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Review

Nitric oxide-matrix metaloproteinase-9 interactions: Biological and pharmacological significance
NO and MMP-9 interactions

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ABSTRACT

Nitric oxide (NO) and matrix metalloproteinase 9 (MMP-9) levels are found to increase in inflammation states and in cancer, and their levels may be reciprocally modulated. Understanding interactions between NO and MMP-9 is of biological and pharmacological relevance and may prove crucial in designing new therapeutics. The reciprocal interaction between NO and MMP-9 have been studied for nearly twenty years but to our knowledge, are yet to be the subject of a review. This review provides a summary of published data regarding the complex and sometimes contradictory effects of NO on MMP-9. We also analyse molecular mechanisms modulating and mediating NO-MMP-9 interactions. Finally, a potential therapeutic relevance of these interactions is presented.

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1. Introduction

1.1. Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a group of structurally similar endopeptidases with a zinc ion in the active site. All are capable of digesting components of the extracellular matrix including collagens, laminins, fibronectin, elastin, and proteoglycans. MMPs play a key role in controlling homeostasis of all extracellular matrix (ECM) proteins. The MMPs regulate cell function, growth and division, host defences, ECM synthesis, morphogenesis, wound healing, tissue repair, skeletal formation, apoptosis, as well as cleavage of transmembrane proteins and bioactive molecules. Dysregulation of the MMPs has been implicated in tumour angiogenesis, invasion and metastasis, inflammatory bowel disease, arthritis, atherosclerosis, respiratory and heart disease and may also play other diverse pathological roles [1–6].

1.1.1. Matrix metalloproteinase-9 and cardiovascular disease

Of MMPs, MMP-9 can be upregulated and it has been implicated in a variety of pathological conditions. A selective inhibition of MMP-9 may have a significant therapeutic relevance for the treatment of various inflammatory diseases. Cardiovascular (CV) disease, diabetes and cancer are responsible for the majority of human deaths in the developed world and have all been associated with MMP-9 abnormalities. For example, changes in the CV extracellular matrix (ECM) are regulated by the gelatinases and their tissue inhibitors and, as key components of CV remodelling, are associated with inflammation and reactive, rather than reparative, fibrosis [7,8]. MMP-2 and MMP-9 knockout models are associated with reduced aortic elastin degradation [9] and protection from pressure overload myocardial hypertrophy, fibrosis and dysfunction [10]. Post-infarction models and models of left ventricular arrythmogenesis have shown that MMP-9 gene promoters are temporally activated specifically in the region of myocardial injury [11,12]. The gene promoter region of MMP-9 includes a proximal activator protein-1 (AP-1) site which mediates an enhanced transcriptional response to a wide variety of cytokine and cellular stimuli [13]. In the clinic, independent associations between myocardial remodelling post-MI, left ventricular dysfunction and heart failure, have been identified with markers of inflammation, fibrosis and MMP-9 [8,14–17].

1.1.2. Matrix metalloproteinase-9 and diabetes

Microvascular and macrovascular complications of diabetes are associated with MMP-9 dysregulation. In an animal model of diabetic retinopathy, increased MMP-9 activity was observed in retinal microvessels and MMP-9 knockout was protective [18]. In patients, increased urinary excretion of MMP-9 supports a role for MMP-9 dysregulation in diabetic renal dysfunction [19] and aortic and coronary arteries of diabetic patients taken at autopsy had higher expression of MMP-9 compared

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to non-diabetics and were correlated with HbA1c as well as apoptosis [20]. Elevated MMP-9 has also been associated with arterial stiffness in patients with diabetes [21]. Furthermore, human genetic polymorphisms associated with MMP-9 elevation support a role for this enzyme in the pathophysiology of vascular disease. The 1562C > T single neucleotide polymorphism (SNP), which affects the promoter region of MMP-9 gene and increases circulating levels of MMP-9, is significantly associated with vascular disease in type 2 diabetes mellitus [22]. In age and sex matched controls, patients with type 2 diabetes, without and with microangiopathy, T allele frequencies were 11.9%, 13.1% and 24.4% respectively ($p < 0.05$).

1.1.3. Matrix metalloproteinase-9 and cancer

Matrix metalloproteinases (MMPs) play a central role in cancer cell intravasation and extravasation and their plasma levels are known biomarkers of breast, ovarian, colorectal, renal, pancreas, bladder and lung cancers [23]. MMP-9, in particular, regulates vascular endothelial growth factors, which, in turn, promote tumour growth and angiogenesis [24]. MMP-9 also modulates tumour-associated inflammation via cytokines and their receptors [25] and is involved in endothelial–mesenchymal-transition (EMT) whereby cells acquire migratory characteristics [26]. While, numerous preclinical studies demonstrate the ability of MMP inhibitors to delay primary tumour growth and block metastasis [27], MMP inhibition in the clinic has been limited by toxicity, including dose-limiting musculoskeletal pain and inflammation [28], while recent research on the development of MMP inhibitors has been focused on selective inhibition of MMPs [29].

1.1.4. Matrix metalloproteinase-9 and other diseases

MMP-9 abnormalities have been associated with disease progression in many other key organs. In the liver, MMP-9 has been associated with the fibrotic response to hepatitis C [30] and in models of fulminant liver failure where MMP-9 expression is increased, inhibition of MMP-9 was associated with improvement outcome when used early in the natural history of the disease [31]. In patients with kidney disease, interstitial fibrosis correlated with MMP-9 expression in the atrophic tubular nuclei [32] and elevated MMP-9 is also associated with the vascular complications of chronic kidney disease associated with diabetes [33]. In children with aggressive chronic renal dysfunction, focal segmental glomeruloscloerosis is associated with elevated MMP-9, which may represent an early diagnostic biomarker as well as a therapeutic target [21]. In the gastrointestinal tract, elevated expression of MMP-9 is a feature of inflammatory bowel diseases such as Crohn's disease [34–36] and MMP-9 expressed in epithelial colonic tissue mediates inflammation in colitis with simultaneous increase in proinflammatory mediators [37].

The above paragraphs highlight the need for an MMP-9 inhibitor; however, to date, clinical trials of MMP inhibitors have been largely unsuccessful. Misguided outcome expectations combined with poor fundamental understanding of the complex role of MMPs in cancer and inflammation are seen as the main contributors to these failures. Several excellent reviews have examined the outcomes and postulate that a greater understanding of the role of MMPs in a given disease setting may yet offer hope for a clinically relevant MMP inhibitor in the future [1,38,39]. Improved selectivity for MMP-9 over constitutive MMPs would certainly be of benefit [40] and also an ability to target the dysregulation of the enzyme that leads to its pathophysiological role. Understanding the interactions of NO and MMP-9 may offer insights into novel mechanisms to inhibit the enzyme in disease states.

1.1.5. Structure and regulation of MMP-9

MMP-9 and MMP-2 are classified as gelatinases, owing to their ability to process synthetic gelatine. This designation may be considered a little arbitrary as they can digest a variety of the matrix proteins and have ability to cleave a growing list of bioactive molecules including transmembrane proteins [41]. Structurally, MMP-9 is composed of several domains, including the pre, pro, and catalytic domains which connect to the C-terminal hemopexin-like domain via a hinge or linker region [42]. The hemopexin domain not only acts as a stubstrate binding domain [43] but can also interact with integrins on the cell surface to anchor MMP-9 and has been shown to trigger anti-apoptotic signalling pathways in B-cell chronic lymphocytic leukaemia [44]. All MMPs possess a catalytic domain of 165–170 amino acids which is essential for proteolysis [42,45]. The catalytic domain varies slightly in groove depth and the accessibility and depth of six side pockets that flank the defining zinc ion which is coordinated at the centre of the cleft by three histidine residues [46]. The S1′ pocket has the greatest variation amongst the MMPs in both depth and amino acid composition. These features have made it an attractive target for small molecule inhibitor development. The gelatinases also have three fibronectin-like inserts in the catalytic domain and these differences account, in part for their differing substrate specificities [47,48].

MMP-9 is principally regulated at the level of transcription by various inflammatory factors but also through post-transcriptional events; secretion of the protein, activation, endogenous inhibitors and cell surface interactions [3]. De novo synthesis of large amounts MMP-9 can be rapidly induced by cytokines, growth factors or changes in cell–cell or cell–ECM interactions [3,49]. Like many other proteases, MMP-9 is secreted in the "pro" form as an inactive zymogen. Latency is conferred by the prodomain which masks the active-site cleft and prevents hydration of the catalytic zinc ion. An interaction between a sulfydryl group on a conserved cysteine residue in the prodomain and the zinc ion constitutes this "cysteine switch" [50–52]. Activation of the enzyme, therefore, requires either proteolytic removal of the propeptide or disruption of the Zn^{2+}-cysteine bond. MMP-9 is most commonly activated by other proteases such as serine proteases, trypsin, plasmin, chymase and other MMPs [38,48] but it can also be activated by conformational perturbants such as heat, substrate binding, heavy metals and organomercury compounds such as aminophenylmercuric acetate, as well as oxidants and alkylating agents [52–56]. It has therefore been agreed that the pro-MMP-9 has to be secreted to the ECM in order to get activated; however other mechanisms can be also involved. Indeed, it has been proposed that pro-MMP-9 activation could take place at the plasma membrane. The interactions of the MT1-MMP/MMP-2 axis with pro-MMP-9 on the plasma membrane induced a full activation of MMP-9 in vitro, and under the same conditions, MMP-3 was also able to activate MMP-9 [57]. In addition, thrombin has been shown to induce pro-MMP-9 activation and association with β1-integrin in a human osteosarcoma cell line through a PI 3-kinase-dependent pathway, a key step in thrombin-induced tumour invasion [58].

1.1.6. Endogenous inhibitors of MMPs

A large number of endogenous inhibitors of MMPs exist, which serve to regulate activity and prevent uncontrolled proteolysis (Table 1). Of these inhibitors, the tissue inhibitors of metalloproteinase (TIMPs) are the most specific for the MMPs. The TIMPs are a family of secreted proteins which can bind all the MMPs in a 1:1 stoichiometry with varying efficiencies; TIMP-1 binds to MMP-9 with high affinity whereas TIMP-2 is a more effective inhibitor of MMP-2 [59,60]. TIMPs (21 to 29 kDa) have an N- and C-terminal domain of ≈125 and 65 amino acids, respectively, with each containing three conserved disulfide bonds. The N-terminal domain folds as a separate unit and is capable of inhibiting MMPs. The main inhibitor of MMPs in tissue fluids is α2-macrogobulin [61]. Limited proteolysis of a bait region of the plasma protein by an MMP induces a conformational change in the macroglobulin which then encloses the enzyme [62]. It is a general proteinase inhibitor but may only bind to activated MMPs which are then irreversible cleared by endocytosis following binding to a scavenger receptor [63].

Other proteins with MMP inhibiting properties, albeit less potent than the TIMPs, include the C-terminal fragment of the procollagen C-terminal proteinase enhancer protein (PCPE) [64]. The noncollagenous NC1

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