Table of Contents

1

Preface — V

	List of contributing authors — VII
	Table of Contents —— XI
	Introduction to Volume 1: Kallikrein-related Peptidases. Characterization, Regulation, and Interactions Within the Protease Web —— 1
	Bibliography —— 3
1	Genomic Structure of the <i>KLK</i> Locus —— 5
1.1	Introduction —— 5
1.2	Kallikreins in rodents — 6
1.2.1	The mouse kallikrein gene family —— 7
1.2.2	The rat kallikrein gene family —— 8
1.3	Characterization and sequence analysis of the human KLK
	gene locus — 9
1.3.1	Locus overview —— 9
1.3.2	Repeat elements and pleomorphism —— 11
1.4	Structural features of the human KLK genes and proteins —— 12
1.4.1	Common structural features —— 12
1.5	Sequence variations of human KLK genes —— 13
1.6	Regulation of <i>KLK</i> activity —— 14
1.6.1	At the mRNA level —— 14
1.6.2	Locus control of <i>KLK</i> expression —— 15
1.6.3	Epigenetic regulation of KLK gene expression —— 17
1.7	Isoforms and splice variants of human KLKs —— 18
1.8	Evolution of <i>KLKs</i> —— 21
	Bibliography —— 22
2	Single Nucleotide Polymorphisms in the Human KLK Locus and Their
	Implication in Various Diseases —— 31
2.1	Introduction —— 31
2.2	KLK SNPs – data-mining from SNPdb and 1000 Genomes — 32
2.3	Functional annotations using web-based prediction tools —— 34
2.4	Experimentally validated functional <i>KLK</i> SNPs —— 35
2.5	KLK SNP haplotypes and tagging —— 36
2.6	Malignant and non-malignant diseases and association with KLK SNPs —— 38
2.6.1	Association studies on high-risk variants in <i>KLK</i> genes — 39



2.6.2 2.7	Association studies on low-risk variants in <i>KLK</i> genes —— 39 Conclusions —— 71 Bibliography —— 71
3	Evolution of Kallikrein-related Peptidases —— 79
3.1	Introduction — 79
3.2	Basic elements of phylogenetic analysis —— 80
3.3	Evolutionary trends at the KLK locus — 80
3.4	Evolution of the KLK1-KLK4 sublocus —— 82
3.4.1	KLK2 and KLK3 originate from a duplicated segment containing both
	KLK1 and KLK15 — 82
3.4.2	A large number of <i>KLK1</i> tandem repeats in the house mouse —— 85
3.4.3	The rat KLK1 sublocus consists of 10 large repeats — 87
3.4.4	Four duplications of <i>KLK1</i> and <i>KLK15</i> in the dog —— 88
3.4.5	A large repeat containing <i>KLK4</i> in the horse —— 90
3.5	KLK genes in non-mammalian species —— 92
3.6	General conclusions and remarks on the evolution of KLK
	genes — 93
	Bibliograph y — 94
4	Structural Aspects of Kallikrein-related Peptidases —— 97
4.1	Introduction —— 97
4.2	Individual KLK structures —— 98
4.2.1	Tissue kallikrein (KLK1) —— 98
4.2.2	Prostate specific antigen (PSA/KLK3) —— 100
4.2.3	Prostase (KLK4) —— 101
4.2.4	Stratum corneum tryptic enzyme (SCTE/KLK5) —— 104
4.2.5	Myelencephalon-specific protease or neurosin (MSP/KLK6) —— 106
4.2.6	Stratum corneum chymotryptic enzyme (SCCE/KLK7) —— 108
4.2.7	Neuropsin (KLK8) —— 110
4.2.8	Other mammalian KLK structures —— 111
	Bibliography —— 112
5	Molecular Recognition Properties of Kallikrein-related Peptidases on
5.1	Synthetic and Endogenous Substrates —— 117
5.1 5.2	Synthetic and Endogenous Substrates —— 117 Introduction —— 117
5.1 5.2	Synthetic and Endogenous Substrates —— 117 Introduction —— 117 Substrate specificities of individual kallikrein-related
5.2	Synthetic and Endogenous Substrates —— 117 Introduction —— 117 Substrate specificities of individual kallikrein-related peptidases —— 121
5.2 5.2.1	Synthetic and Endogenous Substrates —— 117 Introduction —— 117 Substrate specificities of individual kallikrein-related peptidases —— 121 The classical kallikreins (KLK1, KLK2, KLK3) —— 121
5.2	Synthetic and Endogenous Substrates —— 117 Introduction —— 117 Substrate specificities of individual kallikrein-related peptidases —— 121

5.2.5	KLK9/KLK11/KLK15 —— 130
	Bibliography —— 132
6	Natural, Engineered and Synthetic Inhibitors of Kallikrein-related
	Peptidases —— 141
6.1	Introduction —— 141
6.2	KLK diversity —— 141
6.3	The KLK superfamily: Structure and catalytic mechanism —— 141
6.4	KLK inhibition: Rationale and mechanisms —— 143
6.5	Proteinaceous inhibitors —— 144
6.5.1	Kunitz domain inhibitors —— 144
6.5.2	Kazal domain inhibitors —— 146
6.5.3	Other canonical inhibitors —— 147
6.5.4	Serpins — 147
6.6	Naturally occurring small molecule kallikrein inhibitors —— 148
6.7	Engineered KLK Inhibitors —— 149
6.7.1	Approaches to inhibitor design —— 150
6.7.2	Pharmacological challenges for therapeutic inhibitors —— 150
6.7.3	Serpins — 150
6.7.4	Ecotin —— 151
6.7.5	Sunflower Trypsin Inhibitor (SFTI) —— 152
6.7.6	Warhead inhibitors —— 153
6.8	Conclusions and outlook —— 154
	Acknowledgements —— 154
	Bibliography 154
7	Kallikrein-related Peptidases as Pharmaceutical Targets —— 161
7.1	Introduction —— 161
7.2	KLK disease markers as potential therapeutic targets —— 162
7.3	KLKs in oncology —— 165
7.3.1	Prostate cancer —— 165
7.3.2	Ovarian and pancreatic cancer — 167
7.4	KLKs in inflammatory skin diseases —— 169
7.4.1	Kallikrein expressions and activities in skin —— 169
7.4.2	Netherton Syndrome as most relevant clinical model —— 170
7.4.3	Atopic dermatitis, the potential major indication for kallikrein
	targeting —— 171
7.4.4	Psoriasis and relevance of kallikreins —— 172
7.4.5	Other potential skin disorders with kallikrein involvement — 172
7.5	KLKs in neurological disorders —— 173
7.5.1	Alzheimer's disease and dementia —— 173

Multiple sclerosis (MS) —— 173

7.5.2

7.6	Kallikrein inhibitors to treat human diseases —— 174
7.6.1	Design of KLK inhibitors and clinical development —— 174
7.6.2	KLK inhibitors in oncology —— 176
7.6.3	KLK inhibitors in dermatology —— 179
7.7	Conclusions and Outlook —— 180
	Bibliography —— 181
8	Expression of Kallikrein-related Peptidases under (Patho-)Physiological
	Conditions — 187
8.1	Introduction —— 187
8.2	KLK expression in tissues and biological fluids under physiological conditions —— 188
8.2.1	KLKs in the central and peripheral nervous system — 188
8.2.2	KLKs in the female reproductive system —— 192
8.2.3	KLKs in the male reproductive system —— 196
8.2.4	Cellular distribution of KLKs in the gastrointestinal system — 198
8.2.5	KLKs in the skin and skin appendages —— 203
8.2.6	KLKs in the respiratory system — 207
8.2.7	KLKs in the urinary system —— 207
8.2.8	KLKs in lymphatic and endocrine organs (adrenal glands, thyroid gland,
	parathyroid glands, pituitary gland) —— 207
8.2.9	KLKs in the cardiovascular system —— 211
8.2.10	KLKs in the skeletomuscular system —— 211
8.3	Expression of KLKs in non-malignant diseases —— 212
8.3.1	Non-malignant diseases of the CNS —— 212
8.3.2	Inflammatory-related conditions —— 215
8.4	Expression of KLKs in cancer tissues —— 217
8.4.1	Cancers of the brain —— 222
8.4.2	Cancers of the female reproductive system —— 222
8.4.3	Cancers of the male reproductive system —— 223
8.4.4	Cancers of the gastrointestinal system —— 224
8.4.5	Cancers of the skin —— 225
8.4.6	Lung cancer —— 226
8.4.7	Cancers of the urinary system —— 226
8.5	Conclusion —— 227
	Abbreviations —— 227
	Bibliography —— 228
9	Kallikrein-related Peptidases within the Proteolytic Web —— 251
9.1	Introduction —— 251
9.2	KLKs as actors and targets during the initiation and amplification of
	extracellular proteolytic activity —— 252

9.2.1	The KLK-dependent KLK activome —— 252
9.2.2	Cross- and reciprocal activation of KLK and non-KLK proteases —— 256
9.2.3	Inactivation of protease inhibitors — 260
9.3	KLKs in the termination of proteolytic activity —— 260
9.3.1	Proteolytic inactivation of (non-)KLK proteases —— 260
9.3.2	Processing of the uPA receptor —— 261
9.3.3	Disarming of the proteinase-activated receptors —— 262
9.4	Conclusion — 263
	Bibliography —— 264
10	Kallikrein-Kinin Cascade: Bioregulation by Human Tissue Kallikrein 1
	(hK1, KLK1) —— 271
10.1	Discovery of classical (true) tissue kallikrein and kinins —— 271
10.2	Cellular localization —— 272
10.3	Genomics and molecular structure —— 273
10.4	Inhibitors of hK1 —— 276
10.5	Modulation of membrane receptors —— 277
10.6	Epigenetic regulation —— 277
10.7	Kinin receptors and signaling —— 278
10.7.1	Receptor subtypes — 278
10.7.2	Kinin receptor signaling —— 279
10.7.3	Regulation of kinin receptor signaling —— 280
10.8	Human disease —— 281
10.8.1	Hypertension and renal damage —— 281
10.8.2	Cardiac protection — 283
10.8.3	Inflammation and neutrophil function —— 283
10.8.4	Cancer —— 286
10.8.5	Angiogenesis — 286
10.9	Conclusion —— 287
	Abbreviations —— 288
	Bibliography —— 289
11	Role of KLK4 in Dental Enamel Formation —— 295
11.1	Introduction —— 295
11.2	Early studies implicated proteases in dental enamel formation —— 295
11.3	Investigations of enamel proteases discovered KLK4 —— 296
11.4	KLK4 and amelogenesis imperfecta —— 297
11.5	Klk4 ^{lacZ/lacZ} mice —— 297
11.6	Other enamel specific genes —— 302
11.7	Role of KLK4 in enamel formation —— 304
11.8	Conclusion — 307
	Bibliography —— 307

12	Kallikrein-related Peptidases and Semen —— 311
12.1	Introduction —— 311
12.2	Expression pattern and origin of seminal KLKs 312
12.3	Physiological function of seminal KLKs —— 312
12.3.1	Seminal coagulation and fibrinolytic balance — 312
12.3.2	Sperm motility —— 314
12.3.3	Reproductive immune interactions — 316
12.4	Proteolytic pathways of seminal KLKs —— 318
12.4.1	Role of seminal zinc —— 319
12.4.2	Role of seminal KLK inhibitors —— 319
12.4.3	Other inhibitory mechanisms of seminal KLKs —— 320
12.4.4	Seminal proteolytic activation cascade —— 321
12.5	Conclusions and outlook —— 322
	Abbreviations — 323
	Bibliography —— 323
13	Kallikrein-related Peptidases and Inhibitors of the Skin —— 329
13.1	Introduction —— 329
13.2	KLKs in the epidermis —— 331
13.3	Desquamation —— 332
13.4	Regulation of protease activity —— 333
13.4.1	KLK activation —— 333
13.4.2	KLK inhibitors —— 334
13.5	Skin disorders —— 337
13.6	Conclusions and outlook —— 340
	Bibliography —— 341
14	Physiological and Pathophysiological Roles of Kallikrein-related Peptidases
	in the Central Nervous System —— 349
14.1	Introduction —— 349
14.2	KLK expression and roles in CNS physiology —— 349
14.2.1	KLK expression in the CNS —— 349
14.2.2	Physiological roles of KLKs in the CNS —— 353
14.2.3	Pathophysiological roles of KLKs in the CNS —— 359
14.3	Conclusions and outlook —— 363
	Acknowledgements — 364
	Abbreviation —— 364
	Bibliography —— 364
15	Kallikrein-related Peptidases (KLKs), Proteinase-mediated Signaling and
	Proteinase-activated receptors (PARs) —— 373
15.1	Proteinases: shock troops of the innate immune response — 373

15.2	Multiple mechanisms for proteinase-mediated signaling —— 3/4
15.3	Proteinases and PAR-mediated signaling —— 376
15.4	Linking PARs to the KLKs: the prostate connection — 378
15.5	Proteolytic cascades, KLKs and the innate immune response — 379
15.6	KLKs, other serine proteinases, PARs and inflammation —— 379
15.7	KLKs, PARs and inflammation of the central nervous system and
	the skin 380
15.8	KLKs, PARs and cancer — 382
15.9	KLKs and PARs: Therapeutic targets for inflammatory diseases, cancer
	and other disorders —— 383
15.10	Blocking proteinase-mediated PAR activation: PAR-targeted blocking
	antibodies versus proteinase inhibitors — 387
15.11	Summary and outlook for the future —— 389
	Acknowledgements — 389
	Bibliography —— 390

Index — 399