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REGULATION OF THE ACTIVITY OF MATRIX METALLOPROTEINASES AND THEIR ROLE IN THE BODY

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Abstract
The development of inhibitors of zinc-containing metalloproteinases in most cases is aimed at MMP, inhibitors, since excessive concentrations of these proteinases in the body can lead to the development of certain groups of diseases. In this regard, the search for MMP inhibitors has gained great popularity. Inhibitors of other existing metalloprotenases, such as CPA, TLN, NEP, TACE, etc., are created for experimental purposes to study the molecular structure, as a result of which their number is limited. The lack of knowledge about the regulation of MMP activity at the posttranscriptional level, especially in vivo, is an important point that we should take into account in future studies.

Keywords: Inhibitor, metalloproteinases, zinc-containing, regulation, activity.

Introduction

MMP are inhibited by tissue inhibitors of metalloproteinases (TIMP), which are endogenous protein regulators. The TIMP family (TIMP -1-4) are proteins consisting of 184-194 amino acids, the molecular weight of which is 21 kDa. The TIMP family has similar, but not identical, protease inhibition profiles; TIMPs are present in the ECM in soluble form, with the exception of TIMP-3, which is associated with the ECM. All TIMPs inhibit MMPs through a reversible block, forming stoichiometric complexes. TIMPs are also important for the activation and uptake/removal of MMPs from the extracellular environment. TIMP function determines the influence of the ECM on cell phenotype, cell adhesion molecules, cytokines, chemokines and growth factors.

TIMPs consist of two domains that are located side by side (N-terminal and C-terminal domains).

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The N-terminal domain is sometimes called the “inhibitory domain”. TIMPs also have functions independent of MMP inhibition, whereby they directly bind to cell surface receptors. TIMP-1, which is secreted by most cells in the body, is more limited in its inhibitory range than the other three TIMPs. It inhibits all types of MMPs (especially strongly binding to MMP-9 and pro-MMP-9), with the exception of MMP-14, MMP-16, MMP-18, MMP-19, MT1-MMP, MT2-MMP, MT3-MMP and MT5- MMP. TIMP-2 is constitutively expressed in most tissues but is not induced by growth factors. TIMP-3 is expressed in tissues as a matrix protein and in the basement membranes of the eyes and kidneys, while TIMP-4 is expressed in the heart, ovaries, kidneys, pancreas, colon, testes, brain, and adipose tissue. In their specific tissues, TIMPs exhibit specific expression in a

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constitutive or inducible manner, which is regulated at the transcriptional level by cytokines, growth factors and chemokines.

TIMP-2 and TIMP-3 inhibit MMP-3 and MMP-7 to a lesser extent than TIMP-1, which contrasts with their conceit for other MMPs. TIMP-3 is unique among mammalian TIMPs in that it inhibits a broader range of MMPs and also inhibits several members of the ADAM families. TIMPs are also multifunctional proteins with pleiotropic activities mediated through MMP-independent protein-protein interactions. The location of TIMPs on the cell surface (TIMP-2 and TIMP-3), in the matrix (TIMP-3) and in the form of soluble forms (TIMP-1, TIMP-2 and TIMP-4) makes them universal signal regulators. TIMPs also interact with the proforms (zymogen forms) of MMPs, but not as an inhibitor: TIMP-1 and TIMP-3 interact with pro-MMP-9, and TIMP-2 and TIMP-4 interact with pro-MMP-2. In these cases, only the C-terminus is involved, leaving the N-terminus free to bind to a second MMP molecule. TIMPs are also involved in MMP activation and possible modulation through mediating interactions of active MMPs with specific substrates. In vivo studies using MMP inhibitors in mice indicate that MMPs play important roles in infection and host defense. MMP activity is mainly inhibited by TIMPs and 2-macroglobulin, in addition to their regulation at the transcriptional level by ECM components.

To date, the basic structural requirements for inhibitors of various matrix metalloproteinases have been determined. The main one is the presence of a zinc chelating group (ZBG). These groups include hydroxamate (CONHOH), formylhydroxylamine, sulfhydryl (SH), phosphine, aminocarboxyl and carboxyl groups (COOH). And also, the presence of at least one functional group is required, which makes it possible to form a hydrogen bond with enzymes. One important requirement is the presence of one or more side chains that effectively bind to enzymes through van der Waals bonds. The above criteria include a certain number of substances with diverse structures, and it became necessary to divide these compounds into classes:

- natural MMP inhibitors;
- inhibitors containing a carboxyl group;
- inhibitors containing a hydroxamic acid residue;
- thiol-based inhibitors;
- inhibitors containing phosphorus;
- sulfonamide-based inhibitors;
- barbiturate-based inhibitors;
- inhibitors that do not contain a zinc-binding group.

It is important to note that there is a fifth level of regulation that has not been widely reported and involves the regulated uptake/excretion of active proteases from the extracellular environment. The vast majority of the literature is based on analysis of changes at the transcriptional level (level 1), which provides insufficient information about the regulation and biologically relevant activities of proteases that are secreted and activated after translation.

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