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Commentary Article

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Unveiling the Prospects of MMPs and Modulators

Ish Kumar*, Mihaela D Leonida

Department of Chemistry, Fairleigh Dickinson University, Teaneck, USA

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DESCRIPTION

Enzymes have been popular therapeutic targets for any disease in drug discovery. Many diseases arise from a deficiency or excess of specific metabolites due to some infection or aberrant cell growth. A common approach is to normalize the excess metabolite by inhibiting a particular enzyme responsible for the pathological pathway. A compound successful in doing it has the potential as a drug for that disease. The Matrix Metalloproteinases (MMPs) have been therapeutic targets for many diseases, including cancer and autoimmune diseases. These are zinc-containing calcium-dependent extracellular enzymes with tissue remodeling and maintenance as primary functions. Additionally, they play pivotal roles in physiological processes like embryogenesis, morphogenesis, wound healing, etc. There are 26 different human MMPs known to date. The structures of catalytic domains of all MMPs are highly conserved, making the design of specific inhibitors against any specific MMP a challenging proposition.

MMPs are expressed within the cells in inactive forms, with the active site self-protected by the prodomain of the protein. To become active, that domain needs prior cleavage by other MMPs, serine proteases, plasmin, or furin. MMPs are also tightly regulated for their activities by endogenous inhibitors called tissue inhibitors of Metalloproteinases (TIMPs), other proteins that exist simultaneously within tissues. That results in homeostatic balance, which is well maintained in healthy tissues. Over or under-expression of MMPs may lead to the breakdown of homeostasis, associated with pathological conditions such as poor wound healing, cancer, arthritis, atherosclerosis, fibrosis, etc. Thus, scientists may seek exogenous modulators that may help to reestablish the balance, possibly as a remedy for that particular disease.

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For the past two decades, scientists have made numerous attempts to design, synthesize, and evaluate MMP inhibitors. There are many stories of MMP inhibitors which failed as drug candidates in clinical trials. Periostat (Doxycycline Hyclate, a synthetic tetracycline) is the only MMP inhibitor approved by the FDA. This molecule is used for the treatment of periodontitis at sub-antimicrobial doses. Most potential candidates failed for varied reasons, such as lack of specificity, poorly designed clinical studies, and lack of knowledge of the biochemical relevance of MMPs.

The structures of MMPs are well studied, but the biochemical relevance of each part is not fully understood yet. For example, collagenases, subtypes of MMPs, contain a prodomain, a catalytic domain, a linker and a hemopexin domain. Although proteolytic activity resides within the zinc-binding motif of catalytic domain, but additional exosites of proteins might have unique functions that still need further exploration. For example, the hemopexin domain helps in the cooperative binding and modulation of larger substrates (like triple helical collagens) to assist proteolytic activity within the catalytic domain.

Our group currently focuses on the catalytic domains of various MMPs, which are spherical in shape and about 40 Å in diameter. For example, the catalytic domain of MMP-1 contains three helices, five β-sheets, and loops connected to them. The active site containing catalytic zinc is highly conserved with a general sequence of HEXXHXXGXXH. One more zinc ion and three calcium ions are also present and essential for the entire domain's structural integrity. An omega loop connects α2 and α3 helices and it is least conserved region among different MMPs. The amino acid chain length within that loop varies from protein to protein within the family. This loop surrounds the extended S1’ pocket, a subsite of the active site region of MMPs, and is responsible for their substrate specificity. The region has been of primary interest for designing specific inhibitors by extending their structures to this site [1,2].

In a recent study, we reported three inhibitors that bind to active-site pockets like any conventional competitive inhibitor. Interestingly, we have also found one molecule as an exogenous activator to the catalytic domain of MMPs that has shown more specificity towards MMP-1 [3]. Cavity finding and molecular docking suggested binding of the activator within the omega loop of MMP-1. As we know, activators should bind to allosteric sites and induce conformational changes for better substrate binding to the active site pockets. We hypothesize that the binding of the activator to an allosteric site, which possibly is within the omega loop, must be associated with the favorable conformational change for substrate catalysis. In systemic delivery, MMP inhibitors failed, but topical delivery still holds some promise. MMPs get over-expressed when skin cells are exposed to UV radiation, which results in the degradation of collagen proteins and wrinkle formation [4].

MMPs play an important role in wound healing; in foot ulcers of diabetic patients, it was found that the MMP-1 level was low. Moreover, MMP-1 has been found helpful in the case of hypertrophic epithelial scar, where it involves the degradation of excessive collagen. The level of MMP-8 also has been observed to be important during wound healing [5]. It facilitates wound healing. MMP-8 has also been proven to be an anti-target for inhibition, especially in cancer, as it is essential for normal cell physiological functions. Maintaining the homeostatic balance of specific MMPs is important where activators could help. Just like agonists for receptors as targets for various diseases have been well used in medicinal chemistry [6]. Somehow, activators are not well explored in the area. Here, we hypothesize either activators or inhibitors or a combination of both could be beneficial to maintain the activity balance of MMPs.

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