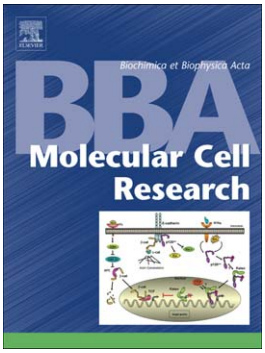

Next Generation Matrix Metalloproteinase Inhibitors – Novel Strategies Bring New Prospects

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Next Generation Matrix Metalloproteinase Inhibitors – Novel Strategies Bring New Prospects

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Abstract

Enzymatic proteolysis of cell surface proteins and extracellular matrix (ECM) is critical for tissue homeostasis and cell signaling. These proteolytic activities are mediated predominantly by a family of proteases termed matrix metalloproteinases (MMPs). The growing evidence in recent years that ECM and non-ECM bioactive molecules (e.g., growth factors, cytokines, chemokines, on top of matrikines and matricryptins) have versatile functions redefines our view on the roles matrix remodeling enzymes play in many physiological and pathological processes, and underscores the notion that ECM proteolytic reaction mechanisms represent master switches in the regulation of critical biological processes and govern cell behavior. Accordingly, MMPs are not only responsible for direct degradation of ECM molecules but are also key modulators of cardinal bioactive factors. Many attempts were made to manipulate ECM degradation by targeting MMPs using small peptidic and organic inhibitors. However, due to the high structural homology shared by these enzymes, the majority of the developed compounds are broad-spectrum inhibitors affecting the proteolytic activity of various MMPs and other zinc-related proteases. These inhibitors, in many cases, failed as therapeutic agents, mainly due to the bilateral role of MMPs in pathological conditions such as cancer, in which MMPs have both pro- and anti-tumorigenic effects. Despite the important role of MMPs in many human diseases, none of the broad-range synthetic MMP inhibitors that were designed have successfully passed clinical trials. It appears that, designing highly selective MMP inhibitors that are also effective *in vivo*, is not trivial (See Fig. 1). The challenges related to designing selective and effective metalloprotease inhibitors, are associated in part with the aforesaid high structural homology and the dynamic nature of their protein scaffolds. Great progress was achieved in the last decade in understanding the biochemistry and biology of MMPs activity. This knowledge, combined with lessons from