ISSN: 2053-3578 I.F. 9.1

СОВРЕМЕННЫЕ ПРЕДСТАВЛЕНИЯ О МЕХАНИЗМЕ ДЕЙСТВИЯ, МАТРИКСНЫХ МЕТАЛЛОПРОТЕИНАЗ И ИХ ТКАНЕВЫХ ИНГИБИТОРОВ.

Базарова Нигина Собиржановна

Ассистент кафедры Организация фармацевтического дела.

Самаркандский государственный медицинский университет, PhD

Почта: Bozorovanigina72@gmail.com ORCID 0009-0006-1391-0283

Аннотация

Данные многочисленных исследований по изучению структуры металлопротеиназ дали огромное количество информации по их строению, подтвердили сложность структуры данной группы ферментов и вариабельность их функций и строения.

Основываясь на их субклеточном распределении и специфичности для компонентов ВКМ, ММП подразделяются на матриксные металлопротеазы мембранного типа (МТ-ММП), коллагеназы, желатиназы, стромелизины и матрилизины. Коллагеназы (ММП-1, ММП-8, ММП-13 и ММП-18) разрушают фибриллярный коллаген тройной спирали, который является основным в костях и связках.

Ключевые слова: Матриксные металлопротеаза, коллагеназа, желатиназа, стромелизина.

MODERN IDEAS ABOUT THE MECHANISM OF ACTION OF MATRIX METALLOPROTEINASES AND THEIR TISSUE INHIBITORS.

Bazarova Nigina Sobirzhanovna

Assistant of the department Organization of pharmaceutical business.

Samarkand State Medical University , PhD

Mail: Bozorovanigina72@gmail.com ORCID 0009-0006-1391-0283

Annotation

Data from numerous studies on the structure of metalloproteinases have provided a huge amount of information on their structure, confirming the complexity of the structure of this group of enzymes and the variability of their functions and structure.

Based on their subcellular distribution and specificity for ECM components, MMPs are classified into membrane-type matrix metalloproteases (MT-MMPs), collagenases, gelatinases, stromelysins, and matrilysins. Collagenases (MMP-1, MMP-8, MMP-13 and MMP-18) break down fibrillar triple helix collagen, which is the main collagen in bones and ligaments.

Key words: Matrix metalloprotease, collagenase, gelatinase, stromelysin.

Relevance of the problem. Matrix metalloproteinases (MMPs) were discovered at the

beginning of the 20th century. Then reports began to appear about the leading role of MMPs in a number of important processes in the body, including fluctuations in blood pressure, autoimmune diseases (rheumatoid arthritis, Crohn's disease), etc.

There are strong arguments in favor of the assumption that matrix metalloproteinases are the main inducers of tissue remodeling. MMPs belong to the endopeptidase family, which contains 27 members. They contain zinc, are calcium dependent, and can degrade and remodel proteins that form the extracellular matrix. The extracellular matrix (ECM) is an additional platform not only for additional cellular and tissue processes, but also for other functions and processes. For example, through the elements of the extracellular matrix, regulation of the cycle and cell motility, apoptosis, as well as the distribution of growth factors and integration of signals into cells occur, and if the MMP malfunctions, various diseases develop and cells die, that is, the remodeling process is disrupted. The ECM is composed of hundreds of molecules, including proteoglycans, glycosaminoglycans, structural proteins (collagen and elastin), adhesion proteins (fibronectin and laminin) and proteases (matrix metalloproteinases) . MMP are also involved in various biological and physiological processes that are regulated by hormones, growth factors and cytokines.

It has become known that the regulation of the enzyme in the inactive phase state is controlled by a "cysteine switch". Initially, matrix metalloproteinases in the body are synthesized as proenzymes (proMMPs); subsequently, activation occurs through proteolytic and non-proteolytic compounds of heavy metals - mercury (HgCl2; 4-aminophenylacetate of mercury), sodium dodecyl sulfate and chaotropic agents. As a rule, a propeptide in the enzyme controls its activity. This process occurs in the catalytic domain upon interaction with zinc, followed by the formation of a coordination bond. The enzyme remains in an inactive phase due to the neutral position of the water molecule in the propeptide, which does not bind to the zinc ion. Matrix metalloproteinases can be activated by cleavage of the propeptide from the catalytic domain. One of the possible scenarios for achieving this is autocatalysis or interaction with other representatives of matrix metalloproteinases .

In the Longley laboratory, the structures of the catalytic domains of MMP were created using X-ray crystallography, and later the crystal structure of collagenase molecules was created. Currently, with the development of molecular diagnostics by spectroscopy, the following types of structure have been identified: MMP-13, MMP-14, MMP-16, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10, MMP-11, MMP-12. The structures of pro-MMP-3 and pro-MMP-9 have not been fully studied. The mechanism of connection of MMP and TIMP molecules and their

relationships were studied, which is the main mechanism of study in the search for new inhibitors.

Gelatinases (MMP-2 and MMP-9) are involved in various cellular processes, including angiogenesis and neurogenesis; these proteases alter the molecules of the basal lamina, which subsequently leads to cell death. Stromelysins (MMP-3, MMP-10, and MMP-11) are small proteases that degrade ECM segments. Matrilysins (MMP-7 and MMP-26) process cell surface molecules and break down ECM components. MT-MMPs have collagenolytic activity and can activate several proteases and cell surface components. MMPs are also classified into eight groups according to their structure; five of them are secreted and three are membrane bound (MT-MMPs) [9].

The results of structural analysis of MMPs , obtained in the laboratories of various authoritative scientific centers, revealed 6 common domains in their structure, which shows the commonality of their structure. Each domain in the MMP structure plays a specific role and provides one or another function of the molecule. The N-terminal signaling domain plays a key role in the composition of the molecule. Another domain, called the Pro domain, which has a specific sequence of amino acids in its composition, controls the state of activity of zinc ions , which act as a catalyst in biochemical processes involving MMPs. The catalytic domain regulates the position of the polypeptide chain during a biochemical reaction, indirectly interacts with zinc and is involved in catalysis. A loop-shaped domain called a linker domain contains a huge number of amino acid residues; proline regulates the formation of molecular bonds. The coordination of newly formed bonds with targeted inhibitors that perform specific roles is carried out through the hemopexin domain. Exclusively membrane-type MMPs contain the very last type of domain, called transmembrane. This domain contains transmembrane and cytoplasmic regions, as well as various glycolipids.

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