## **Table of Contents**

	Preface — V
	List of contributing authors —— VII
	Table of Contents —— XI
	Introduction to Volume 2: Kallikrein-related Peptidases. Novel Cancer-
	related Biomarkers —— 1
	Bibliography —— 2
1	Pathophysiology of Kallikrein-related Peptidases in Lung Cancer — 3
1.1	Introduction —— 3
1.2	Expression pattern of KLKs in the normal lung —— 3
1.3	KLKs in lung cancer —— 6
1.4	Regulation of KLKs in the lung —— 8
1.4.1	Control of gene transcription —— 8
1.4.2	Post-translational control of KLK function —— 10
1.5	Potential KLK targets in the lung —— 11
1.5.1	Substrates involved in host defense —— 11
1.5.2	Cytokines and growth factors —— 13
1.5.3	Pericellular and membrane-associated substrates —— 16
1.6	Conclusion —— 18
	Acknowledgements —— 19
	Bibliography —— 19
2	Clinical Relevance of Kallikrein-related Peptidases in Gastric and Colorectal
	Cancer —— 27
2.1	Introduction —— 27
2.2	Features of gastric and colorectal cancers — 27
2.3	Established biomarkers in gastric and colorectal cancer — 28
2.4	KLKs: novel biomarkers in gastric and colorectal cancer — 30
2.4.1	Review of the clinical relevance of KLK expression in gastric
	cancer — 31
2.4.2	Review of the clinical relevance of KLK expression in colorectal
	cancer — 35
2.5	Proteolytic activity of KLKs in gastric/colorectal cancers — 38
2.6	Effect of KLK expression on cell regulation and metabolic
	pathways —— 39
2.7	Conclusion —— 40
	Bibliography —— 40

3	Pathophysiology of Kallikrein-related Peptidases in Head and Neck
3.1	Cancer —— 45 Introduction —— 45
3.2	A murine orthotopic xenograft model using urinary-type plasminogen activator receptor (uPAR) overexpressing OSCC cells mimics aggressive human OSCC —— 47
3.3	Expression of KLKs in OSCC —— 49
3.4	Potential functional role of KLK5 in regulating cell-cell junctional integrity in OSCC —— 50
3.5	Conclusions and future directions —— 54
	Acknowledgement — 55
	Bibliography —— 55
4	PSA (Prostate-Specific Antigen) and other Kallikrein-related Peptidases in
	Prostate Cancer —— 61
4.1	Introduction —— 61
4.2	The role of KLKs in prostate cancer diagnosis, prognosis and monitoring —— 61
4.2.1	PSA — 61
4.2.2	KLK2 — 65
4.2.3	Other KLKs — 65
4.2.4	Splicing and polymorphic variants —— 66
4.3	Potential functional roles of KLKs in prostate cancer —— 66
4.3.1	Sustaining proliferative signaling and evading growth
7.5.1	suppressors — 67
4.3.2	Resisting cell death —— 69
4.3.3	Inducing angiogenesis 69
4.3.4	Activating invasion and metastasis —— 71
4.3.5	Concerns about biological studies — 72
4.4	Conclusions and outlook —— 72
	Bibliography —— 73
5	Cellular Model Systems to Study the Tumor Biological Role of Kallikrein-
	related Peptidases in Ovarian and Prostate Cancer —— 83
5.1	Introduction 83
5.2	Development of cellular model systems in cancer research —— 83
5.3	Traditional 3D cellular models commonly used in both ovarian and
	prostate cancers —— 84
5.3.1	Soft agar colony assay —— 84
5.3.2	3D-Matrigel™ —— 85
5.4	Novel 3D cellular models in ovarian cancer biology —— 86
5.4.1	Ovarian cancer — 86

5.4.2	3D-suspension model to mimic ascites suspension —— 86
5.4.3	In vitro models for ovarian cancer invasion into the peritoneal
	membrane —— 90
5.4.4	The role of 3D-collagen I matrix in ovarian cancer cell behavior —— 92
5.4.5	A 3D-organotypic model to mimic ovarian cancer metastasis —— 92
5.4.6	Bioengineered 3D culture systems for ovarian cancer — 93
5.5	Cellular models in prostate cancer —— 95
5.5.1	Prostate cancer —— 95
5.5.2	3D-suspension models for prostate cancer growth and
	metastasis —— 97
5.5.3	In vitro models for prostate cancer angiogenesis —— 98
5.5.4	Bioengineered 3D culture systems for prostate cancer growth and
	metastasis —— 98
5.6	Challenges and future direction —— 102
	Acknowledgment —— 102
	Bibliography —— 103
6	Clinical Relevance of Kallikrein-related Peptidases in Breast
	Cancer —— 111
6.1	Introduction —— 111
6.2	Expression of KLKs in normal breast tissue —— 113
6.3	Clinical relevance of KLKs in breast cancer —— 113
6.4	Hormonal regulation of KLKs in breast cancer —— 127
6.5	Tumor suppressor role of KLKs in breast cancer —— 129
6.6	DNA-methylation of KLKs as the basis of KLK downregulation in breast
	cancer —— 130
6.7	Conclusions —— 132
	Bibliography 132
7	Clinical Relevance of Kallikrein-related Peptidases in Ovarian
	Cancer —— 145
7.1	Introduction —— 145
7.2	Ovarian cancer pathology, diagnosis, and therapy —— 145
7.3	KLKs in ovarian cancer 147
7.3.1	Circulating KLKs as screening/diagnostic and/or prognostic ovarian
	cancer biomarkers —— 148
7.3.2	Serum ovarian cancer biomarkers CA125 and KLKs —— 155
7.3.3	Tumor tissue-associated KLKs as prognostic ovarian cancer
	biomarkers —— 156
7.4	Tumor tissue-associated and blood-borne KLKs as predictive ovarian cancer biomarkers —— 157
7.5	Conclusion — 158

8

8.1

8.1.1

Abbreviations —— 159 Bibliography —— 160

Kidney and Other Cancers —— 167 Introduction —— 167

8.1.2	KLK dysregulation in kidney cancer —— 168
8.2	microRNAs (miRNA) —— 169
8.2.1	Biogenesis —— 169
8.2.2	miRNAs and cancer —— 170
8.2.3	miRNA dysregulation in renal cell carcinoma —— 170
8.2.4	The miRNA-KLK interaction —— 171
8.3	miRNA control of KLK expression in renal cell carcinoma —— 174
8.4	miRNA control of KLK expression in other cancers —— 175
8.5	Conclusions and outlook —— 176
	Bibliography —— 177
9	Genomic Instability of the KLK-locus in Cancer —— 183
9.1	Introduction —— 183
9.2	Defining genomic instability —— 183
9.2.1	Defining CIN and its underlying mechanisms —— 184
9.2.2	Methods for detecting CIN —— 185
9.3	Chromosome 19 and the <i>KLK</i> locus in cancer —— 186
9.3.1	Chromosome 19 —— 186
9.3.2	The <i>KLK</i> locus and cancer —— 187
9.3.3	KLK sequence mutations and single nucleotide polymorphisms in cancer —— 188
9.3.4	KLK translocations — 189
9.3.5	Copy-number changes of the <i>KLK</i> locus —— 191
9.4	Closing remarks —— 193
	Bibliography —— 194
10	Kallikrein-related Peptidases as Biomarkers in Personalized Cancer
	Medicine —— 201
10.1	Introduction —— 201
10.2	The role of KLKs as cancer biomarkers for predicting and monitoring
	response to chemotherapy or endocrine therapy 204
10.2.1	Prostate cancer —— 206
10.2.2	Breast cancer — 207
10.2.3	Ovarian cancer —— 207

microRNAs: A New Control Mechanism for Kallikrein-related Peptidases in

KLK expression in normal kidney tissue — 167

10.3	Modulation of expression levels of <i>KLK</i> genes upon chemotherapy
	administration <i>in vitro</i> — 209
10.3.1	Prostate cancer cells —— 210
10.3.2	Gastric cancer cells 210
10.3.3	Breast cancer cells 211
10.3.4	The role of microRNAs (miRNAs) that target KLK expression and the methylation status of KLK genes in the <i>in vitro</i> response of cancer cells
	to chemotherapy —— 212
10.4	Conclusions and future directions —— 213
	Bibliography —— 214

Index —— 219