and nutrients that cells are unable to acquire from their surroundings. While normally operating as a survival system, extreme nutrient deprivation can lead to hyper-activation of autophagy that results in autophagic cell death

when stressed cancer cells have cannibalized so many of their own organelles that they are inviable.

These three quite distinct mechanisms of programmed cell death must be circumvented or attenuated by cancer cells if they and their descendants are to continue their proliferative expansion in number and their evolution to states of heightened malignancy.

Hallmark 4: enabling replicative immortality

A third intrinsic barrier to chronic proliferation is integral to the linear structure of mammalian chromosomes: the telomeres at the ends of chromosomes record—by progressive reduction of their length during each cell division cycle—the number of successive cell generations through which a cell lineage has passed. The telomeres are composed of thousands of tandem copies of a specific hexanucleotide sequence. When the number of telomere repeats is reduced below a certain threshold, a tripwire is triggered, causing p53-dependent cell cycle arrest or apoptosis, the latter historically being termed 'crisis'. Circumventing these p53-induced anti-proliferative responses (e.g., by mutationally inactivating the p53 gene) does not on its own enable the cancer cell to avoid eventual elimination. Instead, continuing telomere erosion produces unstable chromosomes whose ends are no longer protected by telomeres, which can result in chromosomal translocations and rearrangements. If unchecked, these changes lead to mitotic catastrophe and consequent cell death.

Most cancer cells circumvent the barriers erected by the telomere replication clock by activating a mechanism of telomere maintenance used to preserve the replicative capacity of normal embryonic and tissue stem cells. This mechanism depends on upregulating the expression of the telomere-extending enzyme telomerase. Less frequently, they engage an alternative inter-chromosomal recombination-based mechanism for preserving telomere length. Thus, through one strategy or another, cancer cells acquire the capability to maintain their telomeres at healthy lengths, doing so indefinitely. By avoiding the barrier created by overly eroded telomeres, these cells acquire the unlimited replicative potential—termed cellular immortality—that is required to spawn large tumour masses.

Hallmark 5: inducing angiogenesis

Angiogenesis—the growth of new blood vessels—is critical for most neoplastic growths. Like normal organs, tumours require a steady supply of oxygen, glucose, and other nutrients, as well as a means to evacuate metabolic waste to sustain cell viability and proliferation; the vasculature serves these purposes. The deleterious effect that ischaemia has in normal tissue is well established clinically and experimentally: cells die, via one form of programmed cell death or another, causing tissue and organ degradation and dysfunction. Similarly, the growth of developing nests of cancer cells halts when their ability to acquire blood-borne nutrients becomes inadequate, typically when the nearest capillary is more than 200 microns away.

Cells at the diffusion limit from the nearest capillary activate various stress response systems, of which the most prominent involves the hypoxia-inducible transcription factor (HIF) system, which regulates hundreds of genes, including ones that directly or indirectly induce angiogenesis and other stress-adaptive capabilities. Much like cells in ischaemic tissues, cancer cells beyond the diffusion limit for oxygen and glucose will typically die, doing so by necrosis, apoptosis, or autophagy. This explains why most vigorously growing tumours are well vascularized with evidence of ongoing active angiogenesis.

Of note, the tumour-associated neovasculature is usually aberrant, both morphologically and functionally. Tumour blood vessels are torturous, dilated, and leaky, with erratic flow patterns and 'dead zones' in which no blood flow is detectable, in marked contrast to the seamless blood flow operating in the normal microvasculature. Moreover, the degree of vascularity varies widely from one tumour type to another, ranging from intensely vascularized renal carcinomas to poorly vascularized pancreatic ductal adenocarcinomas.

Finally, we note that while chronic angiogenesis is a hallmark of the great majority of solid tumours, some may devise an alternative means to acquire access to the vasculature: in certain cases, cancers evidently co-opt normal tissue vasculature by employing the hallmark capability of invasion (see below). Thus, particular types of cancer cells can proliferate and grow along normal tissue capillaries, creating sleeves around the vessels. While vascular co-option is evident in certain cases (e.g., in glioblastoma) and in some tumours treated with potent angiogenesis inhibitors, most tumours rely to a considerable extent on chronic angiogenesis to support their expansive growth.

Hallmark 6: activating invasion and metastasis

The five hallmarks detailed above stand as logical necessities for the chronic proliferative programmes of cancer cells. The sixth is less intuitive: high-grade cancer cells become invasive and migratory. These interrelated programmes enable cancer cells to invade into adjacent tissue, and into both blood and lymphatic vessels (intravasation). Using these vessels as highways for dissemination, cancer cells can reach microvessels in other organs and extravasate across the walls of these vessels into new tissue parenchyma. Having entered the unfamiliar tissue microenvironments, seeded micrometastases generally die or lay dormant. However, on rare occasion, they may adapt to survival in such ectopic tissue locations and develop proliferative programs in these microenvironments, allowing them generate macroscopic metastases—the process termed 'colonization'.

The regulation of the intertwined capabilities for invasion and metastasis is extraordinarily complex, involving both cell-intrinsic programmes and assistance from accessory cells in the tissue microenvironment. Prominent amongst the cancer cell intrinsic regulatory mechanisms is the activation of a developmental programme termed the epithelial-mesenchymal transition (EMT) [2, 4], which is associated with cell migrations and tissue invasions during embryogenesis and organogenesis. A second overlapping regulatory programme engaged by some invasive and metastatic cancer cells is the aforementioned hypoxia response system, which triggers the activation of the hypoxia-inducible transcription factors HIF1a and HIF2a, consequently altering expression of hundreds of genes [5, 6]. Both transcriptional programmes control genes that can facilitate invasive migration as well as survival in the blood and lymphatic systems and in ectopic tissue locations.

Notably, the acquisition of this hallmark capability can occur at various points along the pathways of multistep tumour development that lead incrementally from normal cells of origin to those found in aggressive malignancies. In some cases, this capability for

invasion and metastasis is acquired early, such that cancer cells in an ostensibly benign tumour may be capable of dissemination long before this growth exhibits the overt histopathological phenotypes associated with high-grade malignancy. More often than not, however, the capability arises late, reflecting the accumulated mutational and epigenetic changes that render a tumour overtly malignant and thus its constituent cells capable of disseminating in large numbers to distant sites in the body. Moreover, there are clear indications that in the case of carcinomas, the EMT programme may become transiently active and functionally important for driving dissemination and seeding, thereafter being switched off in macrometastatic colonies [7]. It remains unclear whether the acquired traits of invasion and metastasis are beneficial and hence actively selected during the evolution of primary tumours or, alternatively, represent incidental byproducts of activating global regulatory networks (e.g. EMT, HIF) that facilitate primary tumour formation via functional contributions to the other five hallmarks.

Hallmark 7: deregulating cellular energetics and metabolism

The concept that cancer cells alter their utilization of energy sources—notably glucose—to support their proliferation was introduced almost 90 years ago by Otto Warburg, who observed that certain cultured cancer cells exhibited enhanced uptake of glucose, which was then largely metabolized by glycolysis. This limited breakdown of glucose occurred even in the presence of oxygen levels that normally would favour the oxidative phosphorylation pathway operative in the mitochondria. The result was counterintuitive, since glycolysis is far less efficient than 'OxPhos' at producing ATP, the primary currency of intracellular energy. We now appreciate that the 'aerobic' glycolysis described by Warburg produces, in addition to ATP, many of the building blocks for the cellular macromolecules that are required for cell growth and division. Indeed, the metabolism of cancer cells resembles that of actively dividing normal cells rather than being a novel invention of neoplasia. Moreover, it is important to appreciate that there is not a bimodal switch from mitochondrial Ox-Phos to aerobic cytosolic glycolysis in cancer cells. Instead, cancer cells continue to utilize in different proportions the Krebs/citric acid cycle-associated Ox-Phos and glycolysis pathways, the balance of which may well be required for optimal growth by cancer cells in different tumour microenvironments.

Although glucose is the primary fuel source used by most cancer cells, glutamine is also emerging as another key blood-borne source of energy and a precursor of lipids and amino acids. In most cases, glutamine likely supplements and enhances glucose in supplying energy and biomaterials for growth and proliferation of cancer cells, although in some cases of glucose insufficiency, glutamine may be able to compensate [8].

A third player in metabolic fuelling is lactate. While long considered to be toxic waste that is secreted by cells undergoing aerobic and anaerobic glycolysis, lactate is now appreciated to have diverse tumour-promoting capabilities [9]. In certain cancer cells, particularly those suffering glucose deprivation, extracellular lactose can be imported via specific transporters and used as fuel for generation of ATP and biomaterials. Similarly, some cancer-associated fibroblasts (CAF) can utilize lactate. Hence, metabolic symbioses can be envisaged within some tumours, between glucose-importing/lactose-exporting cells and lactose-importing cells [9].

Finally, we note a still-unresolved question about this hallmark: Is it significantly independent of the six cited earlier in terms of its regulatory mechanisms, or is it controlled by one of these other hallmark traits and in this sense hardly an independently standing hallmark on its own? Thus, certain mutant cancer genes, such as *Kras, cMyc,* and *p53,* have been found able to reprogramme the energy metabolism of cancer cells. Given this ambiguity, we termed the reprogramming of cellular energetics and metabolism as as an 'emerging hallmark' [2]. Irrespective of this qualification, it is clearly a crucial hallmark component of the neoplastic cell phenotype [10].

Hallmark 8: avoiding immune destruction

The eighth hallmark has been apparent on the horizon for decades. As originally proposed, incipient neoplasias must find ways to circumvent active surveillance by the immune system that would otherwise eliminate aberrantly proliferating pre-malignant cells. While clearly demonstrable in highly antigenic tumours in mouse models, and implicated in virus-induced human cancers, the generality of immune surveillance of cancer cells as a barrier to neoplastic progression and subsequent tumour formation is unresolved. One factor militating against this notion is the phenomenon of immune tolerance: because a normally functioning immune system develops a tolerance toward self-antigens, a tumour may pass under the radar and evade recognition and attack, as it expresses only these normal tissue antigens. Exceptions evidently arise, however, if cancer cells come to express embryonic antigens toward which immune self-tolerance was never established, or express fully novel non-self antigens created by gene mutation or by an infectious agent.

In fact, the immune response to the ~20% of virus-induced human tumours is clear: oncogenic viruses express foreign antigens to which the immune system is not tolerant, resulting in humoural and cellular immune responses that can kill virus-infected cells and thus eradicate incipient neoplasias. The fact that virus-transformed cells can nevertheless succeed in evading immune elimination to produce cancer testifies to immune-evasive capabilities evolved by such tumour viruses or developed by these cells during the course of tumour progression.

Although the incidence of non-virus-induced human cancers is not markedly increased in the context of immunodeficiency, suggesting a lack of immune surveillance of incipient neoplasias in the other 80% of human cancers, various lines of evidence suggest that some tumour types must indeed deal with immune recognition and attack during later stages of tumour progression and, in response, acquire immune-evasive strategies. Here, histopathological and epidemiological analyses have shed light on the potential role of immune attack and immune evasion. For example, among patients with surgically resected colorectal carcinomas, those whose tumours contained dense infiltrates of cytotoxic T-lymphocytes (CTLs) had a better prognosis than patients with tumours of similar grade and size that had comparatively few infiltrating CTLs. Such data implicate the actions of the immune system as a significant obstacle to the progressive growth and dissemination of cancer cells, one that is necessarily circumvented in some aggressive tumour types [11]. Indeed, immune phenotyping of tumours, including their associated stroma, is being evaluated as a new metric in the prognosis of certain tumour types that may enable, when combined with traditional criteria, more accurate predictions of prognosis and more effective treatment decisions [12].

For these reasons, we view anti-tumour immune responses as a significant barrier to be circumvented during the lengthy multistage development of many forms of human cancer. However, rules of immune engagement remain ambiguous across the spectrum of human cancers. Thus, it is generally unclear when during organ-specific tumour development the attention of the immune system is attracted (or not), and what the characteristics and efficacy of resultant immune responses are. Nor is it evident how polymorphic genetic constitutions of patients and the tumours that they harbour may affect anti-tumour immunity. Nevertheless, evading immune destruction seems increasingly to be an important mandate for developing tumours and thus an evident (if still emerging) hallmark of cancer.

Taken together, we view these capabilities acquired by most forms of human cancer to constitute a set of eight distinct hallmarks (Figure 1.1). Importantly, one cannot ignore the complex underlying mechanistic realities: different tumours acquire these hallmarks by diverse mechanisms, co-opting distinct homoeostatic and developmental functions in order to achieve them.

Genomic instability and inflammation: facilitators of hallmark capabilities

The lengthy process of tumour development and malignant progression, long appreciated to involve a succession of rate-limiting steps, reflects the need of evolving cancer cells to acquire the eight hallmark capabilities enumerated above. How then are these functional capabilities acquired? Currently, there are two clearly established means by which the hallmarks are acquired: genome instability and the resulting mutation of hallmark-enabling genes, and inflammation by cells of the immune system that help provide such capabilities.

Genome instability and the consequent mutation of hallmark-enabling genes is the primary means of acquiring hallmark capabilities. The cell genome is subject to routine DNA damage inflicted by a variety of chemically reactive by-products of normal metabolism, by environmental insults, and by errors in DNA replication during cell division. The resulting defects, if left unrepaired, can become cell-heritable mutations, explaining the need for an elaborate array of proteins that continuously monitor DNA integrity and, in response to damage, undertake repair. Irreparable genome damage provokes the elimination of cells, a task orchestrated by the p53 tumour suppressor gene, which has therefore been dubbed the 'guardian of the genome'.

The elevated rates and persistence of ongoing proliferation of cells in neoplastic lesions creates cell lineages that have undergone far more successive growth-and-division cycles than is typical of normal tissues, accentuating the potential for mutation-generating replication errors. Moreover, critically shortened telomeres can catalyse chromosomal rearrangements and fusions; if advantageous, hallmark-enabling mutations result, and if telomerase is subsequently activated to stabilize the mutated genome before the telomere crisis become lethal, then mutant clones of cancer cells can selectively expand.

The fundamental association of genome instability and mutation with cancer has been strengthened by numerous demonstrations that many cancer cells carry identifiable defects in the complex machinery designed to monitor and repair genomic damage. Most apparent are the frequently documented mutant alleles of p53 that have been found in perhaps 40% of all cancers; without p53 on duty, damaged DNA can persist unrepaired and mutant cells can survive and pass their damaged genomes on to their progeny. Other specialized DNA repair enzymes are also found in defective form in many tumours, and inherited familial defects in DNA repair can lead to elevated risk of cancer development, again by enabling the acquisition of tumour-promoting mutations.

The critical roles of somatic mutations in cancer pathogenesis are being further substantiated by the development of high-throughput DNA sequencing technologies and the associated ability to systematically analyse large numbers of independently arising cancer cell genomes. Complemented by other methods for genome scanning, such as comparative genomic hybridization to identify copy number variations, and 'chromosome painting' to detect karyotypic abnormalities such as translocations, the derangements of the cancer cell genome are being revealed in unprecedented detail [13–16].

The observations enabled by these various technologies substantiate the fact that almost every form of human cancer involves cancer cells whose genomes have been rearranged and mutated. The density of genetic alterations varies from one tumour type to another over many orders-of-magnitude, from very low numbers detected in certain paediatric cancers to the blizzards of mutations present in the genomes of UV-induced melanomas and tobacco-induced lung cancers. Thus, the aberrations can range from dozens of point mutations to hundreds of thousands per cancer cell genome, and from quasi-diploid chromosomal karyotypes to widespread aneuploidy, translocations, and multiple large-scale amplifications and deletions.

The data generated by these increasingly high-throughput genomic technologies presents a major challenge to determine which of the myriad mutational alterations actually contribute substantively to hallmark capabilities? The numbers that are being catalogued in many cancer cells greatly exceed those that are likely to be important in reshaping cell phenotype. The recurrence of specific mutations or mutated genes in multiple independently arising tumours of the same cancer type or subtype presents one compelling line of evidence concerning the functional importance of the involved gene. Yet other mutations may simply occur as consequences of the rampant stochastic mutations that accumulate in patients' tumours and, being non-recurrent, can be dismissed as 'passenger mutations' having little likelihood of contributing to tumour development; thus, such mutations would not seem to afford selective advantage and clonal expansion during tumour growth and progression. These phenomena have led to the emerging concept that cancer cells contain two classes of mutations: 'drivers' and 'passengers', the former being functionally important in driving tumour progression forward, while the latter are not. Identifying the important drivers becomes increasingly important as the effort to find potential therapeutic targets within cancer cells accelerates. An added dimension of complexity comes from the observations that certain hallmark traits may be conferred by driver mutations in some tumours, while in others comparable phenotypic advantage may be acquired by changes in the epigenome—the spectrum of heritable changes in chromatin that are not reflected by alterations in nucleotide sequence [17]. The field of cancer genetics is poised for an extraordinary decade during which tens of thousands of cancer cell genomes will be comprehensively

analysed for multiple parameters (DNA sequence and copy number, gene transcription, and histone and DNA methylation). The challenge and the opportunity will be to distill the contributions of specific genomic alterations to hallmark-enabling functions from the mammoth datasets that are being generated, and to exploit such knowledge for improved detection, evaluation, and informed treatment of human cancers.

Tumour-promoting immune infiltration (inflammation) is the second important means by which developing cancers can acquire hallmark capabilities. Above we discussed the mandate of developing tumours to avoid immunological destruction by cells of the adaptive immune system, often by blocking or pacifying infiltrating cytotoxic T cells. At the same time, it is clear that most tumours are nevertheless infiltrated by other cells of the immune system (so-called infiltrating immune cells, or IICs [3]) that are often components of the innate arm of this system and function as mediators of inflammation. In principle, such inflammation by IICs might reasonably be thought to represent failed attempts by the immune system to eradicate tumours. However, the evidence now clearly shows a quite different role: IICs help in the acquisition of multiple hallmark capabilities, encompassing six of the eight hallmarks [3]. Many of these functions reflect the roles that IICs play in the processes of wound healing and associated transient inflammation. Thus IICs can variously supply proliferative and survival signals, pro-angiogenic factors, and facilitate local invasion and blood-borne metastasis. In addition, some of these IICs (T-regulatory and myeloid-derived suppressor cells) can actively suppress the cytotoxic T lymphocytes that have been dispatched by the immune system to eradicate cancer cells.

The identities of the recruiting signals that bring IICs into tumours—including an ensemble of chemokine and cytokine signalling factors—are still incompletely understood. In some cases, the nature of the neoplastic lesion may trigger tissue abnormality signals that attract IICs; in particular, innate immune cells and possibly also B and T lymphocytes of the adaptive arm of the immune system. In other cases, oncogenic signalling, by activating transcriptional networks, induces expression of cytokines and chemokines that recruit IICs. In early stage lesions, the recruited IIC can help incipient cancer cells to proliferate, survive, evade anti-growth controls, or activate angiogenesis. At later stages of progression, IICs at the margins of tumours can facilitate invasiveness. Some experiments reveal that IICs can pair with cancer cells as they migrate through the circulation and become established in distant locations [18]. Additionally, certain IICs, such as macrophages, can subject cancer cells to DNA-damaging reactive oxygen species, thereby contributing to the mutational alteration of the cancer cell genome.

Most types of solid tumours are associated with tumour-promoting immune infiltrations that range from histologically subtle to the obvious inflammatory responses recognized by pathologists. In addition, the long-appreciated epidemiologic association between chronic inflammation and carcinogenesis supports the proposition that pre-existing inflammatory conditions create fertile breeding grounds for the inception and progression of certain forms of cancer. Moreover, chronically inflamed tissues share features with wound healing; both involve induction of angiogenesis and stimulation of cell survival, proliferation and migration/invasion, involving the inflammatory IIC and other cell types (e.g., myofibroblasts) that they activate in the affected tissue. These multiple processes stimulated by inflammatory cells are of course hallmark capabilities, explaining why inflammation represents an important enabler of many types of cancer.

The tumour microenvironment (TME)

Historically, the simplistic description of the stroma posited that endothelial cells, through the process of angiogenesis, provided oxygen and nutrients, while carcinoma-associated fibroblasts (CAFs) provided structural support, and the IICs, discussed above, represented ineffectual anti-tumoural immune responses. We now appreciate the fact that the diverse cells forming the tumour-associated stroma can contribute to acquisition by cancer cells of seven of the eight hallmarks [3]. These three classes of stromal cell—angiogenic vascular cells (AVC), consisting of endothelial cells and pericytes; cancer-associated fibroblasts (CAF); and infiltrating immune (inflammatory) cells (IIC)—remain the most important actors within the TME in terms of their ability to facilitate tumour progression [3]. In fact, there are a number of distinct subtypes of mesenchymal cells within the stroma that have, in the past, been labeled simply as CAFs. The three most prevalent of these originate from alpha-smooth muscle actin-expressing myofibroblasts, mesenchymal stem cells, or connective tissue fibroblasts. These subtypes of CAFs are evidently generated by epigenetic reprogramming of their respective normal cells of origin by paracrine signals produced in the TME, reflecting similar signals that are responsible for orchestrating the complex process of wound healing.

The IIC cells described earlier are now known to be more diverse than previously appreciated. The list of tumour-promoting IICs includes various forms of macrophages, neutrophils, partially differentiated myeloid progenitors, and in some cases specialized B and T lymphocyte subtypes. The endothelial cells and pericytes of the tumour-associated vasculature are, superficially at least, relatively simple by comparison. However, both epitope and gene expression profiling have revealed tissue- and tumour-type-specific features of the endothelial cells, likely with subtle functional implications in terms of their ability to contribute to acquisition of hallmark phenotypes by nearby cancer cells.

This recent and more nuanced view of stromal cells elevates their importance in understanding the disease, by virtue of their hallmark-enabling functional contributions [2, 3]. CAFs, as an example not discussed above, can in different neoplastic contexts secrete proteases and signalling ligands that can, in turn, liberate epithelial cells from the growth-suppressive effects imposed by normal tissue architecture. Alternatively, CAFs may foster tumour-promoting inflammation, facilitate both local invasion and metastatic seeding, and even provide cancer cells with metabolic fuel. CAFs can also induce angiogenesis and, remarkably, act in an immune-suppressive fashion to blunt the attacks of tumoricidal CTLs.

Looking to the future, an important goal will be to continue mapping the multidimensional landscape of stromal cell types and subtypes operating within different tumour types and at different stages of progression, annotating the means of their recruitment and programming, and their respective functional contributions to hallmark capabilities and tumour phenotypes.

Finally, we note an additional dimension of intra-tumoral complexity revealed by findings indicating that most cancers contain distinct subpopulations of cancer cells with a greatly elevated ability to seed new tumours. Such tumour-initiating cells (TICs), often

termed cancer stem cells (CSCs), contrast with the bulk of cells in most tumours, which lack tumour-initiating ability. CSCs typically proliferate relatively slowly and often express the distinctive cell-surface markers of tissue stem cells [7, 19]. The initial concept was that CSC spawned cancer cells much like normal tissue stem cells spawn differentiated progenitors, and indeed there are such cases. For example, the CSCs in squamous cell carcinomas of the skin, which produce partially differentiated cancer cells much as normal skin stem cells produce the squamous epithelium. But in other cases, there appears to a dynamic bidirectional relationship between CSCs and cancer cells, in that cancer cells can be converted into CSCs, and vice versa; in some such cases, the EMT appears to switch on the CSC phenotype in cancer cells, while its converse (the mesenchymal-to-epithelial transition, MET) does the opposite to CSCs [7, 19]. Independent of this interconvertibility, there are indications that more slowly proliferating CSCs are often more resistant to existing anti-cancer drugs, enabling their persistence after initial treatment, laying the foundation for the regrowth of tumours that leads to clinical relapse. As such, therapeutic targeting of CSCs may be crucial to achieving enduring cancer therapies.

Applications to cancer medicine?

What then are the applications to translational and clinical oncology research of this conceptualization that common principles underlie the diversity of human cancer? The most apparent is in helping elucidate the molecular and cellular mechanisms by which particular forms of human cancer develop and progress to malignancy. A wealth of data is being generated by multiplatform analyses of cancer cells and neoplastic lesions in different tumour types (see, for example, [20]). Moreover, there will be other extrapolations of such analytic technologies, including the comparison of the cells present in multiple stages in tumorigenesis and tumour progression including metastatic growths, as well as comparisons of tumours and metastases during the response and relapse phases. The hope is to distill these complex datasets into insights that enable the development of novel mechanism-targeted therapies. The challenges are indicated by a number of formidable problems, including developing computational strategies that will make it possible to integrate all of this information in order to reveal the key determinants of particular tumorigenic pathways, to identify new therapeutic targets within cancer cells, to identify modes of

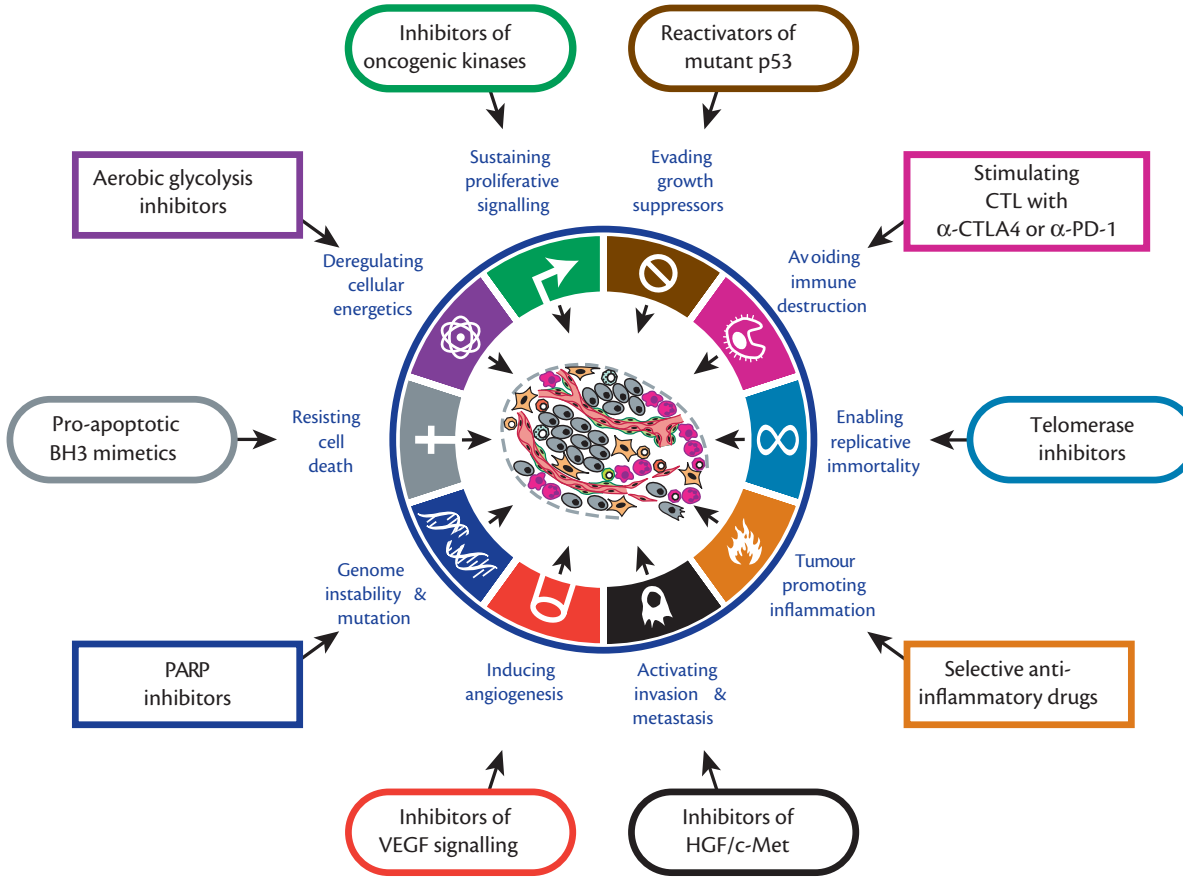

Fig. 1.2 Therapeutic targeting of the hallmarks of cancer. Drugs have been developed that disrupt or interfere with all eight of the hallmark capabilities, and with the two enabling facilitators (genome instability and tumour-promoting inflammation). Some of these hallmark-targeting drugs are approved for clinical use, while others are being tested in late-stage clinical trials; moreover, there is a pipeline full of new hallmark-targeting drugs that are in development and preclinical evaluation. Recognizing that eventual adaptive resistance during therapeutic treatment is apparent for virtually all of these hallmark-targeting drugs, a hypothesis has emerged: perhaps, by co-targeting multiple independent hallmarks, it will be possible to limit or even prevent the emergence of simultaneous adaptive resistance to independent hallmark-targeting drugs; clinical and preclinical trials are beginning to assess the possibilities.

adaptive resistance to therapy, and to use all of these data for diagnosis, prognosis, and treatment decisions. It is plausible, albeit still unproven, that conceptualizing these problems in terms of cancer's hallmarks will prove useful in this integration and distillation.

The hallmarks concept may prove useful in a second way. Thus, there are either approved drugs or drugs in late-stage clinical trials that target each of the eight hallmark capabilities and both of the enabling characteristics (Figure 1.2). For most of the ten, there are multiple drugs targeting a small set of mechanistic effectors. Unfortunately to date, such mechanism-based therapies targeting individual hallmarks have not proven to be been transformative for the treatment of late-stage, aggressive forms of human cancer. Typically, after a period of clinical response by tumours, adaptive resistance mechanisms kick in, enabling the surviving cancer cells (and CSCs) to resume progressive growth.

While different solutions can be proffered, one strategy involves applying the concept of the hallmarks as independent (or quasi-independent) and necessary components of a malignant cancer: by concomitantly targeting multiple hallmarks, it may be more difficult for cancer cells to concurrently develop multiple resistance mechanisms, allowing improvements in both initial efficacy and duration of clinical responses. As is always the case with multi-drug treatments, a major complication will arise from the toxicities that often accompany application of such therapeutic protocols. Anticipating such complications, genetically engineered mouse models of cancer and patient-derived xenografts may prove highly useful in reducing the numbers of drug combinations that should be tested in early phase clinical trials [21].

In conclusion, the hallmarks of cancer may provide the student of modern oncology with a foundation and a framework for absorbing the subsequent topical chapters of this textbook, and more generally for investigating and interpreting mechanisms, and applying such knowledge towards the development of more effective treatments for human cancers.

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CHAPTER 2

Growth factors and uncontrolled proliferation

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Introduction to growth factors and uncontrolled proliferation

In spite of the significant diversity in their protein structures, growth factors have a remarkably similar overall mechanism of relaying signals (Figure 2.1). In general, ligand binding to receptors induces dimer formation (Figure 2.2) and autophosphorylation followed by recruitment of docking proteins and the activation of downstream signalling pathways that eventually modulate transcription. The specificity of growth factor signalling is governed by tissue-specific expression of pathway receptors, modulators, adaptors, and signalling molecules. The orderly regulation of components of growth factor pathways is governed by feedback loops that modulate the intensity and duration of a particular signal. A central feature of the majority of known cancers is the deregulation of one or more components of such feedback loops. Therefore, growth factor signalling pathways have attracted extensive drug discovery and drug development efforts that led to the introduction of many successful targeted therapies in cancer management. In general, these therapies have targeted the inactivation or blockage of ligands, receptors, or downstream signalling pathways (Figure 2.3). Here we outline the mechanisms involved in the regulation of some of the major growth factor signalling pathways, their deregulation in cancer and current approaches for growth factor targeted therapies.

Hepatocyte growth factor

Hepatocyte growth factor (HGF) was originally identified as a growth factor produced by platelets that stimulated DNA production in rat hepatocytes in primary culture that was biochemically distinct from platelet derived growth factor [1]. Subsequently, HGF and its ligand, the MET receptor tyrosine kinase [2] were implicated in various physiological and pathological processes.

HGF belongs to the plasminogen family of proteins and is transcribed and secreted in its inactive form as a single polypeptide, pro-HGF [3]. Subsequent site-specific proteolysis results in the formation of a dimer and this process is required for the biological activity of HGF [4]. This proteolytic step is mediated by a thrombin-like soluble enzyme called HGF activator (HGFA) or by the membrane bound proteolytic enzymes matriptase and hepsin [5, 6]. The activation of HGF is inhibited by proteolytic inhibitors HAI1 and HAI2 [7, 8].

Once HGF is activated, its serine proteinase homology (SPH) domain binds to the semaphorin (Sema) transmembrane domain of its receptor MET at the surface of cells. This binding results in the dimerization of the receptor and subsequent autophosphorylation of multiple tyrosine residues in its kinase domain. This results in subsequent activation and autophosphorylation of the substrate recognition site of the kinase and the adaptor proteins growth factor receptor-bound protein 2 (GRB2) and the GRB2-associated binding protein 1 (GAB1). It is important to note that the dimerization of the receptor is followed by internalization by endocytosis through clathrin-mediated coated pits and vesicles. Internalized receptor retains activity and there is recent evidence to suggest that certain MET mutations result in cytoplasmic localization of the receptor [9]. Once phosphorylated, MET, GBR2, and GAB1 act as docking sites for multiple substrates such as phosphoinositide 3 kinase (PI3K), CRK-like (CRKL) protein, and the protein tyrosine phosphatase SHP2 (also called PTPN11). Cytoplasmic MET becomes either degraded or recycled back to the membrane. Through docking these proteins, the HGF-MET pathway regulates several biological processes such as metabolism (PI3K signalling), proliferation (RAS/MAPK and PI3K signalling), epithelial mesenchymal transformation (EMT) and migration (RAC1/CDC42) [10]. Through modulating these signaling pathways, the HGF-MET pathway regulates important processes such as regeneration after skin [11, 12] or liver damage [13, 14] and EMT of myogenic progenitor cells in development [15].

The physiological regulation of HGF and MET is lost in cancers through multiple mechanisms including transcriptional deregulation, inadequate degradation, receptor crosstalk or synergies in downstream signalling pathways [2, 10, 16]. Induction of germ-line mutations of the HGF pathway in mice results in the generation of a variety of malignancies such as carcinomas, lymphomas, and sarcomas [17]. In addition, conditional activation of MET in the mammary gland results in the formation of basal-like carcinomas [18] and overexpression of MET is observed in a variety of tumours such as lung and renal carcinomas [19]. The activation of this pathway results in persistent activation of the RAS/MAPK pathway and the PI3K/AKT pathway that in turn results in increased proliferation, growth, and resistance to apoptosis. HGF/MET signalling is also a potent inducer of endothelial cell growth and angiogenesis [20–22]. Activation of MET results in increased VEGFA production and inhibition of thrombospondin production and this leads to enhanced angiogenesis [23]. MET also plays an important role in promoting metastasis of cancer cells through its role in regulating the RAS/MAPK [24] and RAC1/CDC42 regulation of the cytoskeleton [25].

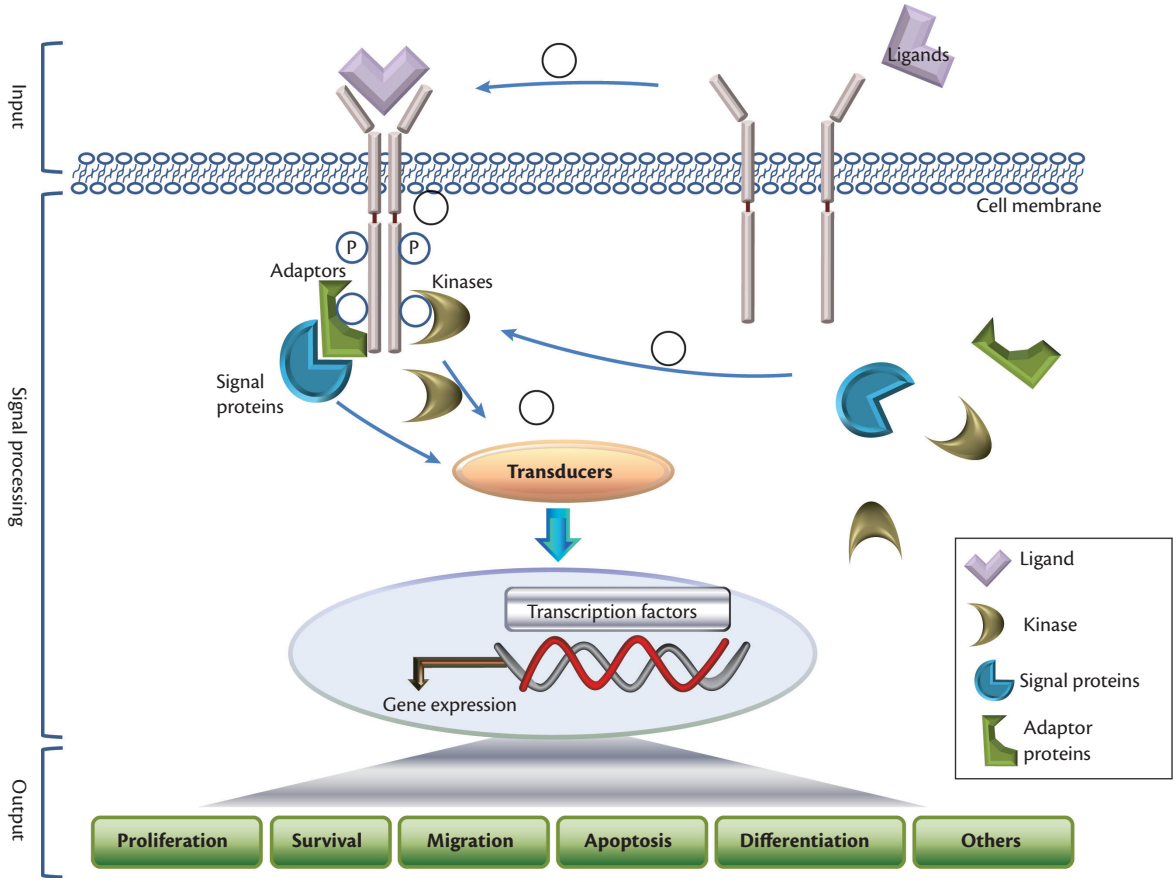

Fig. 2.1 General perspective of growth factor signal transduction. The basic mechanism of activation of growth factor signalling pathway starts by: (1) binding followed by (2) ligand-induced receptor dimerization, activation of intrinsic kinase activity and autophosphorylation at specific tyrosine residues or serine/threonine residues (in the case of TGFβ), then (3) the phosphorylated receptors act as docking sites for adaptor proteins or could directly bind to a wide range of molecules that could (4) activate downstream signalling pathways which, ultimately, regulate a variety of cellular processes. Most of these signalling pathways relay signals from the membrane through the cytoplasm to the nucleus, except for IL-6 which via STATs transmit signals directly from the membrane to the nucleus.

Because of its established role in transformation, tumour growth, metastasis, and angiogenesis, the HGF-MET pathway has been established as a target for therapy in many tumour types [19]. So far, there are several strategies targeting the HGF/MET pathway, including inhibitor of HGF/SF activators, anti-HGF humanized antibodies, MET decoy receptors as well as MET extracellular domain monoclonal antibodies. In addition, several selective and non-selective MET kinase inhibitors are under evaluation in clinical trials. In addition, several combinations of targeted therapies are ongoing in Phase II and Phase III studies [10, 19]. Promising results were obtained from a clinical trial of a MET antibody (METMab®) in combination with an EGFR inhibitor (erlotinib) to treat patients

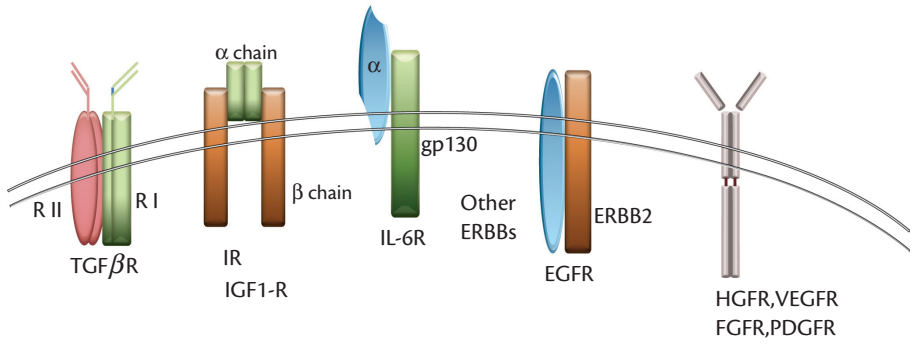

Fig. 2.2 Ligand binding could induce different types of receptor dimer formation depending on both the structural characteristics of the receptors. The most common form of dimerization is the formation of homodimers as is the case with HGF, VEGF, FGF, and PDGF receptors. EGF receptors form heterodimer complexes as not all of them can interact with ligands (e.g., ERBB2) or possess kinase activity (e.g., ERBB3). The TGFβ and IL-6 receptors usually form heteroterametric complexes (sometime hexamerization for IL-6) composed of two different isoforms of the receptor (for TGFβ, they are type I and type II TGFR. For IL-6, they are IL-6Rα and gp130). The IR and IGF1R isoforms are 'half' receptors that comprise a predominately extracellular α-chain and an intracellular β-chain. When actived, two half receptors form a holoreceptor for downstream signalling.

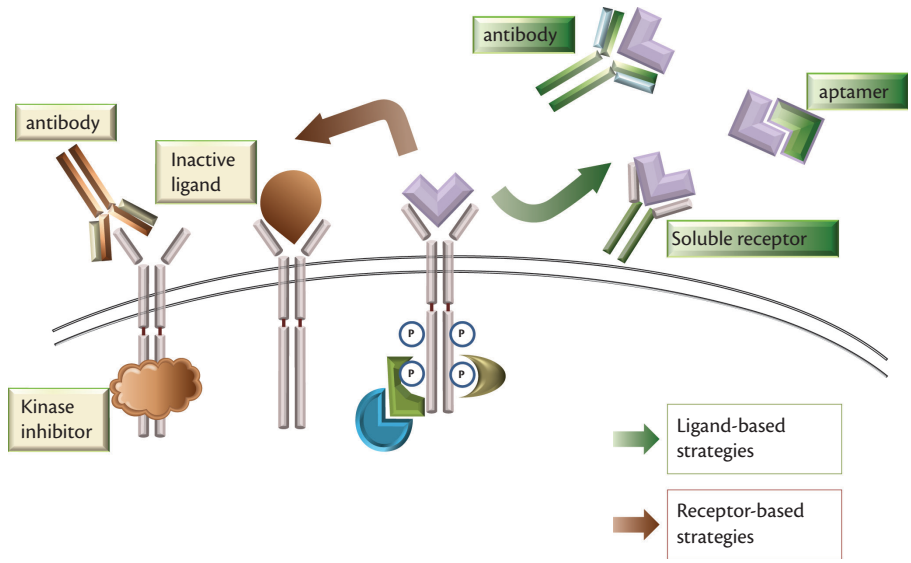

Fig. 2.3 Principles of pharmacological inhibition of growth factor signalling in cancer therapy. In general, the strategies targeting growth factor signalling pathways are divided into two major groups: (1) approaches for blocking the ligand or (2) blocking the receptor. The ligand can be blocked by neutralizing antibodies, dimeric soluble receptor extracellular domains, aptamers (stabilized oligonucleotides which could bind ligand proteins with high specific) or antisense oligonucleotides that target the ligand mRNA. Among the blocking receptor approaches, the receptor kinase inhibitors are the most widely developed pharmacological agents in cancer therapy. In addition, neutralizing antibodies targeting receptors and receptor kinase inhibitors are the most efficient and widely developed pharmacological approaches in cancer therapy.

with non small cell lung carcinoma (NSCLC). The combination treatment increased the progression-free survival (PFS) in cancers with high c-MET expression when compared with the group receiving erlotinib alone. Cancers with low or no c-MET expression showed no response to METMab® and patients had worse overall survival [10].

Insulin growth factor

Insulin is secreted from the β cells of the pancreas and functions as a classic hormone by influencing glucose uptake and carbohydrate metabolism in target cells that are distant from the pancreas. Insulin signals through insulin receptors (IR) that are formed of two αβ glycosylated polypeptides that together form a holoreceptor. The α chain of the receptor is predominantly localized at the surface while the β chain is transmembranous and harbours the kinase domain of the receptor [26]. Binding of insulin to the α chain of the receptor results in its activation and increased glucose uptake and downstream induction of glycolysis. This basic physiological process is crucial for the regulation of circulating glucose levels. IGFs have characteristics of both hormones and tissue growth factors. Similar to insulin, insulin-like growth factor 1 (IGF1) and IGF2 signal through a specific receptor, IGF1R, to regulate glucose metabolism, signal transduction, and a variety of physiological processes. Unlike insulin, IGF1 and IGF2 are widely expressed by many cell types and function in autocrine, endocrine, and paracrine fashions [27]. These ligands and their receptors have been implicated in driving the growth of many tumours [28, 29]. IRs exist in two splice variant isoforms: IRA and IRB, but the IGF1 receptor only has one isoform. IRB recognizes only insulin while IRA, which is most commonly expressed in tumours, recognizes both insulin and IGF2.

IGF1R shares 70% homology with IR (84% homology with its kinase domain [30]) and is a holoreceptor that is formed of αβ chains and together they form part of the transmembrane receptor tyrosine kinase superfamily. IGF1R acts as a receptor for both IGF1 and IGF2. Upon ligand activation, IGF1R undergoes conformational changes that result in binding of ATP to residue Lys1003 and activation of the kinase by autophosphorylation at tyrosine residues 1131, 1135, and 1136 [31] and subsequent binding and activation of docking substrate proteins such as insulin receptor substrates (IRS1-4). IRS tyrosine phosphorylation increases its affinity to the PI3K complex that results in translocation of PI3K to the membrane and its subsequent activation. IGF1R-mediated activation of PI3K as well as RAS/RAF/MAPK represent the key pathways through which IGF regulates cell proliferation and metabolism [27, 32].

There are several lines of regulation of IGF signalling. In general, IGF binding proteins (IGFBPs) have high affinity to insulin growth factors and limit their bioavailability to bind to IGFR1 [33]. IGFBPs expression is induced by p53, as well as many growth inhibitors such as vitamin D, anti-estrogens, retinoids, and transforming growth factor β [28]. Decreased expression of IGFBPs or mutations in TP53 result in increased IGF signalling and increased tumour proliferation [34]. Another line of regulation is through allelic dosing by imprinting and silencing of the maternal-derived allele of IGF2. Loss of imprinting carries a fivefold increased risk of colorectal neoplasia [35]. In addition, IGF2R, which specifically binds IGF2, lacks the kinase activity of IGF1. Therefore, IGF2R binding to IGF2 is thought to be a mechanism of inhibition of the pathway, and loss of function mutations of IGF2R have been found in a variety of tumours [36]. There is strong evidence that IGF signalling is either required for or facilitates the transforming signals of oncogenes. In vivo models demonstrated that loss of IGF2 reduced tumour development following TP53 or PTEN deletions in mice [37, 38].

Because of the strong evidence that the IGF signalling pathway is involved in driving tumour growth [28, 39, 40], it has been intensively investigated as a possible target for therapy. Several strategies

have been evaluated including targeting the ligands or decreasing their bioavailability, developing blocking antibodies targeting the IGF receptors or blocking of downstream signalling via activation of the AMPK pathway. In spite of the continuing enthusiasm in evaluating IGF signalling as a target for therapy, the results from clinical trials have not been encouraging [29].

The IL6/JAK/STAT3 pathway

Initially identified as a T-cell-derived regulating factor in B cell differentiation, Interleukin 6 (IL6) was found to play important roles in a wide range of biological activities such as immune regulation, haematopoiesis, and oncogenesis [41]. IL6 belongs to a group of cytokines that include IL11, leukaemia inhibitory factor (LIF), cardiotrophin (CT1), cardiotrophin-like cytokine (CLC), ciliar neurotrophic factor (CNTF), and oncostatin M (OSM), which all share a common receptor: glycoprotein receptor 130 (gp130) [42]. IL6 binds to its receptor IL6R (composed of ILRα and gp130) leading to its tetramerization/hexamerization, which in turn leads to activation of JAK1/JAK2/TYK2 kinases [42–44]. Activated JAK1/JAK2/TYK2 leads to tyrosine phosphorylation of the cytoplasmic domain of the IL6R leading predominantly to recruitment of signal transducer and activator of transcription 3 (STAT3) via its SH2 domain and its subsequent phosphorylation by JAK1/JAK2/TYK2. Once phosphorylated, STAT3 dissociates from the receptor and forms active dimers in which a phosphorylated SH2 domain of one molecule of STAT3 binds to the phospho-tyrosine 705 of the other molecule. Unlike many other signalling pathways that relay signals from the membrane through the cytoplasm to the nucleus, STATs offer a direct route of signalling from the membrane to the nucleus. STAT3 activation leads to the transcription of pro-survival proteins such as the anti-apoptotic protein BcL-xl, the cell cycle promoter cyclin D1, MCL-1, XIAP, Fas, and the oncogene c-Myc, as well as angiogenic factors [45, 46]. The regulation of the IL6/JAK/STAT3 pathway is mediated by the SOCS (suppressor of cytokine signalling) feedback inhibitors and PIAS (protein inhibitor of active Stat) proteins [41]. In addition to activation of STAT3, IL6 also activates Ras, MAPK, Cox-2, Wnt and PI3K/AKT pathways [47].

Overexpression of IL6 and activation of IL6 pathway are reported in many tumour types such as ovarian cancer, breast cancer, prostate cancer, endometrial cancer, lung cancer, renal cell carcinoma, oral squamous cell carcinoma, and colon cancer [41]. IL6 and STAT3 have also been associated with cancer drug resistance in breast, prostatic, and ovarian cancer. Treatment targeting IL6 or STAT3 could sensitize ovarian cancer to paclitaxel [48–50]. In addition, serum IL6 has been found to correlate with patient survival and could be an independent prognostic factor for cancers [51]. Mutations of IL6 downstream kinases such as the JAK2 V617F have been identified in most myeloproliferative neoplasms [52].

Current therapeutic strategies targeting IL6 mainly focus on monoclonal antibodies against IL6 and IL6R. Several types of chimeric antibodies, such as CNTO 328 (siltuximab) and BE-8, and humanized monoclonal antibodies, such as CNTO 136 and ALD518, are undergoing clinical trials [41, 53]. In addition, strategies have been employed for targeting STAT3 signalling that can be broadly divided into rationalized inhibitor design and screening. Peptides, peptidomimetics, and small molecule derivatives have been developed to interrupt STAT3 dimerization by targeting the SH2 domain or by inhibiting the interaction between STAT3 dimers and DNA [54]. In addition, high throughput cell-based screening identified quinolines as possible inhibitors of STAT3 phosphorylation [55]. Despite intense research for discovering potent STAT3 inhibitors that could be tested in clinical trials, such agents still do not exist. JAK inhibitors such as ruxolitinib elicited significant responses when tested in phase III clinical trials for patients with myelofibrosis [56].

Epidermal growth factor

Epidermal growth factors (EGF) include 13 polypeptide ligands that share the EGF-like domain, a ~50 amino acid sequence characterized by a consensus six cysteine residue peptide and a β-sheet structure. EGF ligands include EGF, HB-EGF, neuregulins (1 through 6), epiregulin, amphiregulin, epigen, betacellulin, and TGFα. [57–59]

EGF ligands signal through a group of receptor tyrosine kinases called epidermal growth factor receptors (EGFRs, also called the ERBB receptors). The ERBB family of receptor tyrosine kinases includes ERBB1, ERBB2, ERBB3, and ERBB4 and share similar structural features. Broadly, they are formed of an extracellular ligand-binding domain, a transmembrane domain, a juxtamembrane domain, a kinase domain and a c-terminal tail that acts as a docking site for signalling proteins. In general, ligand binding results in homo- or heterodimerization, in which ERBB2-containing heterodimers are formed preferentially, and autophosphorylation on tyrosine residues. The latter provides docking sites for various adaptors or enzymes that initiate many signalling cascades [60]. In spite of broad similarities, ERBB receptors have distinct characteristics. For example, ERBB1, once bound to its ligands, undergoes conformational changes and autophosphorylation followed by binding to multiple docking proteins such as growth factor receptor bound 2 (GRB2) and members of the MAPK family of proteins but not PI3K [61]. Mouse knockouts of ERBB1 are fatal because of brain defects [62]. ERBB2, however, is thought to be a non-autonomous receptor tyrosine kinase that is incapable of binding to ligands but is capable of binding to a wide variety of substrates including the formation of heterodimers with other ERBB receptors and is, therefore, responsible for signal amplification in the EGF pathway [63]. ERBB3, while able to bind to ligands, is also thought to be non-autonomous as it lacks tyrosine kinase activity, albeit similar to the IGFR2 [64]. It does, however, form heterodimers with other ERBB receptors and is capable of binding to PI3K resulting in its relocation to the membrane followed by activation. ERBB4 is an autonomous tyrosine kinase that is capable of binding to ligands such as betacellulin, heparin-binding ligand, HB-EGF and epiregulin. Upon activation it is capable of recruiting GRB2, Shc, STAT5, and PI3K.

ERBB receptors are regulated via positive and negative feedback mechanisms. For example, ERBB receptor activation has been shown to induce TGFα and HB-EGF transcription [65]. Negative feedback loops either pre-exist, or are newly synthesized following stimulation of ERBBs by their respective ligands. The former primarily control receptors dephosphorylation and degradation. The latter, which is transcriptional up-regulated, may affect the ERBBs in multiple processes. For example, EGF stimulation results in the increased expression of the suppressor of cytokine signalling 5 (SOC5) that in turn promotes ERBB degradation through recruitment of E3 ubiquitin ligase [66]. In addition, the transmembrane leucine-rich repeat and immunoglobulin-like domains 1 protein (LRIG1) have been shown to inhibit EGF-mediated transformation of NIH3T3 fibroblast possibly through promoting ERBB receptor degradation [67].

Several mechanisms of deregulation of the EGF pathway have been described in cancer, which include overproduction of ligands, overproduction of receptors, or constitutive activation of receptors. In lung cancer, frequent mutations of ERBB1 at the ATP-binding cleft of the kinase domain have been described [68]. Such mutations are capable of activating downstream signalling pathways and increase the ability of ERBB1 to form heterodimers with other ERBB family members. Further, deletions of exon 2 to 7 of EGFR to form the oncogenic EGFRvIII mutant are commonly observed in glioblastoma [69]. In addition, genomic amplification of ERBB1 has been observed in lung, ovary, pancreas, breast, and head and neck cancers [70–72]. ERBB2 amplification and overexpression is frequently observed in breast cancer [73] and results in poor overall prognosis and resistance to taxane chemotherapy [74]. Overexpression results in EGFR-dependent pathway activation through delayed ligand induced degradation.

EGF targeting has been one of the most successful targeted therapy strategies for cancer treatment. Most efforts have concentrated on ERBB2 and ERBB1 owing to their increased expression in certain tumours, as mentioned before. Therapeutic approaches could be divided into immunological strategies (humanized antibody or naked monoclonal antibody), low molecular weight inhibitors (such as inhibitor of Hsp90), tyrosine kinase inhibitors and drug combinations. For example, trastuzumab, a monoclonal antibody against ERBB2, significantly improves survival in breast cancers that overexpress ERBB2 [75]. Similar results have been obtained with the EGFR monoclonal antibody cetuximab in EGF-expressing colorectal cancers that do not possess RAS mutations [76]. Tyrosine kinase inhibitors gefitinib (Iressa®) and erlotinib (Tarceva®) are also indicated in non-small-cell lung cancer [68]. Lapatinib is an ERBB1 and ERBB2 inhibitor that improves survival in ERBB2 positive metastatic breast cancer [77].

Fibroblast growth factors

Fibroblast growth factors (FGFs) [78] play many important physiological roles in regulating angiogenesis, wound repair, cell survival, and proliferation and differentiation. The FGF family includes 18 ligands and four transmembrane receptor tyrosine kinases (FGFR 1 through 4). FGFs are formed of glycoproteins that are secreted to the extracellular matrix and cell surface and are released from the matrix by the action of heparinases, proteases, or specific FGF-binding proteins that enable them to bind and activate their receptors. The specificity of the FGF–FGFR interaction is established by receptor paralogues, alternative splicing of FGFR, and the tissue-specific expression of ligands and receptors [79].

In general, the released FGFs bind to cell surface heparan sulphate proteoglycans (HPSGs) that stabilize the ligand–receptor interaction. FGF's binding to its receptors results in receptor dimerization, and subsequent formation of a ternary complex that comprises two receptor molecules, two FGFs, and one HSPG chain. The FGF signal leads to a conformational change of receptor structure that induces kinase domain activation and tyrosine phosphorylation of both the kinase domain and the receptor tail. This results in docking of a variety of signalling proteins of which the FGFR substrate 2 (FRS2) appears to be a key adaptor largely specific to FGFR. FGFRs phosphorylate FRS2 on several sites, and active FRS2 allows the recruitment of adaptor proteins, growth factor receptor bound 2 (GRB2) and Son of Sevenless 1 (SOS1) protein to promote guanine nucleotide exchange and activation of the RAS/RAF/MAPK pathway [80] and PI3K [81]. FGFRs are also capable of binding to other receptor tyrosine kinases such as anaplastic lymphoma receptor tyrosine kinase (ALK) [82]. Independently of FRS2 binding, the FGFRs could also bind to the SH2 domain of phospholipase Cγ (PLCγ) via its phosphotyrosin residue at the carboxyl terminus [83] and signals through the PKC/Ref/MAPK pathway. Several other pathways are also activated by FGFRs, such as p38 MAPK, Jun N-terminal kinase pathway, STAT signalling pathway [84], and ribosomal protein S6 kinase 2 (RSK2) [85]. The physiological functions of the FGF family are context dependent subject to cell-type specific expression pattern and cross-talk with other pathways. FGFRs play a key role in differentiation. For example, mutations in FGFR2 result in premature activation in development and premature closure of skull sutures resulting in a syndrome called craniosynostosis.

Important negative feedback mechanisms exist to suppress FGF signalling. For example, activation of the pathway has been shown to activate CBL-mediated monoubiquitylation and degradation of FGFRs [86]. MAPK activation downstream of FGFR results in induction of FRS2 expression which competes for and inhibits the binding of GRB2 to FGFR [82]. Further, FGFR signalling activates the MAPK phosphatase 3 (MKP3) which results in dephosphorylation and inactivation of ERK1 and ERK2 and, therefore, limiting MAPK signalling [87]. In addition, ERK1 and ERK2 signalling results in increased expression of Sprouty which either competes with SOS1 for binding to GRB2 and limits FGF-induced RAS activation, or directly binds to RAF to block the subsequent MAPK signalling [88, 89]. Similarly, the transmembrane form of interleukin 17 receptor D (IL17RD, also known as SEF) can directly bind to FGFRs [90] and inhibit ERK phosphorylation [91].

In cancer, several mechanisms of deregulation of the FGF pathway have been described including genomic FGFR alterations that drive ligand-independent receptor signalling such as gene amplifications, mutations, and translocations and alternation that result in ligand-dependent activation [79]. In a screen of more than 1000 somatic mutations found in the coding exons of 518 protein kinase genes from 210 different human cancers, the non-synonymous mutations of FGF signalling pathways were the most commonly identified mutations [92]. Most notably, mutations in the extracellular domain of FGFR3 that result in constitutive dimer formation have been described in 50% of bladder cancers [93]. Similar mutations have been observed in cervix cancer [94], prostate cancer [95] and multiple myeloma [96]. Mutations of FGFR2 occur in 12% of endometrial cancers [97]. Gene amplifications of FGFR2 are frequently observed in cancers such as being amplified in 10% of gastric cancers [98]. Similarly, amplification of the FGFR1-containing locus occurs in 10% of breast cancers [99]. Translocations that result in constitutive activation have also been observed in multiple myelomas where t(4;14) results in an FGFR3 to immunoglobulin H3 fusion which facilitates ligand-independent binding [100, 101]. In addition to FGFR deregulation, ligand-dependent mechanisms have also been observed in cancers through either autocrine production of ligand in cancer cells or paracrine overproduction of ligand from stromal cells that may be expressed physiologically or in response to cancer cells in a "paracrine loop" [79]. For example, antisense-mediated inhibition of FGFR1 or FGF2 regressed the growth of human melanoma xenografts, indicating that an FGF2–FGFR1 autocrine loop promotes the development of some melanoma [102]. FGF1 overexpression, which

functions in a paracrine manner to promote angiogenesis, has been shown to correlate with poor survival in ovarian cancer [103].

Several mechanisms mediate the oncogenic potential of FGF deregulation. FGF signalling could affect cell proliferation, cell survival, migration, invasion, and angiogenesis in different tumour types. For example, activation of the pathway results in enhanced cancer cell survival and proliferation via activation of the PI3K–Akt pathway [104–106]. In addition, overexpression of FGF2 results in upregulation of the anti-apoptotic proteins BCL2, BCLx, XIAP, and IAP1 through the S6 kinase-mediated pathway, therefore promoting resistance to chemotherapy [107, 108, 109]. FGFR1 activation could result in increased MMP3-dependent invasion [110]. Importantly, endothelial blood vessels express high levels of FGFR1 and FGFR2, and FGF stimulation is known to have a potent angiogenic effect [111, 112].

In spite of the known oncogenic potential of FGF signalling, studies have shown that it has tumour suppressive functions in a context-dependent manner. For example, in a mouse model of developing endochondral and membranous bone, the FGFR3 and FGFR2 can negatively regulate proliferation and positively drive differentiation [113, 114]. Several studies of human tumours and cancer cell lines potentially support a tumour protective effect of FGFR2 signalling. For example, the expression of FGFR2-IIIb in FGFR2-IIIb negative bladder tumour cell lines blocks cell proliferation [115]. Given that in some circumstances FGFR2 signalling is clearly oncogenic, it is recognized that context-dependent differences in signalling can lead to either tumour promotion or senescence in response to active FGF signalling [79].

Several therapies targeting the FGF pathway are currently under investigation. FGFR tyrosine kinase inhibitors such as BIBF1120 [116], TK1258 [117], and TSU-68 [118] are in clinical trials. Such inhibitors have the advantage of targeting multiple pro-angiogenic growth factors (such as VEGF, PDGF, and FGF) but lack of specificity increases the potential side effects and limits the ability to deliver drugs at doses required for FGFR inhibition. Specific antibodies against mutant FGFR3 have been shown to be successful in bladder cancer and t(4;14) myeloma [119]. A third approach for targeting is the development of ligand traps. A fusion protein between the extracellular portion of FGFR1-IIIC and the Fc domain of IgG1 targets multiple FGF receptors by preventing ligand binding and has been shown to have anti-proliferative and anti-angiogenic effects [79]. Finally, recombinant FGF7 to stimulate FGFRs are used in treatment of mucositis induced by myelotoxic therapy requiring haematopoietic stem cell support [120].

Transforming growth factor beta

The transforming growth factor beta (TGFβ) pathway plays important roles in many physiological processes such as adhesion, migration, differentiation, apoptosis, and the determination of cell fate [121, 122]. In embryogenesis it plays an important role in germ line specification and patterning. The transforming growth factor family of ligands includes three TGFβ isoforms, four activin β chains, the protein nodal, ten bone morphogenic proteins (BMPs), and 11 growth and differentiation factors (GDFs) [123].

The basic mechanism of ligand-receptor activation includes dimerization of the pre-ligand protein followed by cleavage to generate an active ligand, followed by receptor binding. TGFβ receptors are formed of an extracellular cysteine-rich domain, a transmembrane domain, and a serine-threonine kinase domain that distinguish this family of receptors from other transmembrane receptor tyrosine kinases [124]. TGFβ receptors are classified into two families: type I and type II. Type I family includes activin-like receptors (ALK 1 through 7). Type II includes receptors such as TGFRII, ACTRII, ACTRIIB, BMPRII, and AMHRII. Type II receptors are thought to phosphorylate type I receptors upon ligand activation. Phosphorylated type I receptors consequently recruit and phosphorylate the receptor-regulated TGFβ transducers SMAD proteins 1, 2, 3, 5, and 8 (R-SMADs). These SMADs consequently bind to SMAD4 and are translocated to the nucleus where they regulate transcription through regulating chromatin remodelling and histone modification [124]. In addition to the SMAD-dependent functions of the TGFβ pathway, TGFBRII has been shown to modulate disassembly of tight junctions through PAR6 [125].

Negative regulatory pathways exist to regulate the TGFβ pathway. For example, the inhibitory SMADs (I-SMADs), SMAD6 and SMAD7, are thought to inhibit other SMADs and terminate TGFβ-driven signal transduction [126]. TGFβ and BMP signalling and stimulation of R-SMADs results in the increase of transcription of SMAD6 and SMAD7 which compete with R-SMADs for binding to type I receptors and, therefore, limit signal transduction [127]. In addition, E3 ubiquitin ligases play a central role in regulating TGFβ signalling through the degradation of SMADs. Homologous to the E6-accessory protein C-terminus (HECT) E3 ubiquitin ligases, SMAD ubiquitin regulatory factor 1 (SMURF1) and SMURF2 are examples of key ubiquitin ligases involved in this process [128]. SMAD7 mediates the binding of SMURF1/2 to R-SMADs and their consequent degradation [129, 130]. In contrast, the RING-type E3 ubiquitin ligase Arkadia induces ubiquitination and degradation of SMAD7 and, therefore, augments TGFβ signalling [128]. SMAD6 may specifically compete with SMAD4 for binding to BMPR-activated SMAD1 by forming an inactive SMAD1/SMAD6 complex in the cytoplasm [131]. In addition, cross-talk between the TGFβ and the MAPK pathway (which includes ERK1/2, JNK and p38 pathways) is thought to induce positive and negative regulation of TGFβ signalling [132, 133]. For example, JNK, ERK, and p38 phosphorylate SMAD2/3 independent of TGFβ signalling [134–136]. There is also evidence that SMADs act upstream of MAPKs and mediate their activation. For instance, SMAD signalling plays an important role in promoting the invasive phenotype of human head and neck squamous carcinoma cells by p38-mediated upregulating collagenase expression [137]

The dual role of the TGFβ signalling pathway has recently become clearer [138, 139]. In early tumour formation, TGFβ induces a durable anti-proliferative effect by its cytostatic and apoptotic functions [140]. The cytostatic mechanism is thought to involve the upregulation of p21 and p15 and the consequent inhibition of CDK phosphorylation of retinoblastoma protein, halting the cell cycle [141]. In addition, TGFβ downregulates the transcription of c-Myc in a SMAD3-dependent manner. The apoptotic mechanism of TGFβ has important relationship with some pro-apoptotic target genes, which are controlled by SMAD transcriptional complexes such as the TGFβ-inducible early-response gene (TIEG1), the death-associated protein kinase (DAPK), and the SH2-domain-containing inositol-5-phosphatase (SHIP) [140]. Loss of this tumour suppressive function of TGFβ is thought to be a major step towards cancer progression. However, in established tumours, TGFβ signalling is thought to be overexpressed to create a local immunosuppressive environment that fosters tumour

growth and exacerbates the pro-invasive and metastatic behavior of tumour cells [140]. TGFβ induces the expression of several matrix metalloproteinases (MMPs) that lead to the degradation of the extracellular matrix and facilitate invasion. TGFβ also acts as a potent inducer of angiogenesis through a direct effect on VEGF expression and indirectly through inducing monocytes to release angiogenic cytokines [141]. In vivo models of breast cancer metastasis revealed that TGFβ signalling plays an important role in bone metastasis [142]. In addition, several signalling pathways have been implicated in TGFβ-induced epithelial-mesenchymal transition (EMT), such as SMADs, PI3K/Akt, RHOA, and p38 MAPK [140].

Therapeutic options targeting the TGFβ pathway in tumours have been developed [143, 144]. The most advanced TGFβ signalling antagonists in clinical development are large molecules including monoclonal antibodies and antisense oligonucleotides. For example, DNA oligonucleotides targeting TGFβ2 mRNA has been developed (trabedersen, AP12009, Antisense Pharma) for targeting high-grade gliomas, pancreatic cancer, and malignant melanomas [145]. Similarly, AP11014 is an antisense oligonucleotide against TGFβ1 that has also been developed for targeting non-small-cell lung cancer, colorectal cancer, and prostate cancer [146]. In addition, small-molecular TGFβ type I receptor kinase inhibitors have been the focus of drug discovery efforts, such as the ALK inhibitors SB431542 [147] and SB525334 [148]. Given the dual function of TGFβ signalling and the limitation of these therapeutic molecules, future studies may focus on exploring the potential clinical benefit of large and small molecule combination therapies and on determining the appropriate patient subpopulations for TGFβ therapies [143].

Platelet derived growth factors

Platelet derived growth factors [149, 150] are dimers of disulfide-linked polypeptide chains [151]. They are characterized by growth factor core domains with a conserved set of cysteine residues [152, 153]. The PDGF family consists of PDGFA, PDGFB, PDGFC, and PDGFD. The protein products of the genes form homodimers but PDGF-AB heterodimers have also been described. This family of growth factors is linked structurally and functionally to the VEGF family of proteins. PDGF receptors include PDGFRα and PDGFRβ. The receptors contain five extracellular immunoglobulin loops and a tyrosine kinase intracellular domain. They have structural similarities to FMS, c-Kit, and FLT3 which are the receptors for the CSF1, SCF, and FLT3 ligands, respectively. In vivo evidence confirmed that PDGF-AA and PDGF-CC dimers bind to PDGFRα while PDGF-BB binds to PDGFR-β [152, 154] PDGF expression in cultured cells is induced by several factors including hypoxia, thrombin, cytokines and growth factors including PDGF itself. PDGFA and PDGFC are predominantly expressed in epithelial cells, muscles, and neuronal progenitor cells. PDGFB is expressed in endothelial cells, megakaryocytes, and neurons while PDGFD is expressed in fibroblasts. PDGFR expression is generally low in mesenchymal cells but is increased following inflammation, TGFβ stimulation, estrogen, interleukin 1α, FGF2, and TNFα [151].

Similar to many other receptor tyrosine kinases, ligand binding of PDGF to its receptors induces dimer formation, autophosphorylation of the kinase domain and kinase activation. Phosphorylated sites act as docking sites for downstream signal transduction molecules and activate the RAS/MAPK pathway, the PI3K pathway, and PLC-γ. GRB2 binds via its SH2 domain to phosphorylated PDGFR and via its SH3 domain to SOS1, which in turn activates RAS which signals to the RAF1 and MAPK pathway [155]. PI3K via its SH2 domain of regulatory subunit binds to PDGFR and actives a wide range of cell processes [156]. PLC-γ activation results in mobilization of intracellular calcium ions and the activation of PKC and downstream effects on cell growth and mobility [154]. In addition, PDGFR activation results in activation of the Src family of kinases promoting Myc transcription and mitogenic responses [157] and the FER/FES tyrosine kinases which induce cytoskeletal remodeling and differentiation.

PDGF signalling is controlled by the balance between the stimulatory signals mentioned above and negative feedback loops. SHP2 tyrosine phosphatase binds to PDGFR through the SH2 domain and dephosphorylates the receptor [158]. In addition, RAS-GAP binds to PDGFR-β and inactivates RAS [159]. Ligand-receptor interaction induces endocytotic receptor internalization and lysosomal degradation [160]. In addition, the adapter protein Alix binds to PDGFRB resulting in its increased ubiquitination and degradation via the CBl RING finger E3 ubiquitin ligase [161]. Phosphatase TC-PTP may also act as a negative regulator of PDGFR-β phosphorylation [162].

Many physiological functions have been attributed to the PDGF family. PDGF signalling plays a role in gastrulation and formation of cranial and cardiac neural crest. PDGFA and PDGFR-α null mice have severe impairment of early mesenchymal derivatives. PDGFR-α knockout mice and PDGFA/PDGFC double knockout mice have defective vertebral arch formation. PDGFs also have a conserved morphogenic function in guiding cell migration through the formation of growth factor gradients in the extracellular space. In addition, PDGF plays a key role in the development of several organs and tissue types such as being required for villous morphogenesis in the bowel tract, alveolar septum development, palate formation, glomerular formation in the kidney, hair follicles, and spermatogenesis. PDGFs are also involved in glial cell development and neuroprotection, and in the development of cardiovascular system, axial skeleton, and teeth [152].

PDGF signalling may be involved in modulating tumour behaviour through both autocrine and paracrine routes. Autocrine PDGF signalling has been implicated in glioblastoma, soft tissue sarcomas, and breast cancer, and contributes to proliferation, survival, invasion, and metastasis. A variety of tumours express high levels of PDGFA, PDGFC, and PDFGR-α. Such increased expression may be secondary to stimulation by other growth factors such as TGF-β in the case of some gliomas. Gene amplification has also been described in glioblastoma and esophageal squamous cell carcinoma. In addition to increased expression, activating mutations and chromosomal rearrangements also lead to autocrine PDGF signalling. For example, gastrointestinal stromal tumours that do not possess mutations in KIT frequently possess gain of function mutations in PDGFR-α. Several myeloid disorders and leukaemia have translocations that involve the PDGF receptors such as the ETV6-PDGFRB fusion that result in constitutive activation of the receptor. In addition, dermatofibrosarcoma protuberans (DFSP), a rare mesenchymal neoplasm of the dermis is characterized by a translocation that repositions the collagen type 1α1 promoter adjacent to the PDGF gene resulting in its overexpression and constitutive activation of PDGFR-β. Imatinib, a tyrosine kinase inhibitor that targets several kinases including PDGFR-β elicits up to 50% responses in this tumour [163]. PDGF signalling was

found to be upregulated during TGFβ-induced EMT in breast cancer and promote metastasis in mouse mammary carcinomas. Paracrine PDGF signalling may play a role in malignant transformation by recruiting different types of stromal cells, such as endothelial cells, pericytes, and fibroblasts, to the tumour mass. Through its effect on these non-neoplastic stromal cells, PDGF signalling may directly and indirectly promote tumour growth, blood perfusion, metastatic dissemination, and drug resistance [164]. For example, in mouse fibrosarcoma, paracrine PDGF/PDGFR-β signalling enhances pericyte recruitment to the tumour vasculature, thereby promoting tumour cell growth, survival, and vessel stabilization [165]. PDGFR-β signalling could regulate interstitial fluid pressure (IFP) in normal tissue, and inhibition of PDGFR could reduce tumour IFP and enhance the uptake into tumours [166, 167]. Therefore, the PDGF signalling may be implicated causally in at least three cancer cell traits: self-sufficient growth, angiogenesis and metastasis, as well as in resistance to cytotoxic therapy [152].

Given the important role of PDGF signalling in tumours, several strategies have been tested for targeting this signalling pathway. Strategies include blocking PDGF and inhibiting PDGFR function. Neutralizing antibodies, recombinant dimeric soluble PDGF extracellular domain and nucleic acids (aptamers) have been employed to target PDGF. PDGFR function could be blocked by antibodies, dominant-negative ligands, and kinase inhibitors. Imatinib (ST1571, Gleevec®) is an oral tyrosine kinase inhibitor that inhibits PDGFR-α and PDGFR-β, as well as BCR-ABL fusion protein, c-Kit, and Flt3. Imatininb has been approved by the Food and Drug Administration for the treatment of patients with Philadelphia chromosome positive chronic myelogenous leukaemia and gastrointestinal stromal tumours. Most of the available PDGFR kinase inhibitors available are not completely specific and act on other tyrosine kinase such as c-Kit and Flt3; thus, it is difficult to determine how much of the response to these agents is actually due to the PDGF blockade [168].

Conclusion

While the general mechanisms of activation of growth-factor-dependent signalling are highly similar across multiple pathways, they serve distinct regulatory roles. The selectivity of growth factor function is largely driven by tissue specific expression of regulatory proteins. Deregulation of regulatory elements result in the development of tissue-specific diseases including tumours. The understanding of these pathways is essential for the development of growth factor targeted therapies. The successful development of many such therapies over the past two decades have already contributed to the control of many cancer types. However, major challenges to theses therapies such as tumour heterogeneity, the inevitable development of drug resistance, and the difficulties in achieving therapeutic selectivity are likely to be the focus of future research directions in this field.

Further reading

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CHAPTER 3

Cell signalling pathways

Stefan Knapp

Introduction to cell signalling pathways

Cellular functions are regulated by highly complex signalling networks containing thousands of interconnected nodes that tightly control cellular growth, migration, metabolism, differentiation, and cell death. However, these regulatory networks are far too complex to serve as predictive model systems for our understanding of cell signalling processes, forcing us to adhere to easier directional pathways that describe the main signalling avenues that transmit environmental cues from the plasma membrane to the nucleus. In most cancer types several key regulators in signalling pathways are perturbed, and each of these perturbations provides the cancer cell with a small survival and growth advantage. The advent of large-scale sequencing revealed that there are on average 80 mutations that alter amino acid residues in signalling proteins in a typical cancer biopsy. These mutations are composed of few commonly mutated genes but the majority of mutations occur with low frequency resulting in a complex picture of the cancer genome landscape. Analysis of these mutations by statistical methods predicts that most of the detected mutations have probably little or no functional consequences. However, it has been estimated that nevertheless around 15 mutations contribute either to the initiation, progression, or maintenance of a tumour. In late-stage metastatic cancer, multiple distinct and spatially separated inactivating mutations of tumour-suppressor genes have been identified within a single tumour leading to a considerable degree of intra-tumour heterogeneity, further complicating molecular mechanisms that lead to deregulation of signalling in cancer and consequently the rational design of new therapeutic strategies that target signal transduction pathways.

However, all cancers need to acquire a set of capabilities that are tightly controlled in normal cells. These hallmark capabilities lead to alterations in signalling that sustain growth factor-independent proliferation, evade growth suppression, suppress apoptotic mechanism and detection of cancer cells by the immune system, overcome the limited replication potential of somatic cells, guarantee sufficient nutrition supply by generating new blood vessel formation and by changing the cellular energy supply. These lead finally to the spread of the tumour in the body by inducing cell migration and metastasis. Here I review the principal regulatory mechanisms that control the main signalling pathways, with a particular focus on pathways that have been successfully targeted in cancer therapy.

Receptor tyrosine kinases and growth factor signalling

Tissue homoeostasis is tightly controlled by extracellular signalling molecules such as growth factors that bind to cell surface receptors located in the plasma membrane. Receptors of extracellular growth factors (GFs) are often receptor tyrosine kinases (RTKs) or receptors that tightly associate with RTKs. GF receptors share a number of characteristic regulatory features that allow efficient transmission of extracellular mitotic signals through the plasma membrane and the activation of downstream signalling pathways that transmit signals to the nucleus where they trigger activation of transcriptional programmes. Dysfunction of growth factor signalling is a hallmark of cancer and involves usually GF independent activation of growth-promoting signalling events. Due to the large diversity of GF receptors the description here is limited to three main receptor systems that play a central role in cancer and that are also current targets of drug development efforts.

Insulin and insulin growth factor signalling

The Insulin and insulin-like growth factor 1 (IGF1) signalling pathway has a pivotal role in regulating cellular proliferation and survival. This pathway evolved very early in evolution to regulate growth, body size, and longevity as a response to nutrient supply. The more specific role in regulation of carbohydrate metabolism evolved much later and is a specialized function of insulin and the insulin receptor (IR). IGF1 is mainly expressed in liver where expression of this growth factor is stimulated by growth hormone (GH). The IGF2 isoform is more widely expressed and is not regulated by GH. Free plasma levels of IGF1 and IGF2 are regulated by IGF binding proteins (IGFBPs). It has been estimated that more than 90% of circulating IGF is bound to IGFBPs which inactivate IGFs by competing with receptor binding. However, IGFBs also stabilize IGFs by prolonging their plasma half-life and may have IGF independent growth-inhibitory and pro-apoptotic functions.

The IRs, IGF1, and IGF2 are tetrameric and are composed of so-called half-receptors consisting of an extracellular binding domain (α-chain) and a transmembrane and cytoplasmic RTK (β-chain). The IR is expressed as two splice isoforms. The isoform 'IRB' recognizes exclusively insulin, but the 'IRA' isoform, which is also overexpressed in tumours, recognizes both insulin and IGF2. Two diverse receptors also exist for IGF (IGF1R and IGF2R). IGF2R has no catalytic domain and functions as a sink for free IGF2 and has therefore tumour-suppressor properties. Depending on their relative abundance IGF1R and IR half-receptors may associate into hybrid receptors. The direct downstream targets of IGF1R and IR are the insulin receptor substrates (IRS proteins) that trigger activation of a number of pathways including phosphatidylinositol 3-kinase, AKT, mammalian target of rapamycin (mTOR), and mitogen-activated protein kinases (MAPKs), which will be

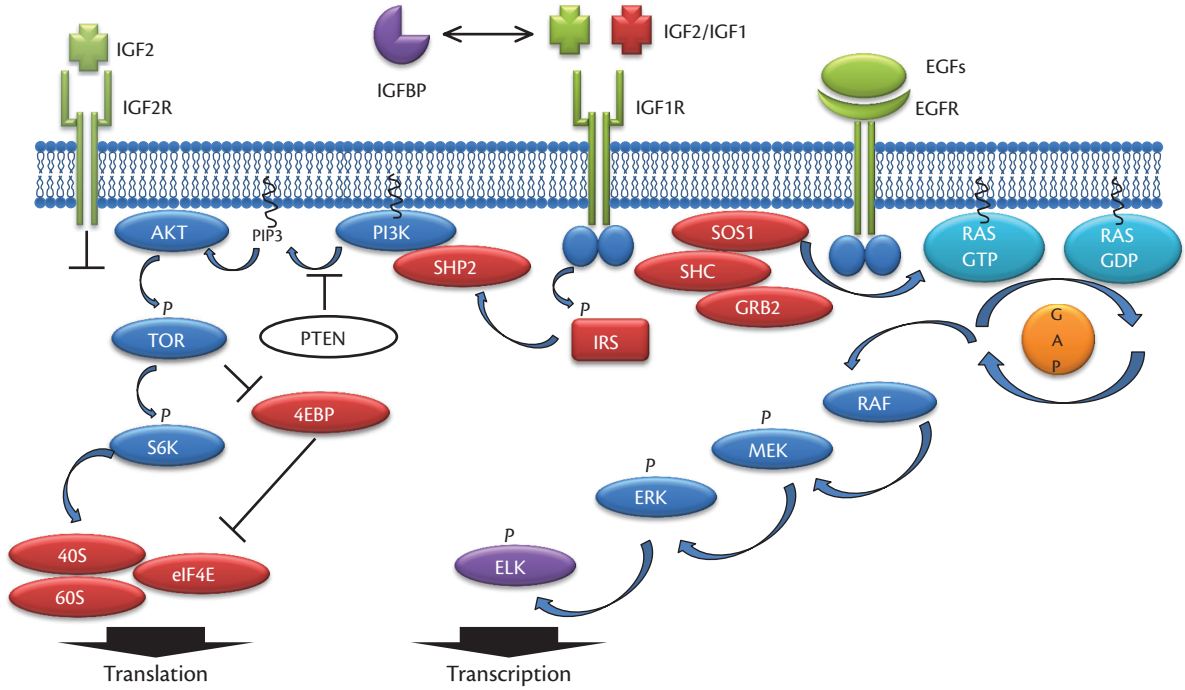

Fig. 3.1 Example of a receptor tyrosine kinase signalling pathway. Kinases are highlighted in blue, receptor tyrosine kinases and their substrates in green, phosphatases in white, GTPases in olive and adaptor and substrate proteins in red.

discussed later in this chapter. A graphical representation of the IGFR signalling pathway is shown in Figure 3.1.

Epidermal growth factor (EGF) signalling

Another group of growth factors comprise epidermal growth factor (EGF)-like proteins and neuregulins which activate members of the EGF receptor (EGFR) family of RTKs and consists of four members (EGFR/ErbB-1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4). These RTKs have been originally named ERB because of their homology to the erythroblastoma viral gene product, *v-erbB*. More than 15 diverse ligands have been identified that contain a conserved EGF domain, creating a highly complex signalling network. However, knockout studies of specific EGFR ligands suggested a significant functional redundancy between EGF growth factors. For instance, knockout mice of EGF and the keratinocyte growth factor amphiregulin showed no significant phenotype. In contrast, deletion of the ErbB1 receptor revealed a non-redundant function of this receptor RTK which has a key role in epithelial cell development in many organs. Depending on the mouse strain used, ErbB1$^{-/-}$ mice die at mid-gestation or shortly after birth.

Similar to IR/IGFR receptors, receptor heterodimers, which may also involve receptors that have either a catalytically inactive kinase domain (HER3) or that lack the capacity binding growth factors (ErbB2), add additional layers of regulation to this complex signalling network. EGF receptors consist of a single polypeptide with an extracellular ligand binding domain as well as a cytoplasmic RTK domain which is activated by ligand induced dimerization. Interestingly, the dimerization of the cytoplasmic kinase domain is asymmetric in such a way that one kinase domain serves as an activator of the second catalytic domain through a docking interaction reminiscent of the activation of cyclin dependent kinases (CDKs) by cyclins. As for other RTKs, kinase activation as well as cross-talk with other receptors and cytoplasmic kinases generates docking sites for adaptor proteins that stimulate signalling. A key adaptor molecule of EGF1R signalling is GRB2 (proteins growth-factor-receptor bound-2) which is responsible for recruitment of RAS and activation of the MAPK pathway. Another direct substrate of EGF1R is STAT5 (signal transducer and activator of transcription-5), which dimerizes upon phosphorylation resulting in nuclear import and increased transcription of a number of growth-promoting target genes. The survival pathway PI3K–AKT is also activated by EGF signalling—not directly but via activation of RAS and signalling through RAS-MAPK and RAS-PI3K pathways.

Inactivation of EGFR signalling occurs primarily through a process called endocytosis which either leads to receptor degradation or to recycling of the receptor to the cell surface. Endosomal trafficking is a key regulatory mechanism controlling receptor turnover. Several internalization mechanisms of membrane receptors have been identified. The best studied one is mediated by clathrin-coated vesicles. Once internalized, the clathrin-coated vesicles containing the receptor fuse with intracellular organelles known as the endosomes. In these early endosomes, which are characterized by low pH and the presence of GTPase proteins, the targeted receptor may be either subjected to a recycling pathway transporting the receptor back to the plasma membrane, or it is ubiquitinylated leading to proteosomal degradation in lysosomes. EGFR degradation is mediated by the ubiquitin ligase Cbl, which is recruited to the receptor by phosphorylation of a single tyrosine residue (Tyr1045). However, it is the stability of the activated ligand–receptor complex in the mildly acidic endosomal environment that determines the level of receptor recycling. For instance, EGFR homodimers are stable and remain bound to Cbl,

resulting in increased receptor degradation, whereas the less stable EGFR–HER2 heterodimers escape lysosomal degradation by dissociating from Cbl, increasing the rate of receptor recycling to the plasma membrane. Interestingly, the oncogenic activity of viral Cbl (v-Cbl) functions by stimulating the receptor recycling pathway.

A number of oncogenic viruses harness EGFR signalling using a variety of different mechanisms that all lead to increased EGF signalling. For example, the hepatitis B virus and Epstein–Barr virus activate EGFR by increasing its expression, whereas the avian erythoblastosis virus expresses a truncated constitutively active viral form of EGFR. The human papilloma virus protein E5 blocks the degradation of EGFR by inhibiting an endosomal ATPase resulting in increased receptor recycling to the plasma membrane. The direct links of EGF pathway dysfunction to cancer development highlight the key role of the EGF pathway in maintaining tissue homoeostasis and offer therapeutic opportunities that have already been successfully explored by the development of HER2/ErbB2 inhibitors and therapeutic antibodies.

Janus Kinases (JAK) and STAT signalling

Janus Kinases (JAK1–3 and TYK2) play an essential role regulating haematopoiesis and proliferation of blood cells. A key discovery in this signalling field was the identification of the point mutation $JAK2^{V617F}$ that leads to activation of the JAK/STAT signalling pathways and development of myeloproliferative diseases (MPD) such as polycythaemia vera (PV), essential thombocythaemia (ET), and primary myelofibrosis (PMF). $JAK2^{V617F}$ is a somatic mutation, which means that it is present only in the haematopoietic cell compartment but not in germline DNA. This mutation has been identified in most MPD patients defining a common genetic mechanism for this disease.

JAKs contain no transmembrane domain and are therefore not receptor tyrosine kinases. They interact with specific cytokine receptors which lacks intrinsic kinase activity. However, much as in RTKs, ligand binding to the cytokine receptor results in JAK activation by autophosphorylation and phosphorylation of the cytokine receptor itself and the recruitment of members of the signal transducer and activator of the transcription (STAT) family. Cytokine receptors have different specificity for one of the JAK kinases, resulting in different signalling outcomes. For instance, genetic ablation of JAK2 blocks erythropoiesis, a result of deficient signalling through the erythropoietin (EPO) receptor that specifically binds JAK2. JAK family members contain seven homology domains (JH1-7) which include the tyrosine kinase domain (JH1), an inactive (pseudo)kinase domain (JH2), and several docking and protein interaction modules (JH3-7). Interestingly, the $JAK2^{V617F}$ point mutation is located in the pseudokinase domain which has an autoinhibitory function. It has been speculated that V617F releases this autoinhibitory block resulting in a constitutively active JAK2 kinase. Indeed, expression of $JAK2^{V617F}$ leads to cytokine hypersensitivity and cytokine-independent growth, a typical feature of haematopoietic colonies grown from PV patients. JAK activity is negatively regulated by binding of SOCS (suppressor of cytokine signalling) ubiquitine ligases which interact with phosphorylations sites on JAK, leading to degradation. JAK also activates the MAPK and PI3K signalling pathway, resulting in increased proliferation and survival of cells harbouring the $JAK2^{V617F}$ mutation.

Signalling downstream of GFRs

A number of protein interaction modules contributed critically to our understanding of the complex molecular events that mediate signalling downstream GFRs. Phosphorylation sites created by activated RTK activity lead to the recruitment of SH2 (Src homology 2) domain containing adapter proteins. The SH2 domain, first identified in the cytoplasmic tyrosine kinase Src, is a small phosphotyrosine specific binding. A second Src homology domain (SH3) is crucial for recruiting further binding partners by interacting with proline rich sequences in target molecules. One of these adaptor molecules is GRB2, which contains one SH2 and two SH3 domains. GRB2 links the activated phosphorylated GFR with the guanine nucleotide exchange factor SOS (Son of Sevenless), named after the Drosophila gene whose inactivation leads to lack of expression of the seventh, central photoreceptor (R7). Interaction with GRB2 stimulates SOS leading to the GDP/GTP exchange and activation of the RAS family of small GTPases. Active GTP-bound RAS activates members of the serine/threonine kinase RAF and consequently the MAPK pathway. Finally the discovery of phospholipid binding pleckstrin homology (PH) domains explained how phospholipid effector molecules can specifically activate protein kinases such as the Ser/Thr kinase AKT also known as protein kinase B (PKB), PKD1 (Protein kinase D1), as well as lipid kinases (PI(3)Ks).

The RAS/RAF/MAPK pathway

The name RAS refers to the discovery of the viral oncogene v-RAS (Rat Sarcoma). Mutations in members of the RAS family of small GTPase (H-Ras, N-Ras, and K-Ras) have been detected in 20–30% of all human tumours, highlighting the central role of these proteins in the regulation of cellular proliferation. Indeed, expression of oncogenic H-RAS is sufficient for driving G0 arrested cells into the cell cycle in the absence of mitotic signals. RAS family members share homology with the G_α subunit of heterotrimeric G proteins (large GTPases). GTPases cycle between a GDP bound-off state and a GTP bound-on state. The exchange of the nucleotide is catalysed by guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs). RAS by itself has GTPase activity. However, hydrolysis of GTP is very slow in the absence of a GAP, which contributes additional catalytic residues leading ultimately to the inactive GDP-bound state. Inactivation of RAS activity by GAPs is a frequent target of somatic mutations found in oncogenic RAS variants. RAS is reactivated by GEFs such as SOS that facilitate reloading of GTP by a nucleotide exchange mechanism. GTP-bound RAS has high binding affinity for a number of effector molecules including the lipid kinase PI3K. RAS is recruited to the plasma membrane by covalent linkage to lipids (prenylation or palmitoylation). This multistep process involves several enzymes. The C-terminal peptide motif "CaaX box" is first farnesylated at the CaaX cysteine residue, loosely inserting RAS into the membrane of the endoplasmatic reticulum (ER) and other cellular membranes. The C-terminal tripeptide "aaX" is subsequently cleaved by a prenyl-protein specific endoprotease and the new C-terminus is methylated by a methyltransferase completing the insertion cycle.

The GTP-bound form of RAS has high affinity for the serine/threonine kinase c-RAF (RAF1), the proto-oncogene homologue to the viral v-RAF oncogene. There are two additional RAF kinases (A-RAF and B-RAF) encoded in humans and mutations in B-RAF

have been found in several tumours. RAFs are MAP kinase kinase kinases (MAP3Ks) that function as the entry point for the MAPK pathway, a major signalling path that transmits membrane receptor signals to nuclear transcription factors.

RAF kinases harbour an N-terminal regulatory RAS binding domain and a C-terminal kinase domain. Oncogenic v-RAF lacks the regulatory domain and is constitutively active. However, activation of c-RAF is a multistep process. RAS binding exposes an inhibitory phosphorylation site (S259) that locks c-RAF in an inactive state to phosphatases such as PP2A, resulting in pS259 dephosphorylation. Several other kinases target c-RAF, introducing phosphorylation at several sites that modulate c-RAF activity but that are on their own insufficient for activation. Activated c-RAF phosphorylates the dual specificity kinase MEK which in turn phosphorylates and activates ERK. Several regulatory and scaffolding proteins guarantee tight control of this signalling pathway. For instance, the pseudokinase KSR (kinase suppressor of Ras) binds to MEK in quiescent cells but interacts with c-RAF and ERK in stimulated cells, whereas RKIP (RAF kinase inhibitor protein) disrupts the interaction between RAF and MEK. ERK has a large number of substrates, including transcription factors such as ELK1 necessary for activation of the proto-oncogene c-fos and Myc. Transcription factors regulated by MAPKs are of particular importance for the expression of proteins that regulate the cell cycle.

The PI(3)K/AKT pathway

Phosphatidylinositol (PtdIns) is a phospholipid located in membranes that can be phosphorylated at the 3, 4, and 5 positions of the inositol ring to generate seven diverse combinations of phosphoinositides. Phosphorylation of these messenger molecules is regulated by PI3K family members and the antagonizing activity of lipid phosphatases such as PTEN. The lipid kinase PI(3)K is recruited to receptor or IRS phosphotyrosine sites by means of SH2 domains located in its non-catalytic alpha subunit. PI(3)K can also be recruited to the cell membrane by means of Ras. Phospholipase C (PLC) hydrolyses PtdIns to generate two so-called second messengers: diacylglycerol (DAG) and inositol-1,4,5- trisphosphate (Ins(1,4,5)P3). Phosphoinositides stimulate phosphorylation dependent signalling by interaction with PH domains. In the protein kinase AKT (PKB), PtdIns(3,4)P2 binds to the PH domain of AKT, thereby releasing an autoinhibitory conformation resulting in partial kinase activation by the kinase PDK1 (phosphoinositide-dependent kinase 1). Full activation of AKT is accomplished by a second phosphorylation event carried out by mTORC2, the mammalian target of rapamycin complex 2, but other kinases have also been identified as secondary activators of AKT.

AKT was originally identified as an oncogene (v-AKT) of the transforming retrovirus AKT8. Three isoforms (AKT1–3) are expressed in mammals. Knockout of AKT1 in mice results in growth deficiency of the animals but normal glucose homoeostasis. AKT2-deficient mice have only mild growth defects but are diabetic, pointing to a pivotal role of this isozyme in signalling downstream of the insulin receptor. One of the main regulators of AKT is the tumour suppressor PTEN, a phosphatase that dephosphorylates PtdIns(3,4,5)P3 to PtdIns(4,5)P2, which removes AKT from the plasma membrane and significantly decreases the rate of AKT activation, leading to insensitivity to insulin and IGF1 growth signals.

AKT is a key regulator for a number of diverse cellular functions including inhibition of apoptotic pathways, regulation of protein synthesis and glucose metabolism as well as regulation of gene transcription and cell migration. In accordance with these diverse functions more than a hundred AKT substrates have been identified comprising, for instance, forkhead box O (FOXO) transcription factors, glycogen synthase kinase 3 (GSK3) in the insulin signalling pathway as well as the RAB GAP that regulates insulin-stimulated exocytosis of glucose transporter type 4 (GLUT4), the tuberous sclerosis 2 (TSC2) tumour suppressor, the pro-apoptotic protein BCL-2 antagonist of cell death (BAD), and the cell cycle regulators p21 and p27. A graphical representation of AKT activation and some downstream signalling partners is shown in Figure 3.2.

The mTOR pathway controls cellular growth and energy metabolism

Cellular systems have developed complex regulatory networks that allow them to transition between anabolic and catabolic states and which also determine if cells will survive, grow, or break down cellular organelles for the recycling of nutrients as a response to nutrient availability. The serine/threonine PI3K-related protein kinase (PIKK) mTOR (the mammalian target of rapamycin) plays a central role in the regulation of these processes. Dysfunction of mTOR has been linked to many diverse diseases and has stimulated a large number of drug development efforts on this signalling pathway. mTOR signalling is mediated by the two large protein complexes mTORC1 and mTORC2 which share the central mTOR kinase subunit. mTORC1 consists of mTOR, the activating subunits Raptor and mLST8, as well as two negative regulators, PRAS40 and DEPTOR. The scaffolding protein Raptor is regulated by phosphorylation and it facilitates substrate recruitment. The mTORC2 complex is not sensitive to rapamycin and, due to the lack of specific inhibitors, this complex is much less studied. Apart from the mTORC1 components mTOR, DEPTOR, and mLST8, mTORC2 also contains the subunits Rictor, mSIN1, Protor (protein observed with rictor-1), and Hsp70. The mSIN1 subunit is important for recruitment and activation of AKT. mTORC2 is activated by growth factors, stimulates AKT signaling, and regulates GTPases of the Rac and Rho family stimulating cell motility and survival.

mTORC1 is regulated by a large diversity of signalling pathways, as for instance insulin and IGF1, which stimulate the PI3K and Ras pathways. A common feature of effector kinases of these pathways (protein kinase B (AKT/PKB), extracellular-signal-regulated kinase 1/2 (ERK1/2), and ribosomal S6 kinase (RSK1)) is that they all phosphorylate and inactivate the tuberous sclerosis TSC1/TSC2 complex, an inhibitor of mTORC1. TSC1/TSC2 functions as a GAP RHEB (RAS homologue enriched in brain), converting it to its inactive GDP-bound form. Since GTP-bound RHEB strongly stimulates mTORC1 activity by binding to the complex, the GAP activity of TSC1/TSC2 leads to mTORC1 inactivation. To date no GEF for RHEB has been identified that would lead to mTORC1 reactivation. AKT additionally activates mTORC1 by phosphorylation of the mTORC1 inhibitor PRAS40, resulting in its dissociation from the mTORC1 complex.

Similarly, mTORC1 can be activated by TSC1/TSC2 phosphorylation by IkB kinase b (IKKb) as a response to inflammatory stimuli such as TNFα or through the Wnt pathway effector glycogen