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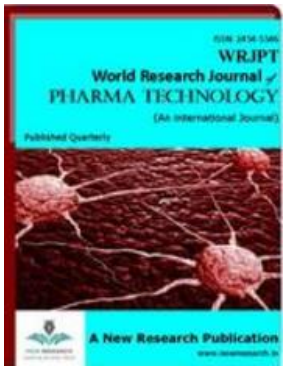

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RESPONSIVE NANOPREPARATIONS BASED ON MATRIX METALLOPROTEASES

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Abstract

Due to the tumor's metastatic, tumor cells can be from the primary tumor, through the blood vessels, lymphatics to the other new parts which is the enormous challenges for cancer treatment, and is also an important cause of the high rates of cancer death. Metalloproteinases (MMPs), especially MMP2 and MMP9, are overexpressed in the tumor microenvironment and play an important role in the process of tumor growth and metastasis by degrading collagen IV which is the main component of matrix membrane. Therefore, MMP2 and MMP9 can be used as tumor therapy, especially the role of metastatic tumor target.

Keywords

Matrix metalloproteinases, stucture and characteristics, role and function, enzyme-responsive nanopreparations.

1. Introduction

Breast cancer is one of the most common cancers in women, and one of the greatest threats to women's health [1]. Metastatic recurrence is the leading cause of death in breast cancer patients [2]. Tumor metastasis is a huge challenge for cancer treatment, and it is also an important reason for the high rate of tumor death, which is the process of tumor cells moving from the primary tumor through the blood vessels,

lymphatic vessels to other new parts and the formation of new tumor tissue. Tumor invasion and metastasis is a multi-step and complex process. In these complex processes, a variety of functional proteins are involved. MMP-2 and MMP-9 plays an important role in tumor growth and metastasis. MMP-2 and MMP-9 are secreted by metastatic tumor cells and stromal cells in the form of zymogens. That can be activated by hydrolysis, specifically degrade type IV collagen in the basement membrane, and play an important role in tumor metastasis by promoting the formation of tumor neovascularization, promoting tumor invasion and metastasis[3].

Breast cancer is one of the biggest threats to the health and recurrence of women. Metastasis is the main cause of death for breast cancer patients. Clinically, systemic treatment of postoperative metastatic breast cancer remains largely dependent on chemotherapy. However, large side effects and poor pharmacological effects caused by the lack of tumor targeting ability will give patients with unspeakable pain, but not conducive to the health recovery. In addition, chronic administration of chemotherapy drugs will produce multidrug resistance and increase the risk of metastasis. Thus, accurate tumor targeting is very important for the effective treatment of breast cancer and the reduction of side effects of chemotherapeutic drugs [4-6].

2. Advances in Matrix Metalloproteinases

Matrix metalloproteases (MMPs) which composes of a variety of zinc ion-dependent enzymes are important enzymes that are capable of degrading extracellular matrix proteins (extracelluarmatrix, ECM) including almost all of the components of the cell matrix (collagen, gelatin, sticky protein, fibronectin, proteoglycans, etc.). MMPs are highly conserved enzymes that are widely distributed in plants, vertebrates, and invertebrates. In 1962 years, after people found the first MMP which derived from the collagenase of the python in the tissue, more than 100 members of the MMPs family were found one after another in the animal and plant. At present, 26 kinds of human MMPs have been found, called MMP family. In the normal steady state of the organization, MMPs expression is very small; and in the

body involved in a variety of physiological and pathological processes, such as inflammation, embryogenesis, angiogenesis, tumor invasion and metastasis, its expression increases[7].

2.1The structure of MMPs

MMPs are zinc ion-dependent endosomes, which vary in size and have different substrates, but MMPs have high homology in structure, with 10 exons and 9 exons. And most MMPs contain the pre- peptide domain, the catalytic domain, the signal domain, and the hemagglutinin-like domain [8]. Details are as follows:

2.1.1MMPs are mainly in the form of zymogen secreting to the extracellular which need to remove the peptide under the action of activator to active the zymogen. The pre- peptide domain constitutes 77 to 87 amino acids, containing a conservative Pro-Arg-Cys-Gly-Val/Asn-Pro-Asp (PRCGV/NPD) sequence and the cysteine residues play an important role in most MMPs zymogen activity. During the activation of the zymogen, that structure will be hydrolyzed out. And MMP-11, 14, 15, 16, 17 directly secrete to to the extracellular as the form of enzyme activity.

2.1.2 The catalytic domain consists of 160-170 amino acids. Two Zn^{2+} locates in the active center involving in the catalytic process of MMPs; the other is the structural Zn^{2+}. The domain contains a very conserved amino acid sequence: HEXGHXXGXX H, where the three histidine (H) is believed to bind to the zinc ion at the center of the enzyme activity to form a coordination bond, which plays an important role in the activity of the enzyme.

2.1.3 Human MMPs in addition to MMP-14 have a signal sequence, composed of 17 to 29 amino acids and the role of signal peptide is to guide the translation of the new peptide to the cytoplasmic endoplasmic reticulum.

2.1.4 In addition to MMP-7, 23 and 22, the C-terminus of the other MMPs has a

hemagglutinin-like domain, which is involved in the identification of macromolecule substrates and the combination of tissue inhibitors of meatlinoprotein inhibitors (TIMPs). Gelatinase (MMP-2, MMP-9) also has a unique gelatin-binding domain within the catalytic domain that may mediate the distribution of gelatinase in the extracellular matrix[9].

2.2 Key features of MMPs[10]

(1) MMPs belong to the zinc-dependent neutral protease family, and the optimum pH is close to neutral.

(2) Their structure has a sequence homology of 40% to 50%, and the cDNA sequence shows homology with collagenase.

(3) They are all in the form of zymogen secreting to the extracellular matrix, and can be activated by protease or organic tonic agents to play a physiological role. The activation process is accompanied by a loss of about 10,000 relative molecular masses.

(4) Catalytic mechanism depends on the existence of zinc ions in the active center and calcium ions also has a certain role on its activity and stability.

(5) Their natural activators and inhibitors exist in the body such as tissue metalloproteinase inhibitors (TIMPs) and plasma inhibition of α2 macroglobulin, while MMPs can also be activated between each other. After activated, the enzyme can hydrolyze one or more extracellular components.

2.3 MMPs classification [11]

MMPs is an important enzyme in the process of extracellular matrix degradation which can be selectivity divided into broadly five categories through structure and substrate :

The first class is collagenase, including interstitial collagen enzyme (MMP-1), polymorphonuclear collagenase (MMP-8), collagenase 3(MMP-13), MMP-18 which the main substrate is the interstitial collagen including I, II, III and VII,X -type collagen, but can not degrade gelatin and IV-type collagen.

The second group is gelatinase also known as IV-type of collagen enzymes, including gelatinase A (MMP-2) and gelatinase B (MMP-9). These enzymes were inserted into three repeating II type fibronectin-like structure in the catalytic domain, respectively binding gelatin, collagen and layer adhesionprotein. The role of the substrate is mainly IV type of collagen and gelatin, which can degrade VII, IX, X type collagen and layer adhesionprotein but can not degrede interstitial collagen while MMP-2 can degrede I, II, III-type collagen.

The third class of stromelysins, including stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11). There are scholars put MMP-11 to the fifth category. The role of the substrate is mainly in the matrix of proteoglycan and baked protein, such as fibronectin (FN), laminin (LN). Stromelysin on the role of collagen is different from the interstitial collagenase and gelatinase, which can degrade the non-helix of IV, V, VIII, X type collagenase and the amino groups of I type collagen, which MMP-3, MMP-10 can degrade III, IV, V-type collagen, gelatin, proteoglycans, and fibronectin, laminin and so on. In addition to degrading the extracellular matrix, MMP-3 is also possible to activate part of the MMPs precursor, which is important for the complete activation of MMP-1.

The fourth category is membrane metalloproteinase. Membrane metalloproteinase is first discovered by Sato etal in1994 years in the invasive lung cancer cell membrane, named MT1-MMP which has been found six kinds of MT-MMPs, including respectively four kinds of transmembrane protein: I type membrane metalloproteinase (MMP-14), II type membrane metalloproteinase (MMP-15), m-membrane plow metalloproteinase (MMP-16), MMP-24 and two kinds of glycosylated phosphatidyl phthalocyanine protease: IV membrane type metalloproteinase (MMP-17), MMP-25. Membrane metalloproteinases are located on the cell membrane of tumor cells and their fibroblasts, which are the receptors of MMPs, and MMPs activators, but also degradation of I, II, IV type collagen and FN. The expression of membrane metalloproteinases is regulated by soybean protein, oncogene and so on.

The fifth class is for other, such as matrix dissolution factor (MMP-7), metal

elastase (MMP-12), CA-MMP (MMP-23), enamelin (MMP-20), RASI-1 (MMP-19), which MMP-7 can degrade IV type collagen, fibronectin and gelatin.

2.4 The role and function of MMPs

Under physiological conditions, MMPs exist in a variety of normal cells, MMPs expression levels and activity of normal adult is low, and only in the system to accept the stimulus or in a pathological state it will rise. After activated, MMPs can degrade a variety of extracellular matrix components, involved in growth, development and tissue repair, recovery of the changes of the size and shape in genital function. The degradation of ECM is a key step in many physiological and pathological processes involving tissue remodeling, tissue infiltration, and so on[12,13].

2.4.1 Degradation of extracellular matrix

Extracellular matrix is an important internal environment of cell survival, which not only contains collagen, glycoprotein, proteoglycan and other ingredients, but also contains a large number of proteases, cytokines, adhesion factors. Extracellular matrix plays an important role in maintaining the institutions and functions of normal tissue as well as in cell growth and differentiation. Proteolytic enzymes which is capable of degrading ECM are serine proteases, semis levuline proteases, aspartic proteases and MMPs. MMPs secreted by connective tissue and tumor tissue synthesis are the most important proteolytic enzymes that degrade ECM. Tissue cells first bind to the receptors on the surface of the basement membrane, such as fibronectin (FN) and laminin (LN), and then secrete MMPs and other degrading enzymes to induce stromal cell secretory enzymes to degradate the basement membrane and matrix.

2.4.2 In the role of neovascularization

The processes of neovascularization include a series of processes of capillary endothelial basement membrane degradation, endothelial cell migration and proliferation, neovascularization and new basement membrane formation. The vitro studies have shown that vascular endothelial cells and tumors can secrete proteolytic

enzymes to degrade ECM during angiogenesis and tumor metastasis. MMPs increase the effect of angiogenic factors such as VEGF, bFGF, TGF-***β***, TGF-***α***. Studies have confirmed that in the early stage of neovascularization in tumor nodules, MMP-2 has an important role. Forsyth believes that MMP-9 is associated with neovascularization, and up-regulate tumor angiogenesis and is a member of the angiogenesis initiation system. It has been reported that MMP-7 can accelerate the proliferation of endothelial cells in vitro in a dose-dependent manner and promote endothelial cells to secrete MMP-1 and MMP-2 to dissolve the basal membrane and P or connective tissue around the blood vessels. Some MMPs degradate X, VIII plow collagen NCI region producing endostatin fragments and the degradation products of fibrinogen can also inhibit the formation of blood vessels.

2.4.3 The regulation of cell growth

It has been reported that some MMPs can regulate cell growth. MMP-11 may inhibit the apoptosis of tumor cells by decomposing insulin-like growth factor binding protein-1, releasing insulin-like growth factor-1 (1GF-1). MMP-7 can degrade Fas ligand on cell membrane, inhibit Fas-mediated cell apoptosis and promote tumor cell growth.

2.4.4 Regulate cell adhesion

Adhesion between tumor cells and between host cells plays an important role in tumor invasion and metastasis. Studies have shown that integrins play an important role in cell invasion and can directly regulate the migration of cells in ECM and regulate the expression of MMPs. Another example is the melanoma cells expressing intercellular adhesion molecule-1 (1CAM-1), can be associated with white blood cells, and is conducive to tumor cells gathering in the blood vessels and piercing tumor cells.

2.4.5 Activate a potentially active protein

Studies have shown that MMPs can activate two kinds of potentially active

proteins, namely plasma fibrin and laminin-5. Folkman has isolated a protein-vasatin with a strong anti-vascular proliferative activity. It was also found that MMP-3, 7, 9 and 12 could degrade plasma fibrin into a similar fragment of angiostatin. Further experiments showed that only activated MMP-2 could cleave laminin-5 and play a role. MMP-2 can activate the potential activity of ECM structural proteins and play an important role in attracting inflammatory cells and spontaneously stimulating tumor cell migration.

3. Enzyme-responsive NP

There are many specific enzymes in the microenvironment of tumor tissue, including MMP, phospholipase, glycosidase and esterase, etc., which is with high concentration and abnormally high activity. Thus, they have been widely used to regulate targeted drug delivery and release[14].

The first method is to directly bind the lipophilic drug to the hydrophilic polymer through an enzyme cleavable bond and further self-assemble into micelles for antitumor drug delivery and tumor imaging, such as MMPs specificity cleavable peptide Gly-Pro-Leu-Gly-Val (GPLGV). PEG-peptide-DOX micelles can improve the release and delivery of DOX in vitro and in vivo.

The second method is to use an enzyme cleavable linker to link the fragments of the polymer or to use a enzymatically degradable material to hold the chemotherapeutic agent or imaging agent and release them by enzymatic degradation, hydrolyzing with hydrogel crosslinking is one of the most commonly used formulations. For example, by loading cisplatin in a PEG-diacrylate hydrogel sheet attached to an MMP substrate and controlling the release of cisplatin from the hydrogel upon degradation of the MMP to improve treatment The treatment of glioblastoma (GBM). Gelatin is another frequently used nanocarrier that can be degraded by MMP-2, which is overexpressed in ECM. A recent study by Wong et al. Showed that multistage NPs covered with a 10 nm quantum dot consisting of 100 nm gelatin cores showed deeper tumor spread. The triggering release of the smaller NP in

MMP degradation reduces the diffusion barrier in the gap matrix compared to the larger NP. At the same time, the lymphocyte clearance rate of 10 nm NP was significantly lower than that of free small molecule drugs

4. Conclusions

The imbalance of matrix metalloproteinases and tissue inhibitors in the extracellular matrix is associated with a variety of pathologic mechanisms, particularly in relation to tumor invasion and metastasis. New MMPs are constantly being found. MMP family is also rapidly expanding, hopeing that with the deep understanding of MMPs function, so that we have a more specific and accurate understanding of the relationship between cells and their living environment, especially the matrix. There is a deep understanding of the role of metalloproteinases in the regulation of cells.

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