The PANCREAS

AN INTEGRATED TEXTBOOK OF BASIC SCIENCE, MEDICINE, AND SURGERY

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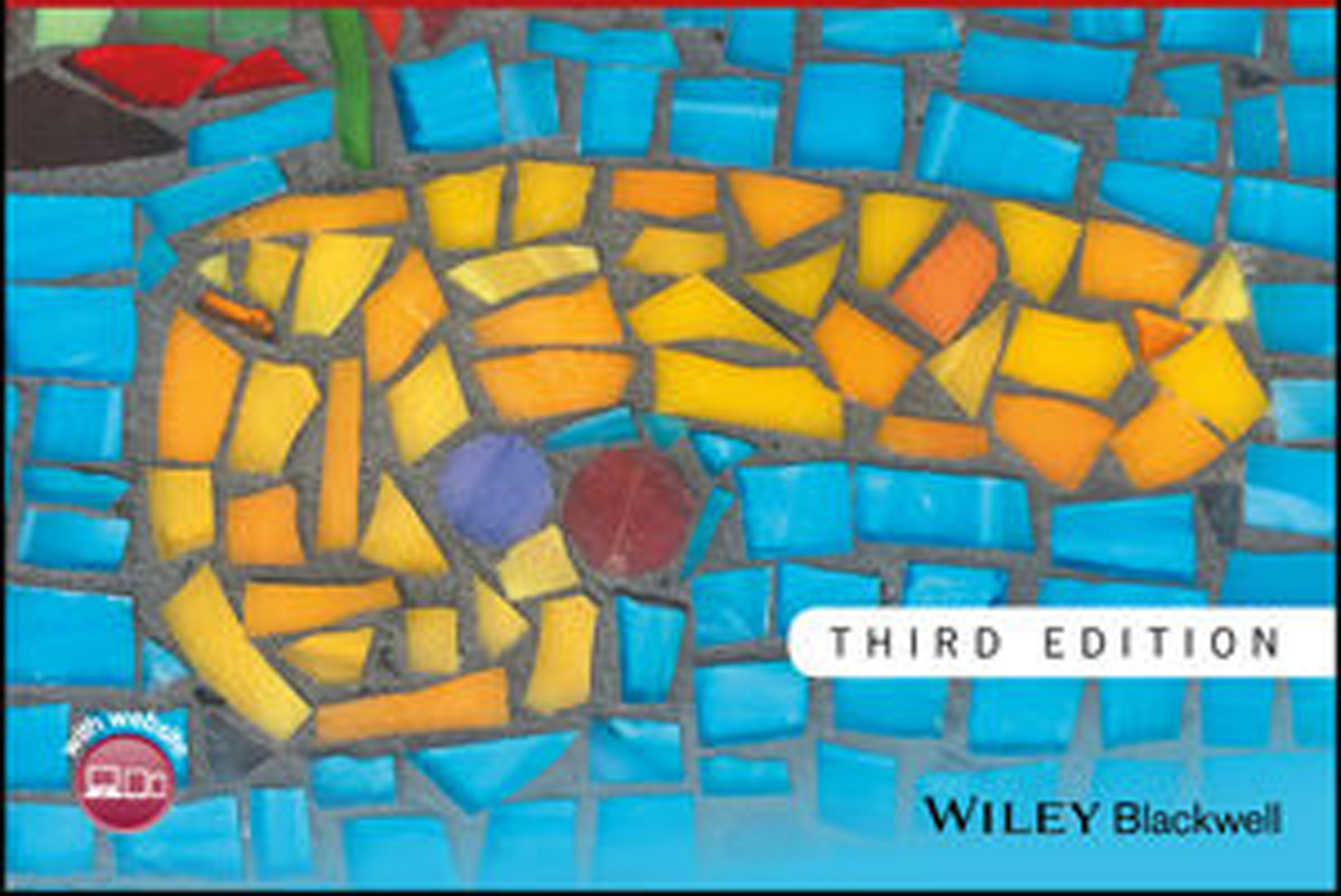

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The Pancreas

An Integrated Textbook of Basic Science, Medicine, and Surgery

Third Edition

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Preface

The pancreas has long been an underappreciated organ. Although Aristotle first acknowledged the pancreas in *Historia animalium*, written between 347 and 335 BCE, Galen insisted that the only function of the pancreas was to pad the abdominal vessels, and so the organ was ignored. It took more than a thousand years for Wirsung to describe, in 1642, the ductal morphology of the gland, as well as the communications of the pancreatic duct with the lumen of the small intestine. Today, we recognize the critical importance of the gland, and understanding the pancreas, its normal and abnormal functions and its morphological pathology has become an international focus of established scientists. The understanding of functions and dysfunctions of the exocrine and endocrine pancreas is derived from molecular biological data on the actions of compounds in subcellular compartments and intracellular transcription pathways. In clinical medicine, new and improved technical devices enable the gastroenterologist and the gastrointestinal surgeon to identify lesions by high-resolution imaging techniques, imaging of metabolic processes, and intrapancreatic ductal investigations. In the last 20 years, the spectrum of diseases of the pancreas has been extended by recognition of new and increasingly identified common disorders of the pancreas such as cystic neoplasms and autoimmune pancreatitis. In pancreatology only ductal pancreatic cancer remains largely an uncontrollable mystery disease.

Medical science is not uniform around the world. However, the impact of information technology, international data exchange, and global communication networks have resulted in a broad, increased level in the understanding and practice of pancreatology. The synergistic interaction of basic scientists, pathologists, gastroenterologists, and gastrointestinal tract surgeons in the field of investigative and clinical pancreatology has led to better understanding of pancreatic diseases through combining the knowledge of each to achieve the best management. Decision making is increasingly based on the evidence of data from clinical trials on treatment. New technical devices—endoscopic visualization of cellular abnormalities, laparoscopic minimal invasive surgical approaches, and robotic surgery—have led to the establishment of a local, parenchyma-sparing surgical approach for neoplastic and inflammatory pancreatic diseases. Although care of patients cannot be made a global affair, this book brings the most recent knowledge on the pancreas from international experts to readers everywhere.

The goal of this third edition of *The Pancreas: An integrated textbook of basic science, medicine, and surgery* is to provide the clinician with the most current data-based synthesis of understanding of pancreatic diseases, functional assessment, diagnostic and technical devices, and treatment options. All chapters are written by leading international experts on the topic. A major part of this edition has been contributed by international basic scientists, who provide an understanding of the molecular basis of pancreatic functions and diseases. The editors acknowledge and are deeply indebted to all authors who have contributed to this edition. Their diligent efforts have provided state-of-the-art knowledge, particularly in regard to clinical decision making based on evidence.

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Abbreviations

4EBP1	initiation factor 4E binding protein 1
5-FU	5-fluorouracil
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine; serotonin
25(OH)D	25-hydroxyvitamin D
α-gal	alpha-galactosylated
α-GI	alpha-glucosidase inhibitor
αSMA	alpha smooth muscle actin
ABP	acute biliary pancreatitis
ACC	acinar cell carcinoma
ACE	angiotensin-converting enzyme
ACG	American College of Gastroenterology
ACh	acetylcholine
ACP	alcoholic chronic pancreatitis
ACS	abdominal compartment syndrome
ACS	American Cancer Society
ACTH	adrenocorticotropic hormone
ADH	alcohol dehydrogenase
ADM	acinar-to-ductal metaplasia
ADP	adenosine diphosphate
ADPKD	autosomal dominant polycystic kidney disease
AFIP	Armed Forces Institute of Pathology
AFP	alpha-fetoprotein
AGA	American Gastroentrological Association
AHPBA	American Hepato-Pancreato-Biliary Association
AID	autoinhibitory domain
AIDS	acquired immune deficiency syndrome
AIH	autoimmune hepatitis
AJCC	American Joint Committee on Cancer
AIP	autoimmune pancreatitis
ALDH	acetaldehyde dehydrogenase
ALI	acute lung injury
ALT	alanine transaminase
ALT	alternative lengthening of telomeres
ANC	acute necrotic collection
anti-SSA	anti-Sjögren syndrome A
anti-SSB	anti-Sjögren syndrome B
AP	acute pancreatitis
AP-1	activator protein-1
APA	American Pancreatic Association
APACHE	acute physiology and chronic health evaluation
APBDU	anomalous pancreaticobiliary ductal union
APC	activated protein C

APC	antigen-presenting cells
APFC	acute pancreatic fluid collection
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
Arg	arginine
ARP	acute recurrent pancreatitis
ARTN	artemin
ARX	aristaless-related homeobox
ASA	acetylsalicylic acid
ASCO	American Society of Clinical Oncology
AST	aspartate transaminase
ATIII	antithrombin 3
ATMDS	alpha-thalassemia myelodysplastic syndrome
ATP	adenosine triphosphate
ATRX	alpha-thalassemia/mental retardation X-linked
AUROC	area under the receiver operating characteristic curve
BAPTA-AM	1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid
BCAA	branched-chain amino acid
BD-IPMN	branch-duct intraductal papillary mucinous neoplasm
BE	balloon enteroscopy
BHOB	β-hydroxybutyrate
BilIN	biliary intraepithelial neoplasia
BMI	body mass index
BMP	bone morphogenic protein
BRCA1	breast cancer 1 gene
BRCA2	breast cancer 2 gene
BRPC	borderline resectable pancreatic cancer
BR-PDAC	borderline resectable pancreatic ductal adenocarcinoma
BSA	body surface area
BSG	British Society of Gastroenterology
BUN	blood urea nitrogen
BWS	Beckwith–Wiedemann syndrome
CA 19-9	carbohydrate antigen 19-9
CA	carbonic anhydrase
CA	celiac axis
cADPR	cyclic ADP-ribose
CAP	College of American Pathologists
CAPS	Cancer of the Pancreas Screening programs
CARS	compensatory anti-inflammatory response syndrome
CAS	celiac artery stenosis
CASR	calcium-sensing receptor
CBCT	cone beam computed tomography
CBD	common bile duct
CBER	Center for Biologics Evaluation and Research
CBP	CREB-binding protein
CCK	cholecystokinin
CDX	caudal-related homeobox transcription factor
CEA	carcinoembryonic antigen
CE-CT	contrast-enhanced computed tomography
CEL	carboxyl ester lipase
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes mellitus
CFTR	cystic fibrosis transmembrane conductor regulator
CG	celiac ganglion
CGRP	calcitonin gene-related peptide
ChA	chromogranin A

CHI	congenital hyperinsulinism
Chr	chromosome
CI	confidence interval
CIT	Clinical Islet Transplantation
CITR	Collaborative Islet Transplant Registry
CLDN2	claudin 2 gene
CNI	calcineurin inhibitor
CNS	central nervous system
CONKO	Charité Onkologie
COX-2	cyclooxygenase 2
CP	chronic pancreatitis
CPA1	carboxypeptidase A1
CPB	celiac plexus block
CPN	celiac plexus neurolysis
CPNT	cystic pancreatic neuroendocrine tumor
CRAC	Ca^{2+} release activated Ca^{2+}
CREB	cAMP response element binding
CRF	corticotropin-releasing factor
CRH	corticotropin-releasing hormone
CRP	C-reactive protein
CRT	chemoradiation therapy
CSF-1	colony-stimulating factor 1
CSF-1/R	colony stimulating factor-1/receptor
CT	computed tomography
CTC	circulating tumor cells
ctDNA	circulating tumor DNA
CTGF	connective tissue growth factor
CTL	cytotoxic T-lymphocytes
CTLA-4	cytotoxic T-lymphocyte associated protein-4
CTRC	chymotrypsin C or chymotrypsinogen C
CTSB	cathepsin B
CTSI	CT severity index
Cy	cyclophosphamide
CYP2E1	cytochrome P450 2E1
DAMP	damage-associated molecular pattern molecule
DAXX	death domain-associated protein
DBC	determinant-based classification
DBDC	distal common bile duct carcinoma
DBE	double-balloon enteroscopy
DBTC	dibutyltin chloride
DCD	deceased cardiac death donor
DEN	direct endoscopic necrosectomy
DGE	delayed gastric emptying
DKA	diabetic ketoacidosis
DM	diabetes mellitus
DMV	dorsal motor nucleus
DNA	deoxyribonucleic acid
DOPA	dihydroxyphenylalanine
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
DOTA-NOC	DOTA-Nal-octreotide
DOTA-TATE	DOTA-Tyr-octreotate
DOTA-TOC	DOTA-Tyr-octreotide
DP	distal pancreatectomy
DPDS	disconnected pancreatic duct syndrome
DPP-4	dipeptidyl-peptidase-4
DPPHR	duodenum-preserving pancreatic head resection

DPPHR-P	duodenum-preserving partial head resection
DPPHR-S	duodenum-preserving total head resection plus segment resection of duodenum and CBD
DPPHR-T	duodenum-preserving total head resection but conserving duodenum and CBD
DRG	dorsal root ganglion
DSS	disease-specific survival
DTPA	diethylenetriaminepentaacetic acid
DWI	diffusion-weighted imaging MRI
DXA	dual X-ray absorptiometry
E8.5	embryonic day 8.5
EBL	estimated blood loss
EBRT	external beam radiation
ECG	electrocardiogram
ECM	extracellular matrix
ED	emergency department
EGF	epithermal growth factor
eIF2α	eukaryotic initiation factor 2 alpha
eIF4F	eukaryotic initiation factor 4F
eIF4G	eukaryotic initiation factor 4G
ELISA	enzyme-linked immunosorbent assay
EMT	epithelial mesenchymal transition
ENETS	European Neuroendocrine Tumor Society
EORTC	European Organization for Research and Treatment of Cancer
EPI	exocrine pancreatic insufficiency
EPO	erythropoietin
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography imaging
ERK	extracellular regulated kinase
ERP	endoscopic retrograde pancreatography
ES	endoscopic sphincterotomy
ESDO	European Society of Digestive Oncology
ESGE	European Society of Gastrointestinal Endoscopy
ESMO	European Society for Medical Oncology
ESPAC	European Study Group for Pancreatic Cancer
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
ESWL	extracorporeal shock wave lithotripsy
EUROPAC	European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer
EUS	endoscopic ultrasound
EUS-AG	EUS-guided antegrade stenting
EUS-BD	endoscopic ultrasonography-guided biliary drainage
EUS-CDS	EUS-guided choledochoduodenostomy
EUS-CGN	EUS-guided celiac ganglia neurolysis
EUS-CPN	endoscopic ultrasound celiac plexus neurolysis
EUS-FNA	endoscopic ultrasound guided fine-needle aspiration
EUS-HGS	EUS-guided hepaticogastrostomy
EUS-RV	EUS-rendezvous technique
FAEE	fatty acid ethyl ester
FAP	familial adenomatous polyposis
FCεR	high-affinity IgE or Fc epsilon receptor
FCPD	fibrocalculous pancreatic diabetes
fcSEMS	fully covered self-expandable metal stents
FDA	Food and Drug Administration (USA)
FDG-PET	[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography
FDP	[^{18}F]fluorodipalmitin
FE-1	fecal elastase-1
FFA	free fatty acid

FGF	fibroblast growth factor
FIBS	fibroinflammatory biliary stricture
FNA	fine-needle aspiration
FNB	fine-needle biopsy
FOLFIRINOX	5-fluorouracil [5-FU], oxaliplatin, irinotecan, and leucovorin
FPC	familial pancreatic cancer
Ga	gallium citrate
GAP-43	growth-associated protein-43
G-CSF	granulocyte colony-stimulating factor
GDA	gastroduodenal artery
GEL	granulocytic epithelial lesion
GEP-NET	gastroenteropancreatic neuroendocrine tumor
GFAP	glial fibrillary acidic protein
GFR	glomerular filtration rate
GH	growth hormone
GHRH	growth hormone-releasing hormone
GI	gastrointestinal
GIP	gastric inhibitory peptide
GIP	glucose-dependent insulinotropic polypeptide
GITSG	Gastrointestinal Tumor Study Group
GJ	gastrojejunostomy
GLP-1	glucagon-like peptide 1
Gly	glycine
GM-CSF	granulocyte macrophage-colony stimulating factor
GNAS	guanine nucleotide binding protein alpha stimulating
GNPNA	*N*-glutaryl-L-phenylalanine-*p*-nitroanilide
GRAGIL	Group de Recherche Rhin, Rhône-Alpes et Genève pour la Transplantation d'Ilots de Langerhans
GRF	growth hormone-releasing factor
GTX	gemcitabine, docetaxel, and capecitabine
GWAS	genome-wide association studies
H2R	histamine 2 receptor
H&E	hematoxylin and eosin (histologic stain)
HbA_{1c}	hemoglobin A_{1c}
HB-EGF	heparin-binding EGF-like growth factor
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
hENT1	human equilibrative nucleoside transporter 1
HES1	hairy and enhancer of split 1
HGD	high-grade dysplasia
HGF	hepatocyte growth factor
HIF	hypoxia-induced factor
HIV	human immunodeficiency virus
HJ	hepaticojejunostomy
HLA	human leukocyte antigen
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HNF	hepatocyte nuclear factor
HNPCC	hereditary nonpolyposis colorectal cancer syndrome
HPF	high power field
HR	hazard ratio
HTG	hypertriglyceridemia
HTK	histidine–tryptophan–ketoglutarate
HTP	hydroxytrytophan
HUS	hemolytic uremic syndrome
IAH	impaired awareness of hypoglycemia
IAK	islet after kidney
IAP	International Association of Pancreatology

IAPN	intra-ampullary papillary tubular neoplasm
IBD	inflammatory bowel disease
IC	immune complex
IC	invasive carcinoma
ICDC	International Consensus Diagnostic Criteria for AIP
ICGC	International Cancer Genome Consortium
ICU	intensive care unit
IDCP	idiopathic duct-centric pancreatitis
IDDM	insulin-dependent diabetes mellitus
IDDS	intrathecal drug delivery systems
IEQ	islet equivalent
IFN-γ	interferon γ
Ig	immunoglobulin
IgE	immunoglobulin E
IGF	insulin-like growth factor
IGF-1	insulin-like growth factor 1
IgG	immunoglobulin G
IgG4-MOLPS	IgG4-related multiorgan lymphoproliferative syndrome
IgG4-RD	IgG4-related disease
IL	interleukin
IL-10	interleukin 10
IL-1β	interleukin 1β
IL-6	interleukin 6
IL-8	interleukin 8
IMRT	intensity modulated radiation therapy
iNOS	inducible nitric oxide synthase
IOPN	intraductal oncocytic papillary neoplasm
IORT	intraoperative radiation therapy
IOU	intraoperative ultrasound
IP_3	inositol 1,4,5-trisphosphate
IPHM	inflammatory pancreatic head mass
IPMN	intraductal papillary mucinous neoplasm
IPTR	International Pancreas Transplant Registry
IQR	interquartile range
IR	insulin receptor
IRE	irreversible electroporation
IRG	immunoreactive gastrin
IRI	immunoreactive insulin
ISGPF	International Study Group on Pancreatic Fistula
ISGPS	International Study Group of Pancreatic Surgery
IT	intrathecal
ITA	intraductal tubular adenoma
ITA	islet transplant alone
ITC	intraductal tubular carcinoma
ITPN	intraductal tubulopapillary neoplasm
ITU	intensive therapy unit
IVE	interventional endoscopy
IVR	interventional radiology
JASPAC	Japan Adjuvant Study Group of Pancreatic Cancer
JBS	Johanson–Blizzard syndrome
JPN CTSI	Japanese CTSI
KRAS	Kirsten rat sarcoma viral oncogene homolog
LA	locally advanced
LAMP	lysosomal-associated membrane protein-2
LAMS	lumen-apposing metal stent
LAPC	locally advanced pancreatic cancer

LAR	long-acting release
LDP	laparoscopic distal pancreatectomy
LEF1	lymphoid enhancer-binding factor 1
LH	luteinizing hormone
LIF	leukemia inhibitory factor
LKM	liver-kidney-microsomal
lncRNA	long noncoding RNA
LNR	lymph node ratio
LOH	loss of heterozygosity
LOS	length of stay
LOT	ligament of Treitz
LP	left pancreatectomy
LPJ	lateral pancreaticojejunostomy
LPL	lipoprotein lipase
LPLD	lipoprotein lipase deficiency
LPS	lipopolysaccharide
LPSP	lymphoplasmacytic sclerosing pancreatitis
LR	lactated Ringer's
LR–LPJ	local resection with lateral pancreaticojejunostomy
M3	muscarinic M3 receptors
MAEC	mixed acinar endocrine carcinoma
MAL	median arcuate ligament
MANEC	mixed adenoneuroendocrine carcinoma
MAPK	mitogen-activated protein kinase
MARPN	minimal access retroperitoneal pancreatic necrosectomy
MBPR	master production batch record
MCN	mucinous cystic neoplasm
MCP1	monocyte chemotactic protein 1
MCS	mean component score
MCT	medium-chain triglycerides
MD	main duct
MDCT	multidetector computed tomography
MD-CTSI	modified CT severity index
MD-IPMN	main-duct intraductal papillary mucinous neoplasm
MDSC	myeloid-derived suppressor cell
MEN1	multiple endocrine neoplasia type 1
MGOO	malignant gastric outlet obstruction
MHC	major histocompatibility complex
MIP	maximum intensity projection imaging
miRNA	microribonucleic acid
MIS	minimally invasive surgery
MIST1 (BHLHA15)	basic helix–loop–helix family member A15
MLL	mixed-lineage leukemia
MMC	migrating motor complex
MMF	mycophenolate mofetil
MMP	matrix metalloproteinase
MOCA	multivariate organization of combinatorial alterations
MODS	multiple organ dysfunction syndrome
MODY	maturity-onset diabetes of the young
MPD	main pancreatic duct
MPN	mucin-producing neoplasms
MPTP	mitochondrial permeability transition pore
MRC	magnetic resonance cholangiography
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MSI	microsatellite instability

MSKCC	Memorial Sloan Kettering Cancer Center
mtDNA	mitochondrial DNA
mTORC1/2	mammalian target of rapamycin complex 1/complex 2
MUC	mucin protein
MX	mixed type
NAADP	nicotinic acid adenine dinucleotide phosphate
NADC	nonampullary duodenum duodenal carcinoma
NADCP	nonalcoholic duct-destructive chronic pancreatitis
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	nonalcoholic fatty liver disease
NAPS2	North American Pancreatitis Study 2
NC	noncontrast
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NEC	neuroendocrine carcinoma
NEN	neuroendocrine neoplasm
NET	neuroendocrine tumor
NET	neutrophil extracellular trap
NEUROD	neuronal differentiation 1
NF	neurotrophic factors
NF1	neurofibromatosis type 1
NFAT	nuclear factor of activated T cells
NFκB	nuclear factor kappa light-chain enhancer of activated B cells
NFκB	nuclear factor-κB
NG	nodose ganglion
NGF	nerve growth factor
NGN3	neurogenin 3
NGS	next generation sequencing
NIPHS	noninsulinoma pancreatogenous hypoglycemia syndrome
NK-1R	neurokinin 1 receptor
NKX2.2	NK homeobox 2
NO	nitric oxide
NOS	not otherwise specified
NPD	nasal potential difference
NR5A2	nuclear receptor subfamily 5 group A member 2
NSAID	nonsteroidal anti-inflammatory drug
NSE	neuron-specific enolase
NTR	neurotrophic factor receptors
NTS	nucleus tractus solitarius
OOI	other organ involvement
OP/SL	open packing/staged laparotomy
OR	odds ratio
OS	overall survival
OTS	ovarian type stroma
PA	pancreas transplantation alone
PACAP	pituitary adenylate cyclase-activating peptide
PACC	Polyanalgesic Consensus Conference
PAF	platelet activating factor
PAK	pancreas transplantation after a kidney transplant
PAMP	pathogen-associated molecular pattern
PanC4	Pancreatic Cancer Case–Control Consortium
PanIN	pancreatic intraepithelial neoplasia
PanNEC	pancreatic neuroendocrine carcinoma
PanNET	pancreatic neuroendocrine tumor
PAR-2	proteinase-activated receptor-2
PAS	periodic acid–Schiff

PAS-D	periodic acid–Schiff with diastase
PAX4	paired box 4
PBC	primary biliary cholangitis
PBD	preoperative biliary drainage
PBF	pancreatic blood flow
PBS	pencil beam scanning
PBT	proton beam therapy, proton therapy
PCA	pancreatic cancer
PCD	percutaneous catheter drainage
PCL	pancreatic cystic lesion
PCN	pancreatic cystic neoplasm
PCS	physical component score
PCT	procalcitonin
PD	pancreatoduodenectomy
PD-1	programmed death-1
PDAC	pancreatic ductal adenocarcinoma
PDEC	poorly differentiated endocrine carcinoma
PDGF	platelet-derived growth factor
PDGFβ	platelet-derived growth factor β
PD-L1/2	programmed death-ligand 1/2
PD-NEC	poorly differentiated neuroendocrine carcinoma
PDP	paraduodenal (groove) pancreatitis
PDS	polydiaxone sutures
PDX1	pancreatic and duodenal homeobox 1
PEG	percutaneous endoscopic gastrostomy
PEI	pancreatic exocrine insufficiency
PERK	endoplasmic reticulum-resident protein kinase
PERT	pancreatic enzyme replacement therapy
PET	positron emission tomography
PFC	pancreatic fluid collections
PFS	progression-free survival
PG	pancreatogastrostomy
PG	plasma glucose
pHi	intramucosal pH
PHPI	purified human pancreatic islet product
PI3′K	phosphoinositide 3′-kinase
PI3K	phosphatidylinositol 3-kinase
PICU	pediatric intensive care unit
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PJ	pancreaticojejunostomy
PJS	Peutz–Jeghers syndrome
PKA	protein kinase A
PKB	protein kinase B
PLA-2	phospholipase A2
PLC	phospholipase C
PMCA	plasma membrane Ca^{2+}-activated ATPase
PMD	pancreatic main duct
PMN-elastase	polymorph-nuclear cell elastase
PMSR	pancreatic middle segment resection
PNET	pancreatic neuroendocrine tumor
PNI	perineural invasion
POF	persistent organ failure
POPF	postoperative pancreatic fistula
PP	pancreatic polypeptide
PP1	protein phosphatase 1
PPARγ	peroxisome proliferator-activated receptor gamma

PPC	pancreatic pseudocyst
PPI	proton-pump inhibitor
PPoma	pancreatic polypeptide-producing tumor
PPPD	pylorus-preserving pancreaticoduodenectomy
PROX1	prospero homeobox 1
PRRT	peptide receptor radionuclide therapy
PRSS1	protease, serine 1 gene (also known as cationic trypsinogen gene)
PS	performance status
PSC	pancreatic stellate cells
PSC	primary sclerosing cholangitis
PSP	pancreatic stone protein
PSTI	pancreatic secretory trypsin inhibitor
PTBD	percutaneous transhepatic biliary drainage
PTC	percutanous transhepatic cholangiography
PTEN	phosphatase and tensin homolog
PTF1A	pancreas-specific transcription factor 1A
PTH	parathyroid hormone
PTH-rP	parathyroid hormone-related polypeptide
PTLD	posttransplant lymphoproliferative disorder
PV	portal vein
PYY	peptide YY
QOL	quality of life
RAC	revised Atlanta classification
RADIANT	RAD001 in advanced neuroendocrine tumors
RAF	rapidly accelerated fibrosarcoma
RAMPS	radical antegrade modular pancreatosplenectomy
RANTES	regulated on activation, normal T-cell expressed, and secreted
RAP	recurrent acute pancreatitis
RBPJk	recombination signal binding protein for immunoglobulin kappa J region
RCT	randomized controlled trial
RECIST	response evaluation criteria in solid tumors criteria
RER	rough endoplasmic reticulum
RF	retroperitoneal fibrosis
RFA	radiofrequency ablation
ROS	reactive oxygen species
RR	relative risk
Rt	response to steroids
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
RTX	rituximab
RyR	ryanodine receptor
S6K	small ribosomal subunit 6-kinase
SAA	serum amyloid A
SACI	selective arterial calcium injection
SAPE	sentinel acute pancreatic event
SASI	selective arterial secretagogue injection
SBE	single-balloon enteroscopy
SBRT	stereotactic body radiation therapy
SC	sclerosing cholangitis
SCA	serous cystadenoma
SCN	serous cystic neoplasm
SDF-1α	stromal-derived factor 1α
SDS	Shwachman–Diamond syndrome
SEER	Surveillance, Epidemiology, and End Results
SEMS	self-expandable metal stents
SF	short form questionnaire

SGLT-2	sodium–glucose cotransporter-2
SHE	severe hypoglycemic episodes
SHH	sonic hedgehog
SHIPS	systemic IgG4-related plasmacytic syndrome
SIK	simultaneous islet kidney
SIRS	systemic inflammatory response syndrome
SIRT	selective internal radiotherapy
SMA	smooth muscle actin
SMA	superior mesenteric artery
sMRCP	secretin-enhanced magnetic resonance cholangiopancreatography
SMV	superior mesenteric vein
SMV-PV	superior mesenteric vein–portal vein
SN	greater splanchnic nerve
SNP	single nucleotide polymorphism
SNRI	serotonin–norepinephrine reuptake inhibitors
SOC	store-operated Ca^{2+} channels
SOD	sphincter of Oddi dysfunction
SOFA	sequential organ failure assessment
SOP	standard operating procedure
SP	substance P
SPECT	single-photon emission computed tomography
SPINK1	serine protease inhibitor Kazal type 1
SPK	simultaneous pancreas–kidney transplantation
SPN	solid-pseudopapillary neoplasm
SR	somatostatin receptor
SRS	somatostatin receptor scintigraphy
SSAT	Society for Surgery of the Alimentary Tract
SSO	Society for Surgical Oncology
SSRI	selective serotonin reuptake inhibitor
SST	somatostatin
SSTR	somatostatin receptor
STZ	streptozotocin
sub-CT	subtraction color map based on dual-energy CT
T cells	thymus cells
T1D	type 1 diabetes
T1W	T1 weighted
T2W	T2 weighted
TACE	transarterial chemoembolization
TAE	transarterial embolization
TAM	tumor-associated macrophage
TAP	trypsinogen activation peptide
TCGA	The Cancer Genome Atlas
TCP	tropical chronic pancreatitis
TERT	telomerase reverse transcriptase
TFF1	trefoil factor 1
TGF-β	transforming growth factor β
Th	T helper
TIGAR-O	toxic–metabolic inflammatory genetic autoimmune recurrent and severe pancreatitis obstructive
TIMP	tissue inhibitor of metalloproteinases
TKI	tyrosine kinase inhibitor
TLNC	total lymph node count
TLR	toll-like receptor
TME	tumor microenvironment
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor α
TOF	transient organ failure

TP	total pancreatectomy
TPC	two-pore channel
TPIAT	total pancreatectomy with islet autotransplantation
TPN	total parenteral nutrition
Treg	regulatory T cell
TRP	transient receptor potential
TRPA1	transient receptor potential cation channel, subfamily A, member 1
TRPV1	transient receptor potential cation channel subfamily V, member 1
TSC2	tuberous sclerosis complex 2
TSD	thoracoscopic splanchnic denervation
TSE	turbo spin echo
TUS	transabdominal ultrasonography
UC	ulcerative colitis
UGT1A1	UDP glucuronyltransferase 1A1
UICC	Union for International Cancer Control (formerly International Union Against Cancer)
UICC/AJCC	Union for International Cancer Control/American Joint Cancer Committee
ULN	upper limit of normal
UNOS	United Network for Organ Sharing
UNSW	University of New South Wales
UPDAC	uncinate process pancreatic ductal adenocarcinoma
UPR	unfolded protein response
US	ultrasonography, ultrasound
UVB	ultraviolet B
VARD	video-assisted retroperitoneal debridement
VAS	visual analog scale
VEGF	vascular endothelial growth factor
VHL	von Hippel–Lindau syndrome
VIP	vasoactive intestinal polypeptide
VIPoma	vasoactive intestinal peptide-releasing tumor
VLDL	very low-density lipoprotein
VLS	vascular leak syndrome
VMAT	volumetric arc therapy
VN	vagus nerve
VPA	valproic acid
VR	volume-rendered imaging
VR1	vanilloid receptor type 1
WBC	white blood cells (leukocytes)
WDEC	well-differentiated endocrine carcinoma
WDHA	watery diarrhea, hypokalemia, and achlorhydria
WD-NET	well-differentiated neuroendocrine tumor
WES	whole-exome sequencing
WHO	World Health Organization
WNT	wingless-type MMTV integration site family
WOPN	walled-off pancreatic necrosis
WT	wild type
XBP1	x-box binding protein 1
XCR1	C–X–C motif receptor
YY1	Yin Yang 1
ZES	Zollinger–Ellison syndrome
ZG	zymogen granules

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The website includes:

- PowerPoints of all figures from the book for downloading
- Videos

Section 1

Anatomy of the Pancreas

1

Development of the Pancreas and Related Structures

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Anatomy of the Pancreas

The pancreas is a unique exocrine and endocrine organ located in the retroperitoneal region of the upper abdominal cavity. In humans, when fully formed, the organ has a distinct head, body, and tail, with the head of the pancreas contacting the duodenal region of the intestines (the main pancreatic duct drains into the duodenum) and the tail of the pancreas abutting the spleen. The greatest mass of the organ is present in the head, which is composed of tissue derived from two independent anlagen (see later). In other mammals, such as dogs and mice, the organ has a far less distinct structure and is identified as an amorphous pink tissue adjacent to the mesentery that runs along the upper intestinal wall.

The cells of the pancreas are arranged into distinct lobules composed primarily of the digestive enzyme-producing cells of the exocrine pancreas, which are arranged into acini (so-called acinar cells), the ductal structures that conduct these digestive enzymes to the intestines, and distinct clusters of endocrine cells, the islets of Langerhans, that secrete hormones and function to regulate glucose uptake and release and serum glucose levels. There are five recognized cell types within the islets, the α, β, δ, ε, and PP cells, which produce the hormones glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively. The majority of the pancreatic tissue mass (more than 90–95%) is present within the exocrine compartment of the organ, with the islets of Langerhans, scattered throughout the tissue. The pancreas also has connective tissue, derived from the embryonic mesenchyme, which forms the septa that separate the many lobules of the organ. Mesenchyme-derived stromal cells are also present in the interlobular regions surrounding the pancreatic ducts, blood vessels, and nerves. In the following sections, we explore how these disparate cell types come together to form the pancreas.

Organogenesis in the Region of the Pancreas

Around day 14, the embryonic bilaminar germ disk is composed of a layer of epiblast and a layer of hypoblast. At this time, a faint groove appears along the longitudinal midline of the germ disk that develops into a structure called the primitive streak [1]. Around day 15, epiblast cells near the primitive streak undergo a morphologic change and migrate through the primitive streak into the space between the epiblast and hypoblast in a process known as gastrulation (Fig. 1.1). Some of the ingressing epiblast cells invade the hypoblast, which is eventually replaced by a new layer of epiblast-derived cells known as the definitive endoderm. Additional migrating epiblast cells occupy the space between the epiblast and the definitive endoderm to form a third layer of cells called the intraembryonic mesoderm (Fig. 1.1). As cells of the germinal disk migrate anteriorly to form a head process and lateral regions roll underneath to form an approximately cylindrical body shape, the endoderm is rolled into a tube that projects into the developing head region of the embryo surrounded by the mesoderm layer. This is the primitive digestive tube. The pancreas is specified by two separate outgrowths that arise on the dorsal and ventral surfaces of the primitive digestive tube. The epithelial cells of the pancreas originate from the interior lining of the primitive gut tube, which consists of a single layer of endoderm. A layer of

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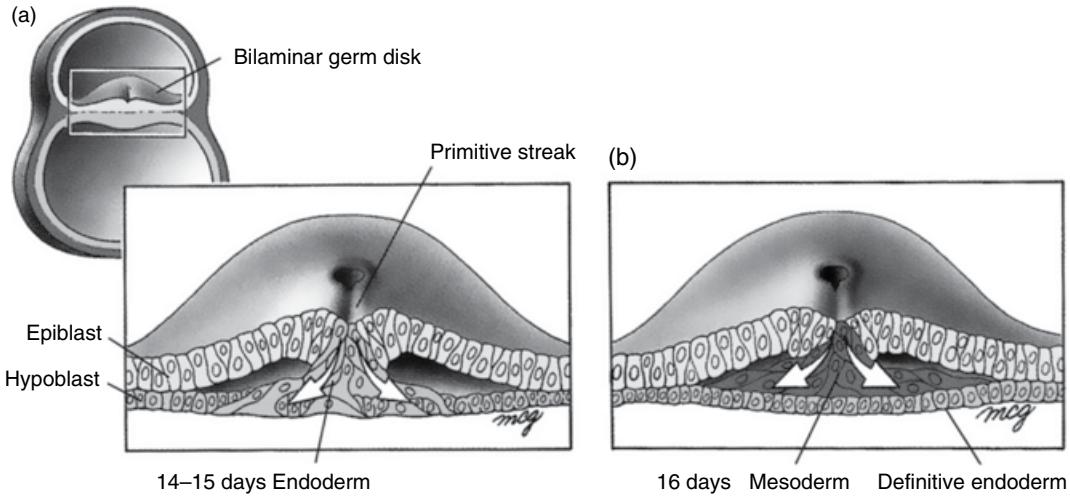

Figure 1.1 Germ disks sectioned through the region of the primitive streak, showing gastrulation. (a) On days 14 and 15, the ingressing epiblast cells replace the hypoblast to form the definitive endoderm. (b) The epiblast that ingresses on day 16 migrates between the endoderm and epiblast layers to form the intraembryonic mesoderm. Source: Larsen 2001 [1]. Reproduced with permission of Elsevier.

mesenchyme, from which the muscle and connective tissue of the gastrointestinal organs are derived, surrounds the endoderm.

The anterior regions of the endoderm form the foregut; regions posterior to the foregut form the midgut and hindgut. The most anterior regions of the foregut give rise to the esophagus and stomach. Just posterior to the foregut, the endoderm is continuous with the yolk sac, which extends outside the embryo, in a region known as the anterior intestinal portal. Endodermally derived cells close to the anterior intestinal portal specify the pancreas. The duodenum and liver are also specified by foregut endoderm in this region.

Thus, many gastrointestinal tissues are specified at the same time from a fairly restricted region of the gut endoderm. How are each of these organs specified in the appropriate anatomic location, and how do they differentiate properly into mature functional organs? The epithelial organs of the developing embryo originate as buds from the endoderm as the appropriate temporal and spatial cues are received. Thus, proper initiation and location of endodermally derived organs are regulated by the activation status of important signal transduction pathways involved in animal development, including the hedgehog, notch, and fibroblast growth factor signaling pathways.

Early Pancreatic Development

During the fourth week of gestation, two buds appear on the dorsal and ventral sides of the foregut near the anterior intestinal portal. These epithelial buds indicate the specification of the pancreas. These buds initially grow and differentiate independently, but later fuse to form a single organ. The anlage on the dorsal side, the dorsal pancreatic bud, appears first and gives rise to the dorsal pancreas. The cells of the dorsal pancreas will give rise to the head, body, and tail of the mature pancreas. The second pancreatic anlage appears shortly after the appearance of the dorsal pancreatic bud. This bud, which appears on the ventral side of the gut tube, is appropriately called the ventral pancreatic bud and develops into the ventral pancreas, which forms part of the head of the pancreas. Both pancreatic buds develop simultaneously, and the proliferating epithelial cells grow as projections into the surrounding mesenchymal tissue. During this time, the development of the intestines, and importantly the duodenum, continues. Rotation and asymmetric growth of the duodenum move the originally ventral part to a dorsal location, carrying with it the ventral pancreas and the primordial common bile duct. As the duodenum begins to rotate into its appropriate anatomic location, the ventral pancreas also rotates around the gut tube such that the ventral and dorsal pancreata lie adjacent to each other. These pancreatic rudiments then fuse to form a single organ. While both developing pancreatic buds independently form pancreatic ducts, the lumens of which are continuous with the lumen of the primitive gut, after they fuse their primary ducts anastomose to form the main pancreatic duct (Fig. 1.2). The region of the primary duct of the ventral pancreas proximal to the duodenum fuses with the primary duct of the dorsal pancreas and becomes the primary drainage into the duodenum, entering the duodenum immediately adjacent to the common bile duct. The proximal region of the primary duct of the dorsal pancreas sometimes remains as an accessory drainage but often regresses.

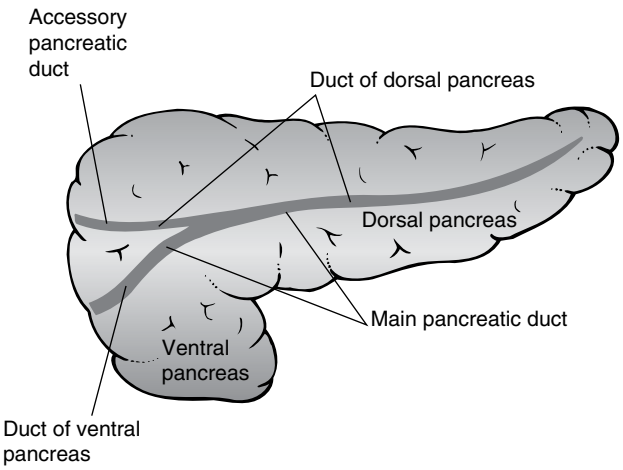

Figure 1.2 Contributions of the dorsal and ventral pancreas to the definitive organ. The ventral pancreas becomes most of the head. The dorsal pancreas becomes the remainder of the head, plus the body and tail. The duct of the dorsal pancreas contributes a large part of the main pancreatic duct plus the accessory duct. The duct of the ventral pancreas becomes the part of the main duct nearest the duodenum.

The ducts sometimes fail to fuse, in which event two independent duct systems drain into the duodenum.

Signaling Governing Early Pancreatic Development

Early pancreatic development and establishing pancreatic identity are governed by the interplay between several critical transcription factors and intercellular signaling pathways. PDX1 and PTF1A are among the earliest transcription factors expressed in the pancreatic progenitor populations, and their functions are critical for pancreatic development [2–5]. In mice, PDX1 expression is first detected in the primitive gut tube at embryonic day 8.5 (E8.5), demarcating the prospective pancreatic domain, which is then followed by PTF1A expression in pancreatic endoderm at E9.5 [5–7]. Mice lacking either transcription factor display pancreatic agenesis [2,3,5,8].

In addition to the transcription factors, several key intercellular signaling pathways between gut endoderm and mesenchyme, including the hedgehog and fibroblast growth factor (FGF) pathways, play important roles in establishing the pancreatic identity and controlling the expression of these transcription factors. Research studies have shown that sonic hedgehog (SHH) is excluded from the prospective pancreatic region, but is present in the region of foregut that becomes the duodenum, and ectopic expression of SHH in the pancreas induces an intestinal fate, suggesting that SHH signaling may specify a duodenal versus pancreatic fate in the posterior foregut [9,10]. Another well-understood pathway mediating the mesenchymal–epithelial interaction is the FGF signaling pathway, in particular the FGF10–FGFR2 ligand–receptor pair. During early pancreatic development, FGF10 is highly expressed in the primitive mesenchyme, whereas its receptor FGFR2 is present in the pancreatic epithelium [11]. Mouse genetic experiments demonstrated that FGF10 provides the pro-proliferative signal to promote the expansion of the progenitor pool in the pancreatic epithelium [11]. In addition, FGF10 signaling from the mesenchymal cells is critical for maintaining the epithelial expression of SOX9 [12]. SOX9 is another transcription factor critical for early pancreatic development, and it exerts its function in part by controlling the expression of the FGF10 receptor FGFR2 [12,13]. Together, the complex regulatory loop between these signaling pathways and transcription factors in the epithelium and mesenchyme coordinates early organ growth and the establishment and maintenance of pancreatic identity.

Differentiation of Pancreas Cell Types

The acinar, ductal, and endocrine cells of the pancreas are all produced through the proliferation and differentiation of the epithelial cells of both pancreas primordia. The cells appear homogeneous during the early stages of development as they proliferate and grow into the surrounding mesenchyme as finger-like projections. The epithelial cells form undifferentiated tubules that branch and anastomose as they penetrate into the mesenchyme to generate a tubular network, which resembles an immature (and nonfunctional) duct system. The acinar cells appear as clusters of cells at the ends of branches of this tubular network. The endocrine cells appear as cells that delaminate from the tubular epithelium and reaggregate in isolated clusters embedded within the developing parenchyma. The existing cells within these small isolated endocrine clusters proliferate, and these clusters therefore expand to form the islets.

Apparent differentiation of pancreas epithelial cells into endocrine cells can be identified beginning at 12 weeks of gestation with the detection of endocrine granules. Most of the endocrine differentiated cells identified at this time express glucagon and are therefore believed to be α cells. Importantly, lineage-tracing experiments performed in mice demonstrated that these early α cells do not act as endocrine progenitors, as β cells, the predominant cell type in the mature islet, are derived from glucagon-negative cells [14]. Differentiation of acinar cells is detected at approximately 16 weeks, as identified by the appearance of zymogen granules. Interestingly, not all enzymes are elaborated at once—detection of

trypsinogen does not occur until approximately 22 weeks. The digestive enzyme-positive cells arise as clusters from the undifferentiated tubules, the expansion of which is rapid such that the acinar cells become the dominant population within the organ. Although they are not yet mature acinar cells, the cells in the acinar clusters display some of their hallmark features, including basolaterally located nuclei. As differentiation continues, the cells become arranged in recognized acini and defined lobules surrounded by connective tissue. The ductal system arises after maturation of the immature tubular network. The specific morphologic changes that accompany this change are unclear, although some work suggests that WNT signaling is involved in this transition [15].

Transcriptional Mechanisms Underlying Pancreatic Cell Fate Decision

Much information about pancreatic cell fate determination and cell type differentiation has been obtained from studies in animal models. Elegant genetic and cell-based experiments in mice have identified a gene regulatory network controlled by many transcription factors to specify different cell lineages in the developing pancreas.

Development of the Endocrine Lineage

Endocrine cell specification begins with the expression of NGN3, a bHLH (basic helix loop helix) transcription factor, in a subset of progenitor cells within the trunk region of the pancreatic bud [16–18]. The NGN3-expressing cells eventually give rise to all endocrine cell types: insulin-producing β cells, glucagon-producing α cells, somatostatin-producing δ cells, ghrelin-producing ε cells, and pancreatic polypeptide-producing PP cells [16–18]. NGN3 initiates endocrine lineage specification by inducing the expression of downstream transcription factors, including NeuroD, NKX2.2, PAX4, and ARX. Among them, NKX2.2, NeuroD, and PAX4 play key roles in the specification of β cells [19–21]. Mutant mice lacking any of these transcription factors display a phenotype of dramatic or total loss of β cells [19–21]. Further studies revealed that the opposing actions of PAX4 and ARX determine the fate choice between α and β cells. During endocrine differentiation, loss of ARX leads to a complete loss of α cells, but a concomitant increase in β and δ cells [22], whereas loss of PAX4 results in an opposite phenotype with loss of β and δ cells and expansion of α cells [20,22]. It is believed that this effect on cell fate choice is mediated by the reciprocal transcriptional repression between these factors.

Differentiation of Acinar Cells

Pancreatic acinar cells are primarily derived from precursor cells in the tip region, and their differentiation is coordinated by the transcription factor PTF1A, a master regulator of pancreatic development. Prior to exocrine differentiation, PTF1A forms a complex with the bHLH transcription factor RBP-Jk, and is required for activation of RBP-Jl, an acinar-specific paralog of RBP-Jk [23,24]. The more active RBP-Jl then replaces RBP-Jk to form the complex with PTF1A, thereby directly inducing the expression of many acinar-specific genes, including secretory peptides and digestive enzymes [23,24]. Interestingly, PDX1, another factor important for early pancreatic morphogenesis, is also involved in acinar differentiation. Although not essential for initial acinar specification, it appears that PDX1 is required for terminal differentiation of acinar cells [25]. Other transcription factors, such as NR5A2 and MIST1, are also required for acinar differentiation and homeostasis, likely through the interaction with the PTF1A/RBP-Jk/l complex [26,27].

Ductal Cell Differentiation and Lineage Plasticity

In comparison with the endocrine and exocrine lineages, how ductal cells undergo differentiation remains poorly understood. It appears that, during development, NGN3-positive cells in the trunk region of the pancreatic bud give rise to endocrine cells, whereas NGN3-negative trunk epithelial cells contribute to the ductal system [28,29]. A number of transcription factors, such as SOX9, PROX1, HES1, and HNF6, are expressed in the ductal lineage and play various roles in ductal differentiation, including primary cilia formation in the ductal epithelial cells [30–33]. Although the three lineages (endocrine, exocrine, and ductal) are specified during early development, the adult pancreatic cells from different lineages show remarkable plasticity and trans-differentiation capacity in pancreatic injury, pancreatitis, and tumorigenesis, which may shed light on the mechanisms underlying these pancreatic pathologies.

Development and Disease

Molecules important in the development of the pancreas are also causally associated with pancreatic disorders. Several of the signaling pathways involved in normal pancreas development, such as the notch, hedgehog and WNT signaling pathways, are commonly activated in

pancreatic ductal adenocarcinomas [34–38]. Aberrant activation of WNT signaling drives the development of other pancreatic tumor types such as acinar carcinomas, pancreatoblastoma, and mucinous cystic neoplasms [39–42].

In diabetes, mutation of the transcription factor PDX1, which is important for pancreas specification and for proper β-cell maturation and function, is a cause of maturity-onset diabetes of the young (MODY) [43]. Other transcription factors that are critical for β-cell development (as determined by genetic studies in the mouse), such as hepatocyte nuclear factor 1α (HNF1α), HNF1β, HNF4α, and NeuroD, are all also mutated in additional MODY complementation groups [43]. More recently, scientists have utilized our growing understanding of normal pancreas development to promote the differentiation of induced pluripotent stem cells into insulin-producing cells in a new potential therapeutic approach for diabetes [44,45].

Collectively, these findings illustrate the importance of key regulators of pancreas development and differentiation in pathologic disease states and how knowledge of normal pancreas development may drive new therapeutic strategies for pancreatic diseases.

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2

Anatomy, Histology, and Fine Structure of the Pancreas

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Introduction

This chapter reviews the anatomy, histology, and ultrastructure of the pancreas, including the exocrine and endocrine portions. The exocrine pancreas produces and secretes digestive enzymes into the duodenum and includes acinar cells and ducts with associated connective tissue, vessels, and nerves that comprise more than 95% of the pancreatic mass. The endocrine pancreas (islets) makes and secretes insulin, glucagon, somatostatin, and pancreatic polypeptide into the blood. The islets comprise 1–2% of pancreatic mass.

When the anatomic terms *anterior* and *posterior* are used in this chapter, they pertain to relationships in the human, standing erect. Similarly, *superior* and *inferior* mean toward the head and toward the feet, respectively. We will adopt the convention that *right* and *left* (unqualified) indicate the subject's right-hand and left-hand sides. However, when describing the location of structures within an image, *image right* and *image left* are used to denote relationships without reference to the subject's right or left side.

The organization and content of this chapter are based in part on a recent Pancreapedia chapter on pancreatic anatomy and histology [1].

Gross Anatomy

The pancreas (meaning all flesh) lies in the posterior portion of the upper abdomen behind the stomach. It is largely retroperitoneal and is covered by peritoneum on the anterior surface of the head and body and is surrounded by fat in this region. It is customary to refer to various portions of the pancreas as head, body, and tail. The head abuts the C-shaped second portion of the duodenum in the right upper quadrant of the abdomen. The tail emerges into the peritoneal cavity (covered by peritoneal serosa) and extends to the hilum of the spleen in the left upper quadrant. The pancreas weighs about 100 g and is 14–25 cm long [2]. Figure 2.1 shows a human pancreas that has been dissected to isolate it from surrounding fat and adjacent organs and Fig. 2.2 depicts a pancreas that has been dissected to reveal the pancreatic and common bile ducts.

The pancreas is intimately associated with several adjacent organs. Relationships of the pancreas to surrounding organs and structures are depicted in Figs 2.3, 2.4, 2.5, and 2.6. As noted above, as the duodenum exits the stomach it loops around the head of the pancreas. The tail of the pancreas lies near the hilum of the spleen. The body of the pancreas lies posterior to the pyloric region of the stomach.

The portion of the pancreas that lies anterior to the aorta is somewhat thinner in the anterior–posterior axis than the adjacent portions of the head and body of the pancreas. This region is designated as the neck and marks the junction of the head and body (Fig. 2.1b). The proximity of the neck of the pancreas to major blood vessels posteriorly, including the superior mesenteric artery, superior mesenteric-portal vein, inferior vena cava, and aorta, limits the option for a wide surgical margin during pancreatectomy (Fig. 2.5).

There is no anatomic landmark for the junction between the body and tail of the pancreas [3]. Hellman defined the tail as one-fourth of the pancreas from the

The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

Figure 2.1 This pancreas, from the autopsy of a 47-year-old woman, measures 22.5 cm in length and has been dissected free of most surrounding fat. (a) Anterior view with the head at image left. (b) Posterior view. A thin layer of fat (translucent yellow) covers a portion of the head at image right. Note the thin neck region just to the left of the head. (c) Cut surface of a transection through the head of the pancreas showing the lobular pancreatic parenchyma. *Source:* Dissection and photo by Catherine M. Nicka, MD.

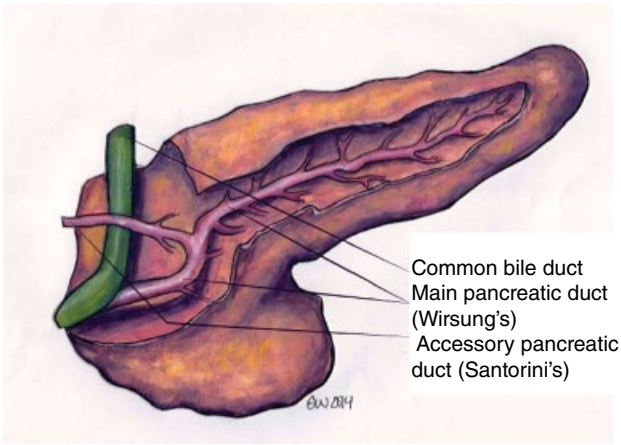

Figure 2.2 A pancreas dissected to reveal the pancreatic ducts and common bile duct as it traverses the head of the pancreas, ending as it joins the main pancreatic duct near the ampulla of Vater. Interlobular branches of the main duct are depicted but smaller ducts (intralobular ducts and ductules) are not. Eponyms identify the anatomist, embryologist, or physician who is credited with first describing a structure. Wirsung and Santorini were such scientists. *Source:* Drawing by Emily Weber.

tip of the tail to the head [4] whereas Wittingen and Frey defined the junction between the body and tail as the point where the gland sharply narrows [5]. This point is difficult to define in some pancreases.

The common bile duct passes behind the upper portion of the head and then runs through the pancreas to join the main duct in the duodenal wall (Figs 2.2, 2.5, and 2.7b). The accessory pancreatic duct drains into the duodenum at the minor papilla in most humans, and the main pancreatic duct enters the duodenum at the major papilla (Fig. 2.3). See Chapter 3 for discussion of pancreas divisum and other anomalies with possible clinical significance.

Typically, the bile duct and main pancreatic duct join into a "common channel" referring to the fused portion of the bile and pancreatic ducts proximal to its entry into the duodenal lumen. The common channel varies in length from a few millimeters to about 1 cm. A long common channel due to junction of the bile and pancreatic ducts proximal to the duodenal wall is regarded as an anomaly [6]. Less often, there is no common channel because the

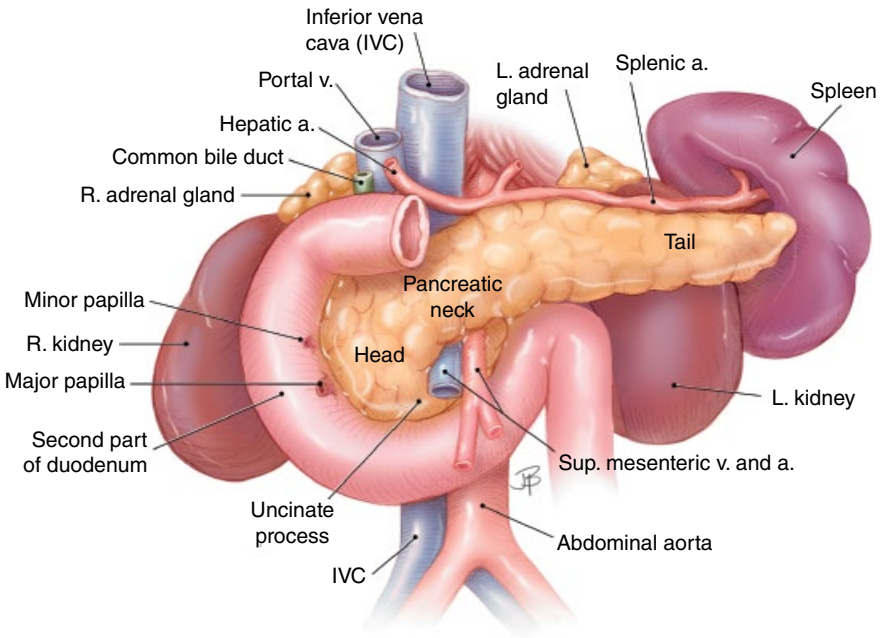

Figure 2.3 Relationships of the pancreas to surrounding organs. This two-dimensional drawing depicts structures that lie in several different planes; for example, the kidneys lie lateral to the spine and posterior to the pancreas. The superior mesenteric artery and vein lie anterior to the aorta and inferior vena cava. *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

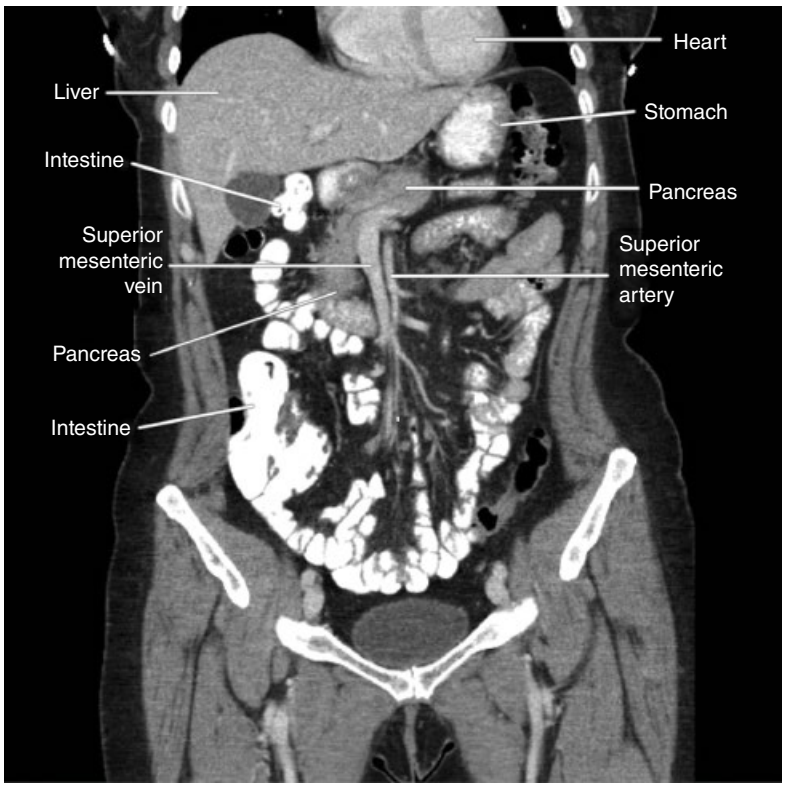

Figure 2.4 Frontal CT scan in the plane of the head and body of the pancreas. The technology dictates that all structures shown lie in the same plane. The tail of the pancreas is not shown because it lies posterior to the depicted plane. *Source:* Image provided by Jason Ferreira.

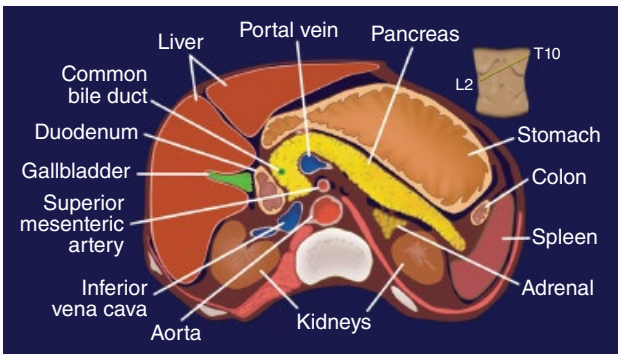

Figure 2.5 Diagram of the upper abdomen at the level of the pancreas based on a CT scan. Note that the plane of the image is angled upward on the left as indicated, upper image right. The vertebral column is unlabeled bottom center. *Source:* Image contributed by Fred Gorelick.

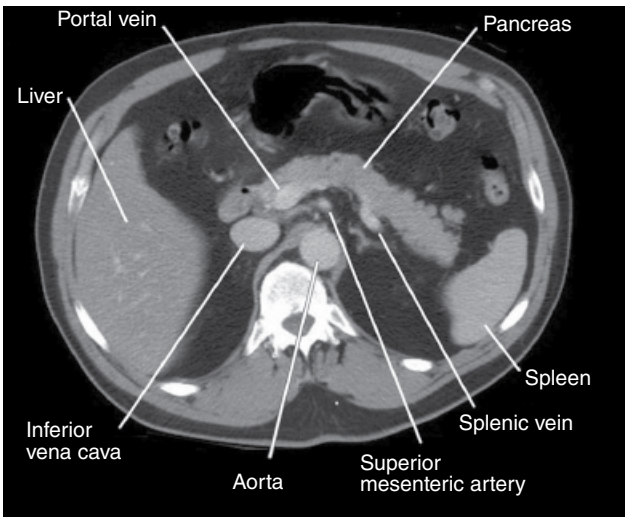

Figure 2.6 Axial CT scan of the upper abdomen at the level of the pancreas. This scan is oriented with the abdominal wall at the top and the spine and muscles of the back at the bottom as viewed from below. Key structures are labeled. *Source:* Image provided by Jason Ferreira.

ducts open separately into the duodenum at the major ampulla. The common channel has received much attention because stones in the biliary tract (gallstones) may lodge in the common channel, causing obstruction of both pancreatic and biliary duct systems. Such an obstruction is frequently the cause of acute pancreatitis.

The arterial blood supply to the pancreas is through branches of the celiac trunk and the superior mesenteric artery (Fig. 2.7). Both arise from the abdominal aorta and have multiple branches that supply several organs. Anastomosis of their branches provides collateral circulation that generally assures a secure arterial blood supply to the pancreas. Most of the arteries are accompanied by veins that drain into the superior mesenteric, portal, and splenic veins as they pass behind the pancreas, as shown in Fig. 2.7b. The superior mesenteric vein becomes the portal vein when it joins the splenic vein (Fig. 2.7b).

The typical locations of lymph nodes surrounding the pancreas are shown in Fig. 2.8. There is significant individual variation in the location of lymph nodes, so the locations shown are a generalization. In general, two systems of lymph nodes drain the organ: one surrounding the edges of the pancreas (Fig. 2.8a), and the other associated with the anterior surface of the aorta and celiac trunk (Fig. 2.8b). Various node groups have been assigned "station numbers" that may be used to designate their location [1,2,7]. These are rarely used in Western literature and are not illustrated here. Lymphatics arise in the interstitium of the pancreas and course with blood vessels and nerves draining to the nodes and then to the thoracic duct.

A rich plexus of autonomic nerves lies behind the head, neck, and body of the pancreas connecting to the celiac ganglia that lie along the aorta (Fig. 2.9).

Histology and Ultrastructure

Overview

The exocrine pancreas is a network of tubules composed of acinar and duct cells that synthesize, secrete, and carry digestive enzymes into the intestine. The small tubules in the lobular tissue are largely composed of acinar cells. The acinar tubules connect to the smallest terminal portions of the duct system that are commonly called ductules, although intercalated duct has also been used to denote these components of the duct system. In this chapter, we will use *ductule* to denote these small terminal portions of the duct system that link the acinar tubules to larger ducts, including small intralobular ducts. At the level of gross anatomy, the acinar tubules, ductules, and small ducts appear as solid lobular tissue as seen in Fig. 2.1c. The following descriptions include both histology and ultrastructure for each major cell type.

Acinar Tissue

An acinus is a cluster of acinar cells that contain zymogen granules, the storage compartment for pancreatic digestive enzymes. For many years, it was considered that acinar tissue was composed of clusters of acini arranged like grapes at the ends of a branching duct system. However, more recent studies have demonstrated that pancreatic acini and tubules are arranged as an anastomosing tubular network [8]. The duct cells at the interface of acinar tubules and ductules are referred to as centroacinar cells and these cells may also be