Volume 2, Issue 3, March 2024 ISSN (E): 2938-3765

NEW ASPECTS OF PATHOLOGY AND NORMS OF MATRIX METALLOPROTEINASES

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Abstract
The first discovered activity of MMPs was their ability to hydrolyze extracellular matrix proteins. The expression of MMPs in a wide range of cells and tissues ensures their participation in a variety of physiological processes. Neutrophils, monocytes, macrophages, lymphocytes, mast cells, fibroblasts, osteoclasts, chondrocytes, keratinocytes, endothelial, epithelial and smooth muscle cells, as well as cells of various tumors are capable of producing MMPs.
Degradation of extracellular matrix components ensures tissue remodeling, maintaining its architecture and homeostasis, and also frees up space for cell migration, which is especially important for embryogenesis, embryo implantation, growth and development, angiogenesis, and wound healing.

Keywords: Degradation, expression, angiogenesis, extracellular matrix, fibroblasts.

Introduction

MMPs can affect cell-cell contacts and modulate cell-matrix interactions, which are critical for cell proliferation and differentiation. The breakdown products of the extracellular matrix may themselves have biological activity. For example, the short peptide Pro-Gly-Pro, formed during the specific degradation of collagen, regulates endothelial permeability and is involved in the induction of an inflammatory response. Cleavage of laminin 5 and collagen IV releases hidden sites of these proteins that activate cell migration
Such molecules were called matrikines and matricryptins. In addition, MMPs are capable of releasing cytokines and growth factors from the extracellular matrix, which serves as a reservoir for biologically active molecules. Fibroblast growth factor (FGF) and transforming growth factor beta have high affinity for components of the extracellular matrix.
It was later shown that the substrate specificity of MMPs is by no means limited to the components of the extracellular matrix. MMPs hydrolyze a variety of protein growth factors, tyrosine kinase receptors, cytokines, chemokines, other MMPs, complement components, FasL, various adhesion molecules and membrane proteins (eg, E-cadherin, β4 integrin, CD44)
This can lead to both activation and inactivation of the corresponding substrates. In particular, MMPs degrade IGF-binding protein, releasing IGF; activate latent forms of TGF-β, TNF-α, IL-1β, pro-α-defensin, chemokines CCL7, CXCL6, CXCL8, CXCL12; cleave IL-2Rα on the surface of T lymphocytes; inactivate the chemokine SDF-1; process VEGF. Consequently, MMPs modulate various aspects of the immune response, apoptosis, cell proliferation, differentiation and migration, being an important component of the normal functioning of tissues and organs.

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The ability to regulate a wide range of biological reactions and the imbalance of MMP activity determine their participation in a number of pathological processes: inflammatory, autoimmune, neurodegenerative, cardiovascular, infectious and oncological diseases. Changes in MMP production in various tissues have been detected in Alzheimer's and Parkinson's diseases, multiple sclerosis, amyotrophic lateral sclerosis, acute and chronic kidney diseases, osteoarthritis and osteoporosis, rheumatoid arthritis, atopic dermatitis, psoriasis, periodontitis, diabetic nephropathy, chronic glomerulonephritis, primary open-angle glaucoma, atherosclerosis, abdominal aortic aneurysm, arterial hypertension, preeclampsia, ischemic myocardial damage, varicose veins of the lower extremities, trophic ulcers, inflammatory bowel diseases (eg, Crohn's disease), HTLV-1-associated myelopathy, viral and bacterial meningitis, chronic follicular conjunctivitis caused by Chlamydia trachomatis, staphylococcal septic arthritis, tuberculosis, anaphylactoid purpura, respiratory distress syndrome. The involvement of MMPs in the pathogenesis of diseases makes them an attractive target for drugs.

To date, a large number of MMP inhibitors have been developed for targeted therapy of various pathologies, ranging from low-molecular inhibitors that bind to the active centers of proteases, to macromolecular inhibitors that act on MMP exosites, allosteric inhibitors, drugs based on endogenous inhibitors, antibodies, etc. However, the involvement of MMPs into multiple molecular pathways, broad and often overlapping substrate specificity, expression in many tissues, and a high level of homology between different MMPs are possible reasons why the drugs being developed could not pass clinical trials. MMP inhibitors can be broadly classified as non-synthetic (eg, endogenous) or synthetic. Several potent MMP inhibitors have been identified, including hydroxymates, thiols, carbamoylphosphonates, hydroxyurea, hydrazines, β-lactams, squaric acids, and nitrogenous ligands.

There are three classes of commonly used metalloproteinase inhibitors:

- Class 1: In vitro, EDTA, 1,10-phenanthroline and other chelating compounds reduce the metal concentration to the point where the metal is removed from the enzyme active site.
- Class 2: Classic lock-and-key inhibitors such as phosphoramidon and bestatin bind tightly, approaching the transition state of peptide hydrolysis, preventing it from acting on other substrates.
- Class 3: Protein inhibitors such as α2-macroglobulin are known to work with metalloproteinases.

I. Inhibitors containing a hydroxamic acid residue:

The first generation of MMP inhibitors was based on the structure of the collagen molecule. In the design of these inhibitors, the core protein backbone of collagen is retained, but the amide bond is replaced by a zinc-binding group. This group of inhibitors contains a hydroxamate group (-CONHOH) which binds the zinc atom in the active site of the MMP enzyme, hence this group is called "hydroxamate-based MMP inhibitors". An example can be seen in Marimastat, a first generation inhibitor that has a similar backbone and side chain format to collagen.

Ilomastat and batimastat were the first two MMP inhibitors to be tested in patients. They are both hydroxamate-based MMP inhibitors and have similar general structures. Hydroxamate-based MMP inhibitors exhibit excellent antitumor activity in tumor cells, but the clinical performance of these compounds has been disappointing. A contributing factor to this disappointment was that they are broad-spectrum inhibitors of many MMP subtypes, which in many cases can also inhibit members of the ADAM family of proteases. When they were tested in patients they caused dose-limiting muscle and skeletal pain in a number of patients.

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The pioneering hydroxamate-based inhibitors were followed by a set of “next generation” molecules with characteristics including a substituted aryl, sulfonamide, and hydroxamate zinc-binding moiety.

II. Thiol-based inhibitors:

Rebimastat is a broad-spectrum MMP inhibitor with a zinc thiol-binding moiety. It has oral bioavailability and is a non-peptide collagen mimetic. Rebimastat has some selectivity because it does not inhibit all MMP activities. Metalloproteinases that secrete TNF-alpha, TNF-II, L-selectin, IL-1-RII and IL-6, for example, are not inhibited by Rebimastat.

In phase I clinical trials, there was no evidence of dose-related joint toxicity or stable disease. Arthralgia was noted in early phase II breast cancer trials and was associated with MMP inhibitor toxicity. Rebimastat was used in paclitaxel/carboplatin treatment in phase III. The trial results showed a higher incidence of adverse reactions with no improvement in survival.

III. Pyrimidine-based inhibitors:

Ro 28-2653 is highly selective for MMP-2, MMP-9 and membrane type 1 (MT-1)-MMP. It is an antitumor and antiangiogenic agent with oral bioavailability. Inhibition of TACE and MMP-1 is associated with the musculoskeletal side effects seen with hydroxamate metalloproteinase inhibitors, but this compound spares the enzymes. It has been shown to reduce tumor growth in nasal cancer in rats, as well as in prostate cancer cell cultures. The compound had only a moderate effect on the fatty tissue of mice and did not affect the joints. Based on this, it is concluded that the inhibitor class is less likely to cause neuromuscular side effects.

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