Contents

List of Contributors ix

1 Matrix Metalloproteinases: From Structure to Function 1
Maciej J. Stawikowski and Gregg B. Fields

1.1 Introduction 1
1.2 Structures of MMPs 1
  1.2.1 General MMP structure and domain organization 1
  1.2.2 Catalytic domain 2
  1.2.3 Catalytic mechanism 3
  1.2.4 Fibronectin type II-like inserts 3
  1.2.5 Linker region 4
  1.2.6 Hemopexin-like domain 6
  1.2.7 Transmembrane domain and cytoplasmic tail 7
1.3 Overview of MMP substrate specificity 8
  1.3.1 ECM substrates 9
  1.3.2 Cell surface substrates 10
  1.3.3 Intracellular MMP targets 11
1.4 Selective mechanisms of action 13
  1.4.1 Collagenolysis 13
  1.4.2 Gelatinolysis 15
Acknowledgments 16
References 16

2 Dynamics and Mechanism of Substrate Recognition by Matrix Metalloproteases 23
Ivan E. Collier and Gregory I. Goldberg

2.1 Introduction 23
2.2 Conformational flexibility of MMPs is inexorably linked to collagen proteolysis 24
2.3 Dynamics of MMP-2 and MMP-9 interaction with gelatin 26
2.4 Surface diffusion: a common mechanism for substrate interaction adapted by MMP-2 and MMP-9 26
2.5 Dynamics of MMP interaction with collagen fibrils 28
2.6 Mechanism of interaction of MMP-1, MMP-2, MMP-9, and MMP-14 with collagen substrate involves surface diffusion 28
2.7 Mechanism of MMP-1 diffusion on native collagen fibrils 30
vi  Contents

2.8  Triple helical collagen cleavage – diffusion coupling 31
2.9  Conclusions 34
References 36

3  Matrix Metalloproteinases: From Structure to Function 41
Marco Fragai and Claudio Luchinat
3.1  Introduction 41
3.2  Classification and structural features 42
3.3  Catalytic mechanism 45
3.4  Intra- and inter-domain flexibility 47
3.5  Elastin and collagen degradation 47
References 54

4  Metzincin Modulators 61
Dmitriy Minond
4.1  Inhibitors 61
4.1.1  Antibodies: targeting beyond the active site 61
4.1.2  Peptide-based inhibitors 65
4.1.3  Small molecules: non-zinc binding exosite inhibitors 68
4.1.4  Protein-based inhibitors 78
Summary and future directions 80
References 81

5  Therapeutics Targeting Matrix Metalloproteinases 85
Jillian Cathcart, Ashleigh Pulkoski-Gross, Stanley Zucker, and Jian Cao
5.1  Introduction 85
5.2  Peptidomimetic MMP inhibitors 86
5.3  Structure-based MMPI drug design 87
5.4  Mechanism-based MMPI design 89
5.5  Allosteric MMPI design 90
5.6  Macromolecular MMP inhibitors 91
5.7  Chemically-modified tetracyclines 93
5.8  Alternative approaches 94
5.9  MMPs as anti-targets 95
5.10  Conclusions 97
References 98

6  Matrix Metalloproteinase Modification of Extracellular Matrix-Mediated Signaling 103
Howard C. Crawford and M. Sharon Stack
6.1  Introduction 103
6.2  The extracellular matrix as a source for signaling ligands 104
6.3  ECM and mechanosensory signal transduction 106
6.4  Matrix remodeling and modification of mechano-sensory signaling 108
6.5  Conclusions and future directions 109
References 109
7 Meprin and ADAM Metalloproteases: Two Sides of the Same Coin? 115
Christoph Becker-Pauly and Stefan Rose-John

7.1 Introduction 115
7.2 Meprin metalloproteases 116
7.3 Structure of meprin α and meprin β 116
7.4 Proteomics for the identification of meprin substrates 118
7.5 Meprins in health and disease 118
7.6 Proteolytic back-and-forth of meprins and ADAMs 119
7.7 Collagen fibril formation 119
7.8 Angiogenesis and cancer 120
7.9 Inflammation 121
7.10 ADAM Proteases 121
7.11 The ADAM family of proteases 123
7.12 Orchestration of different pathways by ADAM17 123
7.13 Regulation of ADAM17 activity 123
7.14 Role of ADAM17 in vivo 125
7.15 Role of ADAM17 in humans 125
References 126

8 Subtracting Matrix Out of the Equation: New Key Roles of Matrix Metalloproteinases in Innate Immunity and Disease 131
Antoine Dufour and Christopher M. Overall

8.1 The tale of a frog’s tail 131
8.2 The MMP family 132
8.3 Making the cut as immune regulators 133
8.4 Enter the “omics” era: genomics, proteomics and degradomics 137
8.5 ECM versus non-ECM MMP substrates 138
8.6 Moonlighting protein substrates: intracellular proteins cleaved outside the cell 142
8.7 Intracellular protein substrates cleaved inside the cell by MMPs 143
8.8 Non-proteolytic roles of MMPs: missed in the myth? 145
8.9 The fairy tail of a frog has an unexpected ending 149
Acknowledgements 149
References 149

9 MMPs: From Genomics to Degradomics 153
Barbara Grünwald, Pascal Schlage, Achim Krüger, and Ulrich auf dem Keller

9.1 Introduction 153
9.1.1 Genomics: general aspects 154
9.1.2 The genomics approach to MMP function in cancer 155
9.1.3 Taking first steps towards MMP inhibition in cancer therapy 156
9.1.4 Lessons from the failure of unselective MMP inhibition 157
9.1.5 Limitations of the genomic approach to MMP function 160
9.1.6 Approaching proteolysis as a system 161
<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.2 Degradomics – An Overview</td>
</tr>
<tr>
<td>9.2.1 Global assessment of MMP expression and activity</td>
</tr>
<tr>
<td>9.2.2 Defining MMP active site specificity</td>
</tr>
<tr>
<td>9.2.3 MMP substrate degradomics</td>
</tr>
<tr>
<td>9.2.4 Targeted degradomics</td>
</tr>
<tr>
<td>9.2.5 Data integration and repositories</td>
</tr>
<tr>
<td>9.3 Conclusions</td>
</tr>
<tr>
<td>Acknowledgments</td>
</tr>
<tr>
<td>References</td>
</tr>
<tr>
<td>10 MMPs in Biology and Medicine</td>
</tr>
<tr>
<td>Di Jia, Roopali Roy, and Marsha A. Moses</td>
</tr>
<tr>
<td>10.1 Introduction</td>
</tr>
<tr>
<td>10.2 Functional roles of MMPs and ADAMs</td>
</tr>
<tr>
<td>10.2.1 ECM remodeling</td>
</tr>
<tr>
<td>10.2.2 Processing of growth factors and receptors</td>
</tr>
<tr>
<td>10.2.3 Modulation of cell migration, invasion, proliferation, and epithelial to mesenchymal transition (EMT)</td>
</tr>
<tr>
<td>10.2.4 Regulation of angiogenesis</td>
</tr>
<tr>
<td>10.3 MMPs as diagnostic and prognostic biomarkers of cancer</td>
</tr>
<tr>
<td>10.3.1 Breast cancer</td>
</tr>
<tr>
<td>10.3.2 Prostate cancer</td>
</tr>
<tr>
<td>10.3.3 Lung cancer</td>
</tr>
<tr>
<td>10.3.4 Pancreatic cancer</td>
</tr>
<tr>
<td>10.3.5 Ovarian cancer</td>
</tr>
<tr>
<td>10.4 MMPs/ADAMs as diagnostic and prognostic biomarkers for non-neoplastic diseases</td>
</tr>
<tr>
<td>10.4.1 Cardiovascular diseases</td>
</tr>
<tr>
<td>10.4.2 Endometriosis</td>
</tr>
<tr>
<td>10.4.3 Preeclampsia</td>
</tr>
<tr>
<td>10.4.4 Arthritis</td>
</tr>
<tr>
<td>10.5 MMPs as biomarkers of therapeutic efficacy</td>
</tr>
<tr>
<td>10.6 MMP-specific molecular imaging for noninvasive disease detection</td>
</tr>
<tr>
<td>10.7 Conclusions</td>
</tr>
<tr>
<td>Acknowledgments</td>
</tr>
<tr>
<td>References</td>
</tr>
<tr>
<td>Index</td>
</tr>
</tbody>
</table>