

# Contents

<i>Contributors</i>	<i>ix</i>
<i>Preface</i>	<i>xiii</i>
<b>1. Notch signaling pathway in pancreatic tumorigenesis</b>	<b>1</b>
Wen-Cheng Chung and Keli Xu	
1. Introduction	2
2. Roles of Notch signaling in pancreatic ductal adenocarcinoma (PDAC)	6
3. Roles of Notch signaling in pancreatic neuroendocrine tumor (PNET)	25
4. Perspective	26
References	30
<b>2. Deciphering epithelial-to-mesenchymal transition in pancreatic cancer</b>	<b>37</b>
Creighton Friend, Parash Parajuli, Mohammed S. Razzaque, and Azeddine Atfi	
1. Significance	39
2. Introduction	40
3. Defining EMT and its molecular mechanisms and pathways	41
4. The role of EMT in promoting tumor development and metastasis	47
5. EMT influences the initiation, survival, and metastasis of pancreatic cancer	50
6. EMT as a therapeutic target for PDAC	60
7. Perspectives, challenges and future directions	64
Glossary	66
References	66
<b>3. In vivo models of pancreatic ductal adenocarcinoma</b>	<b>75</b>
Vignesh Vudatha, Kelly M. Herremans, Devon C. Freudenberger, Christopher Liu, and Jose G. Trevino	
1. Introduction	76
2. Spontaneous tumor models	79
3. Implantation models	96
4. Conclusions	104
Acknowledgments/Funding	104
References	104

<b>4. Interplay between MAP kinases and tumor microenvironment: Opportunity for immunotherapy in pancreatic cancer</b>	<b>113</b>
Sandeep Kumar, Sunil Kumar Singh, Piush Srivastava, Swathi Suresh, Basabi Rana, and Ajay Rana	
1. Introduction	114
2. Current treatments and drug resistance in pancreatic cancer	116
3. Pancreatic cancer TME and drug resistance	120
4. Expression and function of ICPs in pancreatic cancer	122
5. MAP4K → MAP3K → MAP2K → MAPK signaling module in pancreatic cancer	124
6. Targeting ICPs and MAPKs in pancreatic cancer	130
7. Summary	134
Acknowledgments	134
Author contributions	134
Competing interests	134
References	134
<b>5. Targeting KRAS in pancreatic cancer: Emerging therapeutic strategies</b>	<b>145</b>
Sajid Khan, Vivekananda Budamagunta, and Daohong Zhou	
1. Introduction	148
2. Biochemistry of KRAS	150
3. KRAS signaling pathways	150
4. KRAS mutations in PC	152
5. Emerging KRAS-targeted therapies	154
6. KRAS-targeted combination strategies	161
7. KRAS and cellular senescence	167
8. Challenges for effectively targeting KRAS in PC	173
9. Future perspectives and conclusions	175
Acknowledgments	176
Conflict of interest	177
References	177
<b>6. Racial disparities in pancreatic cancer clinical trials: Defining the problem and identifying solutions</b>	<b>185</b>
Allison N. Martin and Rebecca A. Snyder	
1. Introduction	186
2. Racial implicit bias as a barrier to enrollment	187
3. Access to trials and study design barriers	189

4. Impediments to clinical trial recruitment	191
5. Increasing pancreatic cancer trial diversity—A way forward	195
References	198
<b>7. Tumor heterogeneity: An oncogenic driver of PDAC progression and therapy resistance under stress conditions</b>	<b>203</b>
Antônio M. Palma, Vignesh Vudatha, Maria Leonor Peixoto, and Esha Madan	
1. Introduction	204
2. PDAC tumoral heterogeneity	208
3. PDAC adapts to grow in stress conditions	215
4. PDAC therapeutic options	229
5. Tumor heterogeneity contributes to treatment resistance	233
6. Conclusion	236
Acknowledgments	237
References	237
<b>8. Oncogenic signaling pathways in pancreatic ductal adenocarcinoma</b>	<b>251</b>
Rahul Agrawal and Kedar Nath Natarajan	
1. Introduction	252
2. Oncogenic signaling pathways in PDAC	254
3. MYC: Master regulator of PDAC aggressiveness	263
4. Elucidation of PDAC heterogeneity through single cell genomic approaches	267
5. Conclusions and future directions	272
Acknowledgments	273
References	273
<b>9. Chemoresistance in pancreatic ductal adenocarcinoma: Overcoming resistance to therapy</b>	<b>285</b>
Praveen Bhoopathi, Padmanabhan Mannangatti, Swadesh K. Das, Paul B. Fisher, and Luni Emdad	
1. Introduction	289
2. PDAC treatment strategies and chemoresistance	290
3. Methods to predict PDAC chemoresistance	291
4. Role of EMT in PDAC chemoresistance	293
5. Role of non-coding RNAs in PDAC chemoresistance	294

6. Role of the microenvironment in PDAC chemoresistance	298
7. Role of nucleoside transporters in PDAC chemoresistance	302
8. Role of autophagy in PDAC chemoresistance	306
9. Role of metabolism in PDAC chemoresistance	307
10. Role of extracellular vesicles (EV) and exosomes in PDAC chemoresistance	310
11. Role of signaling pathways in PDAC chemoresistance	311
12. Role of pancreatic tumor microbiome in PDAC chemoresistance	317
13. Future directions: Methods to sensitize pancreatic cancer to therapy	320
Acknowledgments	323
Conflict of interest	323
References	323

**10. Tumor microenvironment interactions with cancer stem cells in pancreatic ductal adenocarcinoma** **343**

Antônio M. Palma, Grace G. Bushnell, Max S. Wicha, and Rajan Gogna

1. Introduction	344
2. Clinical issues in pancreatic ductal adenocarcinoma	345
3. Cancer stem cells in pancreatic ductal adenocarcinoma	346
4. Tumor microenvironment in pancreatic cancer	351
5. Metastasis in pancreatic ductal adenocarcinoma	360
6. Conclusion	363
Acknowledgments	364
References	364