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Matrix metalloproteinases (MMPs) in health and disease: an overview

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1. ABSTRACT

Matrix metalloproteinases (MMPs) are members of an enzyme family that require a zinc ion in their active site for catalytic activity. MMPs are critical for maintaining tissue allostasis. MMPs are active at neutral pH and can therefore catalyze the normal turnover of extracellular matrix (ECM) macromolecules such as the interstitial and basement membrane collagens, proteoglycans such as aggrecan, decorin, biglycan, fibromodulin and versican as well as accessory ECM proteins such as fibronectin. Members of the MMP family include the "classical" MMPs, the membrane-bound MMPs (MT-MMPs) the ADAMs (a disintegrin and metalloproteinase; adamlysins) and the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motif). There are more than 20 members in the MMP and ADAMTS family including the collagenases, gelatinases, stromelysins, some elastases and aggrecanases. Adamlysins are membrane-bound MMPs that also degrade aggrecan, but more importantly, one ADAM family member (i.e.ADAM-17) is a tumor necrosis factor-alpha (TNF-alpha)-converting enzyme (TACE) that activates pro-TNF-alpha. Most of the MMPs are synthesized as inactive latent enzymes. Conversion to the active enzyme is generally mediated by activator systems that include plasminogen activator or the pro-hormone convertase, furin. MMP activity is regulated by a group of endogenous proteins, called, tissue inhibitor of metalloproteinases (TIMPs) that bind to active and alternative sites of the activated MMP. Significant advances have occurred in the understanding of the regulation of MMPs, ADAMs and ADAMTSs gene expression. In addition, development of MMP inhibitors to study MMP structure/function relationships spawned many studies to determine the effectiveness of MMP inhibitors in regulating abnormal connective tissue turnover. In addition, development of MMP null mice carrying specific MMP deletions has provided an opportunity to explore the role of MMPs in normal development as well as in such diverse conditions and diseases as skeletal dysplasias, coronary artery and heart disease, arthritis, cancer, and brain disorders.

2. INTRODUCTION

The critical role played by matrix metalloproteinases (MMPs) in connective tissue turnover gained prominence during the past 25 years as a result of the commitment of many laboratories world-wide to understand the mechanism(s) by which MMPs mediated synovial joint inflammation as well as aberrant cartilage and bone extracellular matrix (ECM) turnover in the arthritides (1-5). During this period it became quite evident that the "classical" MMPs as well as other newly discovered members of the MMP enzyme family also played prominent roles in epiphyseal cartilage dysplasias, cancer metastasis, heart failure and cerebral ischemia (6-9). Molecular pathways critical to the regulation of MMP gene transcription as well as MMP synthesis and activation of pro-MMPs during normal development led to the discovery of endogenous inhibitors of MMP activity (4) and the development of synthetic MMP inhibitors (10) that could be employed to study their effectiveness in regulating abnormal ECM turnover in animal models of disease. Intracellular signaling pathways involving stress-activated protein kinases and tyrosine-receptor protein kinases that regulate MMP gene expression after cytokine, chemokine or growth factor activation have also been uncovered (11). It can now be hypothesized that experimental manipulation of intracellular signaling pathways may be feasible for devising novel therapeutic strategies for treating skeletal dysplasias, arthritis, metastasis, arteriosclerosis and stroke. This special issue of the *Encyclopedia of Bioscience*, entitled, "Matrix Metalloproteinases in Health and Disease" addresses the fundamental concepts underlying the role played by MMPs in embryonic development as well as in abnormalities of the growth plate, in heart failure, in arthritic synovial joints, in cancer, and ischemic brain injury. It is proposed that novel medical strategies will emerge from gaining additional knowledge about the cellular mechanisms that regulate MMP activity in health and disease.

3. REGULATION AND FUNCTION OF MMPs

3.1. Regulation of MMP synthesis

MMP gene expression is regulated principally by transcription (12). Post-transcriptional regulation exemplified by alterations in MMP mRNA stability can also modulate MMP synthesis (13, 14). These cellular processes are responsible for up-regulation (positive regulation) or down-regulation (negative regulation) of MMP synthesis. Arturo Mancini and John A. Di Battista (McGill University, Montréal, Canada) review the pertinent mechanisms that regulate MMP transcription in response to cytokines, chemokines, growth factors, bacterial endotoxin, phorbol esters, hormonal stress and oncogenic transformation as well as those events activated by cell to cell and cell to ECM interactions that modulate MMP gene expression. A central theme has emerged in which specific stimuli are critical in activating intracellular protein kinase signaling pathways resulting in activation of either positive or negative regulatory elements in MMP promoter elements. In this regard, Paul M. Reuben and Herman Cheung (University of Miami School of Medicine, Miami, FL) critically review the role of receptor-activated intracellular protein kinase signaling pathways that control MMP promoter activity.

3.2. MMP structure and function studies

Studies designed to decipher the physiological damage caused by MMPs and ADAMTs in vitro and in vivo resulted in the development of synthetic MMP inhibitors with potential clinical efficacy. Carl R. Flannery (Wyeth Research, Cambridge, MA) reviews the functional MMP studies that may lead to a rationale approach towards altering MMP activity for therapeutic benefit. Of note, significant degradation of ECM occurring as a response to inflammation and other cellular processes is often characterized by an imbalance between MMP activation and endogenous MMP inhibition favoring ECM degradation (15). What emerges from these considerations is the view that future medical therapy for human diseases characterized by overproduction of MMPs and reduced endogenous MMP inhibitory activity will almost certainly require that MMP structural analysis be combined with functional studies in animal models, although a greater understanding of the physiologically relevant physiological processes underlying ECM degradation is necessary (16) before any efficacy of small-molecule MMP inhibitors can be clinically useful.

4. MMPs IN HEALTH AND DISEASE

4.1. Skeletal development and growth plate disorders

The compelling body of experimental evidence linking MMPs to skeletal long bone growth and endochondral ossification is reviewed by Charles J. Malemud (Case Western Reserve University School of Medicine, Cleveland, OH). Among the MMPs, MMP-13 (collagenase-3), MMP-9 (92-kDa gelatinase; gelatinase B) and MMP-14 (MTl-MMP) appear to be most prominent in regulating cellular migration, ECM protein transformation, ECM degradation and apoptosis in the growth plate (17). Although normal endochondral ossification is also dependent to a significant extent on the activities of members of the hedgehog protein family, parathyroid hormone-related peptide and parathyroid hormone-related peptide receptor (18) as well as specific stress-activated and tyrosine receptor protein kinases (19), ablation of the MMP-9 (20), MMP-13 (21, 22) or MT1-MMP (23) genes to produce MMP-specific null mice resulted in temporospatial modulation in growth plate development. Of note, no specific murine growth plate defects were described resulting from deletion of the ADAMTS-4 or ADAMTS-5 genes (24, 25) despite strong evidence that ADAMTS -4 and -5 play a critical role in articular cartilage degeneration in osteoarthritis (OA). Because the MMPs defined as critical for normal murine growth plate development have also been implicated in human skeletal development (26, 27), genetic manipulation to correct defective or dysfunctional MMP gene expression or MMP catalytic activity associated with human skeletal maturation could provide a potential clinical platform for novel therapies designed to correct short stature and chondrodysplasias.

4.2. Cardiovascular development and heart disease

The active and continuous changes in cell-cell adhesion, cell migration, cell proliferation, apoptosis and

remodeling that are required for normal vascular and heart development involve MMP gene expression and activation of pro-MMPs. Philip Brauer (Creighton University School of Medicine, Omaha, NB) reviews the role of MMPs and the ADAMTS in vasculogenesis and angiogenesis pertinent to normal cardiac tube formation and looping, heart septation and cardiac remodeling during development in animal models. For example, MMP-2 activity was diminished in the Patch-deficient mice resulting in cardiovascular abnormalities (28). In cardiovascular pathology, aberrant MMP catalytic activity has also been linked to atherosclerotic plaque formation and plaque instability (29), vascular smooth muscle cell migration and restenosis (30), development of aortic aneurysm (31) and progressive heart failure in animal models (32) and humans (33).

4.3. Arthritis

Degradation of cartilage, tendon and bone ECM proteins by MMPs is a hallmark of synovial joint arthritis. MMPs also appear to play a prominent role in the early T-cell mediated phase of rheumatoid arthritis (RA) (34), the cytokine-induced inflammatory response which promotes progressive ECM protein degradation (35) and in dysfunctional apoptosis (36) all of which are prominent features of arthritis pathophysiology. Peter Burrage, Kimberlee Mix and Constance Brinckerhoff (Dartmouth Medical School, Lebanon, NH and University College, Dublin, Ireland) review the role MMPs play in the irreversible destruction of cartilage, tendon and bone in arthritis. MMPs are up-regulated in arthritis by elevated synovial fluid levels of IL-1beta and TNF-alpha where MMP-1 (collagenase-1) and MMP-13 (collagenase-3) activity predominate (37). By contrast, TIMP levels do not appreciably increase or may even decrease resulting in a strong MMP/TIMP imbalance in favor of MMPs (4). MMP-1 and MMP-13 mediate the degradation of Type II collagen, the principal collagen isotype of articular cartilage and Type I collagen, the principal interstitial collagen of tendon and bone. Although MMP-3 (stromelysin-1) is capable of degrading cartilage proteoglycans, ADAMTS-4 and -5 appear to be the main mediators of aggrecan degradation in RA and OA (38, 39). The development of MMP inhibitors that act either directly on MMP catalytic activity or cytokine receptors that cause MMP gene up-regulation or synthetic inhibitors of intracellular protein kinases that regulate MMP gene transcription (11, 15) are promising avenues of potential novel therapies for suppressing joint destruction in arthritis. In an RA clinical trial, the TNF-alpha monoclonal antibody, Adalimumab (Humira®, Abbott Laboratories) proved efficacious in treating the clinical symptoms of RA in patients receiving concomitant methotrexate as well as reducing circulating serum levels of MMP-1 and MMP-3 (40).

4.5. Cancer and metastasis

MMPs play a salient role in cancer (41). MMP-2 and MMP-9 (72kDa gelatinase and 92kDa gelatinase) are the prominent MMPs responsible for basement membrane ECM protein degradation that facilitates the migration of tumor cells to blood vessels. Barbara Fingleton (Vanderbilt University School of Medicine, Nashville, TN) reviews the many roles that MMPs play in tumor development and growth as well as metastasis. In one aspect unrelated to the capacity of MMPs to degrade ECM proteins, MMPs are intimately involved in stimulating angiogenesis which is required for tumor progression beyond 1-2mm^3 (42). In conjunction with its ability to stimulate neovessel formation, MMP-9 also appears to be active in releasing tissue-bound fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) that facilitates tumor cell growth. In another aspect, single nucleotide polymorphisms that result in elevated MMP gene expression also appear to be associated with the DNA from patients with more advanced cancer, suggesting that elevated MMP levels contribute to cancer progression (43). MMPs may also be involved in dysfunctional apoptosis (44) and altered immune-mediated tumor killing (45) that are both characteristic of malignancy. In this regard, specifically designed synthetic MMP inhibitors are not likely to prove efficacious as a cancer therapy if they interfere with anti-angiogenesis pathways or immune-mediated tumor killing

4.6. Diseases of the central nervous system and ischemic brain injury

MMPs play a significant role in diseases of the central nervous system (CNS) because they mediate disruption of the blood brain barrier, regulate ECM protein destruction and remodeling as well as tissue inflammation in response to oxidative stress (46). Yvan Gasche, Paola Soccal, Michiko Kanemitsu and Jean-Christophe Copin (Geneva University Hospital, Geneva, Switzerland) review the way in which MMPs suppress brain tissue recovery after ischemic injury by disrupting the blood brain barrier resulting in vasogenic edema. Because an intact brain tissue ECM is necessary for neuronal survival, MMP degradation of brain tissue ECM is also likely responsible for hemorrhagic transformations of the injured brain tissue. MMP-8 and MMP-9, in particular, appear to mediate central nervous tissue injury in bacterial infections including meningitis (47), multiple sclerosis (48), Alzheimer's disease (46), inflammatory myopathies (49) and tumors of the CNS such as glioma (50).

5. FUTURE DIRECTIONS

MMPs occupy a secure position as major determinants for normal embryologic development as well as for tissue injury characteristic of inflammatory disease processes. Assessing the relevancy of specific MMP inhibitors for use in regulating aberrant ECM protein turnover should occur first in animal models of skeletal dysplasias, cardiovascular abnormalities, arthritis, cancer and CNS disturbances as the results of these studies will likely be of the utmost importance for judging the potential usefulness of these MMP inhibitors in human clinical trials. The design of MMP inhibitors for use in the clinic must also take into account their potential for disrupting critical pathways required for tissue homeostasis.

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