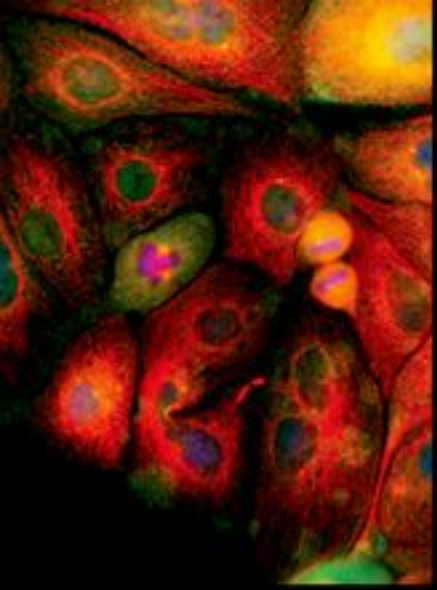

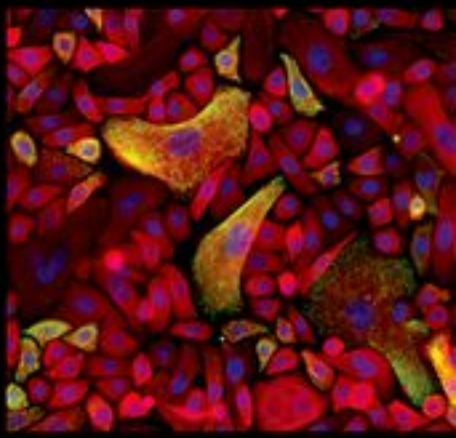

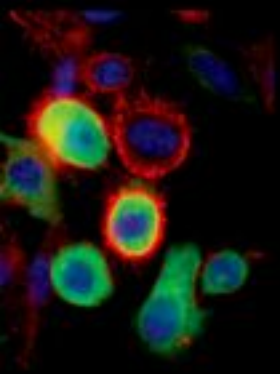

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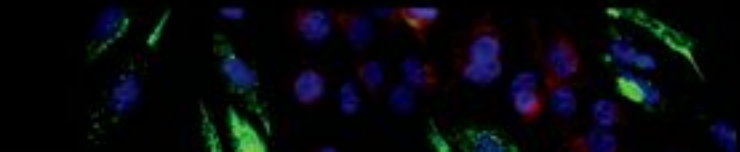
TUMOR IMMUNOLOGY AND IMMUNOTHERAPY

Edited by
ROBERT C. REES



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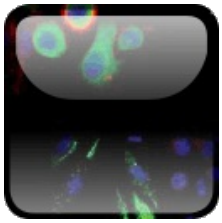

Tumor Immunology and Immunotherapy

Edited by Robert C. Rees

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DOI: 10.1093/med/9780199676866.001.0001

Print Publication Date: May 2014
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Dedication

This publication is dedicated to the work of one of the pioneers in the field of cancer immunology, Robert Baldwin. Bob's publications in the 1950s were amongst the first to provide evidence for the existence of immunity to cancer. These seminal papers set the scene for a lifelong quest to introduce immunotherapy into clinical practice, which others seek to emulate today. Bob inspired many young scientists working in the field of cancer research and he will be remembered as an innovator and founding father of the subject.

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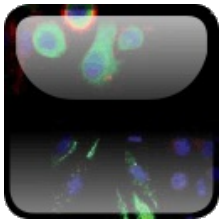

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Foreword

It is by now well established that immune responses to malignant tumors do occur and act as an immune surveillance system throughout life, although they are generally somewhat inefficient in eradicating established tumors. In fact, many types of tumors develop ways to escape from the effects of immune responses by suppressing them. In addition, certain tumors may decrease or impair their antigenic properties thus reducing their capacity to elicit untoward immune functions.

As thoroughly discussed in this volume, efforts are continuously being made to clarify the mechanisms involved in the immunological responses to tumors and to exploit the knowledge so acquired towards the development of more effective immunotherapies.

The pathways critical to antigen recognition, the process of immunoediting, tumor plasticity also as related to the function of stem cells and the capacity of certain tumors to undergo epithelial–mesenchymal transition are all illustrated in detail and are analysed for their capacity to affect negatively the development of effective immunotherapy.

The modulation of adaptive immunity by regulatory T cells or by myeloid-derived suppressor cells, the impairing functions of the microenvironment on immune responses, and the capacity of certain tumors to become ‘invisible’ to immunity by decreasing or eliminating their antigenic expression are each discussed as contributing to tumor escape from the immunotherapy attack.

Therapies with monoclonal antibodies are currently the most successful types of immunotherapy. It is indeed appropriate to note that the late Dr Robert Baldwin, Professor Emeritus of the University of Nottingham and a co-founder of the Journal Cancer Immunology and Immunotherapy, was a major leader in tumor immunology and a pioneer in anticipating with his work the value of antibody-based immunotherapy. In fact it is fair to say that he established an important background for today's advances in this type of immunotherapy. Antibody-based therapies are well illustrated in this volume with emphasis on both their successes and the remaining difficulties to be overcome.

The identification of tumor antigens is essential for the development of immunotherapy. In some cases tumors exhibit viral antigens that are useful handles for the stimulation of antibodies as well as the construction of vaccines. Treatments with vaccines are extensively discussed herein. Novel approaches are indicated such as the development of vaccines using tumor DNA or utilizing newly identified antigens, for instance in leukaemia. The usefulness of mucin present on tumor cells as a therapeutic target is also illustrated and represents an antigen to which many of us have preexisting immune responses. The development of vaccines based on multiple antigenic determinants is indicated as a means to improve the effectiveness of this type of treatment.

The role of natural killer cells in providing mechanisms of defence against tumors is discussed with attention to the functional interactions of these cells with the responses of adaptive immunity. Therapeutic approaches with dendritic cells are considered with a view to utilizing their antigen presentation mechanisms for therapeutic intervention in a way that might minimize the onset of some of the tumor escape mechanisms. In this volume the complex mechanisms conditioning tumor escape from immune responses are given appropriate attention.

Adoptive transfer of T cells is now recognized as a potent type of immunotherapy and the use of TCR transgenic T cells can improve their therapeutic effectiveness. These approaches are considered in this volume within the frame of reference to other cell based treatments.

In addition, gene therapies based on the expression of chimeric antigens is considered among the therapeutic avenues to be further explored. The FDA approval of Ipilimumab as a "new generation" of checkpoint blockade therapy represents an important milestone in the development of treatments designed to mobilize the immune system against cancer.

As is indicated above, in this volume key aspects of tumor immunity and immunotherapy are critically discussed. Each chapter puts emphasis on the difficulties involved in the application of each modality of treatment as well as on the promises realistically offered in each case, and thus becomes an important reference for the topic considered. Indeed as a whole this volume should provide for a significant stimulation of new ideas which would be pivotal for the development of fruitful further investigations. There is little doubt that increasing further our knowledge of the mechanisms involved in tumor immunity and our understanding of the phenomena conditioning tumor escape are essential in order to improve the effectiveness of immunotherapy and thus to fulfil the promises offered in this important area of cancer therapeutics.

Enrico Mihich

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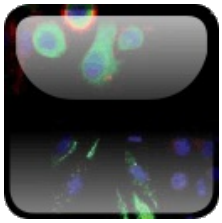

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Preface

Within the past two decades, the field of cancer immunotherapy has grown, not only as an academic discipline, but also as a viable treatment option for many cancer sufferers. Pharmaceutical companies are developing cancer therapeutics that are based on vaccines which induce protective adaptive anti-tumor immunity, or antibodies which directly interact with cell surface antigens such as HER2/neu, or act to blockade molecules that have a role in inhibiting immune function. The latter approach is exemplified by current trials that are assessing the efficacy of anti-PD-1 antibody therapy. It is also recognized that antibody therapy can enhance adaptive T cell immunity to further promote tumor rejection.

This publication includes contributions from experts internationally recognized for their outstanding research in their fields and provides an up-to-date and comprehensive treatise of tumor immunity and immunotherapy. The importance of the innate (natural killer cells, macrophages) and adaptive (T cells, antibodies) immune systems for inducing robust anti-tumor activity and tumor rejection is considered in detail by several leading authorities. Several reviews also provide insight into how tumors escape host immune recognition either by downregulating major histocompatibiliy complex antigen expression and/or fostering an immunosuppressive tumor microenvironment that induces immune tolerance or anergy. Immunosuppressive mechanisms, involving regulatory T cells, myeloid suppressor cells, suppressive cytokines, or cell surface receptor–ligand interactions are discussed in depth.

Emphasis on the essential requirements for success in the clinic has been channelled through

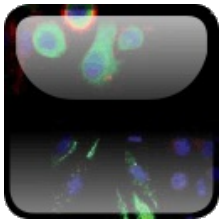
pre-clinical investigations and translated into patient care. The promotion of CD8 and CD4 T-cell immunity by vaccine-driven delivery of appropriate tumor antigens, activation of innate responses using Toll-like receptor agonists and treatments that are designed to limit pathways of immune suppression are now ‘centre stage’, driving advances in the clinical application of immunotherapy as a fourth treatment modality for cancer. In many instances, combining immunotherapy with conventional therapy clearly provides distinct advantages over single agents. In summary, the reviews in this publication provide scientists and clinicians with a comprehensive and in depth critique of the major areas of cancer immunology and insight into future trends in cancer immunotherapy.

Robert C. Rees PhD

Professor of Tumor Biology

Director of The John van Geest Cancer Research Centre, Nottingham

Oxford Medicine



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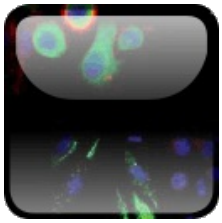

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Abbreviations

5-FU
5-Fluorouracil
ACT
Adoptive T-cell therapy
ADC
Antibody-dependent cytotoxicity
ADC
Antibody–drug conjugate
ADCC
Antibody-dependent cellular cytotoxicity
AE
Adverse events
Ag
Antigen
AICD
Activation induced cell death
AIDS
Acquired immunodeficiency syndrome
AIF
Allograft inflammatory factor

AL
Ad libitum
ALL
Acute lymphoid/lymphoblastic leukaemia
AML
Acute myeloid leukaemia
ANGPT2
Angiopoietin 2
APC
Antigen-presenting cells
APM
Antigen-processing machinery
AR
Androgen receptor
ASCI
Antigen-specific cancer immunotherapeutic
ATC
Activated patient T cells
ATM
Adipose tissue macrophages
ATRA
All-trans retinoic acid
BCG
Bacillus Calmette-Guerin
BCR
B-cell receptor
BCSC
Breast cancer stem cells
bFGF
Basic fibroblastic growth factor
ß2m
ß2-Microglobulin
BiTE
Bi-specific T-cell engager
BM
Bone marrow
BMP
Bone morphogenic protein
BMT
Bone marrow transplantation
BsAb
Bi-specific antibodies
BSCS
Breast cancer stem cells
CAR
Chimeric antigen receptor
CB

Cord blood
CBT
Cord blood transplantation
CCyR
Complete cytogenetic response
CDC
Complement-dependent cytotoxicity
CDR
Complementarity determining regions
CEA
Carcinoembryonic antigen
c-FLIP
FLICE inhibitory protein
CGAP
Cancer genome anatomy project
CIBMTR
Center for International Blood and Marrow Transplant Research
CID
Cancer Immunome Database
CIN
Cervical intraepithelial neoplasia
CIP
CIMT Immunoguiding Program
CK
Cytokeratin
CLL
Chronic lymphocytic leukaemia
CLP
Common lymphoid progenitors
CML
Chronic myeloid leukaemia
CMP
Common myeloid progenitors
CMV
Cytomegalovirus
CNS
Central nervous system
COG
Cost of goods
COX2
Cyclooxygenase 2
CR
Caloric restricted
CR
Complete response
CRC
Colorectal cancer

CRP
C-reactive protein
CRPC
Castrate-resistant prostate cancer
CRS
Cytokine release syndrome
CSC
Cancer stem cell
CSF
Colony stimulating factor
CT
Cancer/testis
CTA
Cancer testis antigen
CTC
Common toxicity criteria
CTL
Cytotoxic T cell/lymphocytes
CTL
Cytotoxic T-cell lines
CTLA
Cytotoxic T lymphocyte antigen
Cy
cyclophosphamide
DAA
Disease-associated antigen
DAMP
Damage-associated molecular pattern
DART
Dual-affinity re-targeting
DASL
DNA-mediated annealing, selection, and ligation
DC
Dendritic cell
DCT
Dopachrome tautomerase
DD
Differential display
DFI
Disease-free interval
DFS
Disease-free survival
DISC
Death-inducing signalling complex
DLI
Donor lymphocyte infusion
DNMTi

DNA methyltransferase inhibitors
DOX
doxorubicin
DR
Death receptors
DTH
Delayed-type hypersensitivity
EBV
Epstein-Barr virus
ECD
Extracellular domain
ECM
Extra cellular matrix
EGF
Epidermal growth factor
EGFR
Epidermal growth factor receptor
ELISA
Enzyme-linked immunosorbent assay
ELISpots
Enzyme-linked immunosorbent spots
ELN
European LeukemiaNet
EM
Effector memory
EMAPII
Endothelial monocyte-activating polypeptide-II
EMT
Epithelial–mesenchymal transition
EP
Electroporation
ER
Endoplasmic reticulum
EROTC
European Organization for Research and Treatment of Cancer
ES
Embryonic stem
EST
Expressed sequence tags
FADD
Fas-associated death domain
FDA
Food and Drug Administration
FFA
Free fatty acid
FL
Follicular lymphoma

FR4
Folate receptor 4
GAVI
Global Alliance for Vaccines and Immunisation
GBM
Glioblastoma multiform
GM-CSF
Granulocyte-macrophage colony-stimulating factor
GMP
Good manufacturing practice
GPA
Granulomatosis with polyangiitis
GS
Gene signature
GvHD
Graft-versus-host disease
GvL
Graft-versus-leukaemia
GvL
Graft-versus-leukaemia
GvT
Graft-versus-tumor
HBC
Hepatitis C virus
HBV
Hepatitis B virus
HCC
Hepatocellular carcinoma
HCGP
Human cancer genome project
HCV
Hepatitis C virus
HDACi
Histone deacetylase inhibitors
HGF
hepatocyte growth factor
HHV-8
Human herpesvirus type 8
HIF
Hypoxia-inducible factor
HIV
Human immunodeficiency virus
HLA
Human leukocyte antigen
HMGB1
High-mobility group box 1
HNV

Hematopoietic necrosis virus
HPV
Human papillomavirus
HRE
Hypoxia responsive elements
HSC
Haematopoietic stem cells
HSCT
Haematopoietic stem cell transplantation
HSP
Heat shock protein
HSV
Herpes simplex virus
HTLV
Human T-lymphotropic virus
IAP
Inhibitors of apoptosis proteins
IC
Immune complexes
ICD
Immunogenic cell death
ICS
Intracellular cytokine staining
IDO
Indoleamine 2,3 dioxygenase
IFN
Interferon
IL
Interleukin
iNKT
Invariant natural killer T cell
iNOS
Inducible nitric oxide synthase
IPF
Idiopathic pulmonary fibrosis
IRF-I
Interferon regulatory factor 1
IRP
Immune risk profile
irRC
Immune-related response criteria
ITAM
Immunoreceptor tyrosine-based activation motif
KIR
Killer-cell immunoglobulin-like receptors
KS
Kaposi’s sarcoma

KSHV
Kaposi's sarcoma-associated herpes virus
LAA
Leukaemia-associated antigen
LAK
Lymphokine-activated killer
LAT
Linker for activation of T cells
LCSC
Leukaemia cancer stem cells
LDH
Lactate dehydrogenase
LEF
Lymphoid enhancer binding factor
LOH
Loss of heterozygosity
LSC
Leukaemic stem cells
MA
Malignant ascites
MAb
Monoclonal antibody
MAGE
Melanoma associated antigen
MAMP
Microbe-associated molecular patterns
MBC
Metastatic breast cancer
MCA
methylcholanthrene
MCRPca
Metastatic castrate resistant prostate cancer
MDS
Myelodysplastic syndrome
MDSC
Myeloid-derived suppressor cells
MET
Mesenchymal-epithelial transition
MGUS
Monoclonal gammopathy of unknown significance
mHag
Minor histocompatibility antigens
MHC
Major histocompatibility complex
MM
Metastatic melanoma
MM

Multiple myeloma
MNP
Magnetic particles
MO-MDSC
Monocytic MDSC
MOMP
Mitochondrial outer membrane permeabilization
mOS
median overall survival
MPA
Microscopic polyangiitis
mPIN
Mouse prostate intraepithelial neoplasia
MRD
Minimal residual disease
MRI
Magnetic resonance imaging
MSC
Mesenchymal stem cells
mTTF
Median time to treatment failure
MUC-1
Mucin-1
MVA
Modified vaccinia Ankara
NCCLS
Northern California Childhood Leukemia Study
NCI
National Cancer Institute
NCR
Natural cytotoxicity receptors
NGS
Next-generation sequencing
NHL
Non-Hodgkin’s lymphoma
NK
Natural killer
NLR
Neutrophil/lymphocyte ratio
NMA
Non-myeloablative
NMDP
National Marrow Donor Program®
NO
Nitric oxide
NOS2
Pitric oxide synthase 2

NPM1
Nucleophosmin-1
NSCLC
Non-small-cell lung cancer
NSIT
Non-specific immunotherapy
ODN
Oligodeoxynucleotides
OPSCC
Oropharyngeal squamous cell cancers
OR
Objective responses
ORR
Objective response rates
OS
Overall survival
OV
Oncolytic viruses
PAF
Population attributable fraction
PAMP
Pathogen-associated molecular pattern
PAP
Prostatic acid phosphatase
PBMC
Peripheral blood mononuclear cells
PBSC
Peripheral blood stem cells
PbV
Polyepitope-based vaccines
PCR
Polymerase chain reaction
PD-1
programmed death-1
PDGF
Platelet-derived growth factor
PGE2
Prostaglandin E2
PIN
Prostate intraepithelial neoplasia
PMED
Particle-mediated epidermal delivery
p-MHC
MHC-bearing target peptides
PMN-MDSC
Polymorphonuclear MDSC
PR

Partial response
PRAME
Preferentially expressed antigen of melanoma
PRC
People’s Republic of China
PRR
Pathogen recognition receptors
PSA
Prostate-specific antigen
PSCA
Prostate stem cell antigen
PSK
Polysaccharide krestin
PSMA
Prostate-specific membrane antigen
PTEN
Phosphatase and tensin homologue
PTX
paclitaxel
PVS
Perivascular space
RA
Rheumatoid arthritis
RAGE
Receptor for advanced glycation endproducts
RCC
Renal cell carcinoma/cancer
RDA
Representational difference analysis
RECIST
Response Evaluation Criteria In Solid Tumors
REP
Rapid expansion protocol
RHAMM
Receptor for hyaluronic-acid mediated motility
RNA-seq
RNA sequencing
ROS
Reactive oxygen species
RP
Recombinant proteins
RR
Response rate
RT
Radiation therapy
SAA
Serum amyloid A

SAGE
Serial analysis of gene expression
SASP
Senescence-associated secretory phenotype
scFV
Single chain antibody fragment
SCID
Severe combined immunodeficiency
SCLC
Small cell lung cancer
SCT
Stem cell transfer/transplantation
sctb
Triple bodies
SD
Stable disease
SEREX
Serological identification of antigens by recombinant expression cloning
SHIP1
SH2-containing inositol-5´-phosphatase 1
siRNA
Small interfering RNA
SIT
Specific immunotherapy
SITC
Society for Immunotherapy of Cancer
SLIP
Short-living proteins
SLP
Synthetic long peptides
SMAC
Second mitochondria-derived activator of caspases
SNP
Single-nucleotide polymorphism
SOP
Standard operating protocols
SPF
Specific pathogen free
SSH
Suppressive subtractive hybridization
SSX2IP
Synovial sarcoma X breakpoint 2 interacting protein
STAT3
signal transducer activator of transcription 3
STEAP
Six-transmembrane epithelial antigen of the prostate
STR

Short tandem repeat
TA
Tumor antigen
TAA
Tumor-associated antigens
TAG
T antigens (small and large)
TAM
Tumor-associated macrophage
TAP
Transporter associated with antigen processing
TB
Tuberculosis
TBI
Total body irradiation
T_{conv}
Conventional T cell
TCR
T-cell receptor
TEM
Tie2-expressing monocytes
TERT
Telomerase reverse transcriptase
TES
Thymic epithelial spaces
TGF
Transforming growth factor-β
Th
T-helper cell
TIL
Tumor-infiltrating lymphocytes
Tim-3
T cell immunoglobulin 3
TKI
Tyrosine kinase inhibitor
TLR
Toll-like receptor
TNF
Tumor necrosis factor
TP
Thymidine phosphorylase
TRAIL
TNF-related apoptosis-inducing ligand
TRAMP
Transgenic adenocarcinoma of the mouse prostate
T_{reg}
Regulatory T cell

TSA
Tumor-specific antigen
TSDA
Tissue-specific differentiation antigens
TUMAP
Tumor-associated peptide
VACV
Vaccinia virus
VEGF
Vascular endothelial growth factor
VLP
Virus-like particles
VNTR
Variable number of tandem repeats
VSV
Vesicular stomatitis virus
VZV
Varicella-zoster virus
WHO
World Health Organization
WNV
West Nile virus
WT
Wild-type
WT1
Wilms' tumor antigen 1

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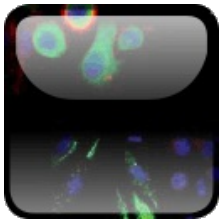

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