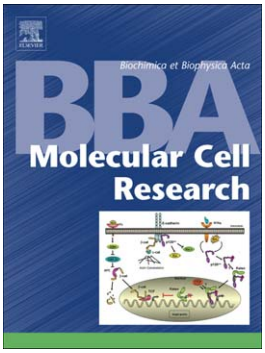

Selective Small-Molecule Inhibitors as Chemical Tools to Define the Roles of Matrix Metalloproteinases in Disease

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PII: S0167-4889(17)30105-2
DOI: doi:10.1016/j.bbamcr.2017.04.011
Reference: BBAMCR 18080

To appear in: *BBA - Molecular Cell Research*

Received date: 7 February 2017
Revised date: 15 April 2017
Accepted date: 17 April 2017

Please cite this article as: Jayda E. Meisel, Mayland Chang, Selective Small-Molecule Inhibitors as Chemical Tools to Define the Roles of Matrix Metalloproteinases in Disease, *BBA - Molecular Cell Research* (2017), doi:10.1016/j.bbamcr.2017.04.011

Title. Selective Small-Molecule Inhibitors as Chemical Tools to Define the Roles of Matrix Metalloproteinases in Disease

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Keywords. Matrix metalloproteinases; gelatinases; thiiranes; ND-322; ND-336; MMP roles

Abstract. The focus of this article is to highlight novel inhibitors and current examples where the use of selective small-molecule inhibitors has been critical in defining the roles of matrix metalloproteinases (MMPs) in disease. Selective small-molecule inhibitors are surgical chemical tools that can inhibit the targeted enzyme; they are the method of choice to ascertain the roles of MMPs and complement studies with knockout animals. This strategy can identify targets for therapeutic development as exemplified by the use of selective small-molecule MMP inhibitors in diabetic wound healing, spinal cord injury, stroke, traumatic brain injury, cancer metastasis, and viral infection.

Introduction. Matrix metalloproteinases (MMPs) are a family of over 26 structurally similar proteinases that possess proteolytic activity towards components of the extracellular matrix. Classification of MMPs has historically proceeded by identification of their endogenous substrate preference. For example, MMPs demonstrating preference for collagen are classified as collagenases, and those that preferentially process gelatin are gelatinases. Proteinases related to the MMP family include the ADAMs (a disintegrin and metalloproteinases), ADAMs with thrombospondin motifs (ADAMTS), and membrane-bound MMPs (MT-MMPs). These proteinases contain a zinc ion in the active site and consist of a signal peptide domain, a propeptide domain containing a conserved cysteine switch motif (Pro-Arg-Cys-Gly-Xxx-Pro-Asp), and a catalytic domain.[1] The active site of MMPs contains the common sequence motif His-Glu-Xxx-Gly-His-Xxx-Xxx-Gly-Xxx-Xxx-His, where the three histidines coordinate the catalytic zinc.[2] The gelatinases (MMP-2 and MMP-9) have an additional fibronectin-like domain within the catalytic region.[3]

MMP expression and regulation is multifaceted. MMPs are expressed from cells as inactive zymogens (proenzymes) that require removal of the prodomain for activation. The cysteine of the cysteine switch motif interacts with the zinc, blocking the active site and maintaining the pro-MMP in its inactive zymogen form.[4] The pro-MMP can be activated by other MMPs (for example, MMP-14 can activate MMP-2)[5] and other proteinases (for example, protein C and thrombin also activate MMP-2)[6,7]. Once activated, MMPs are further regulated by non-covalent binding with endogenous tissue inhibitors of matrix metalloproteinases (TIMPs) of which there are four isoforms. Over 130 three-dimensional structures for MMPs exist; a comprehensive list has been compiled recently by Aureli *et al.*[8] Methodologies to delineate MMP culprits in disease pathology have significant limitations primarily because of the complex nature of the regulation of this class of proteinases. Existing methods to identify MMPs in human tissue include genomic techniques to measure mRNA, immunoassays, activity-based protein profiling such as TAPI-2, gelatin zymography and *in situ* zymography.[9] These methods, except for activity-based profiling, cannot differentiate between TIMP-complexed MMPs (inactive) and active MMPs, which is the form relevant in pathogenesis or physiology. This makes the