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Opinion

Research Progress of Matrix Metalloproteinases Deriving from Parasites

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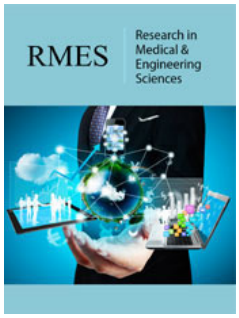

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Opinion

Matrix metalloproteinases (MMPs) is a large family. It is named because it needs metal ions like Ca2+, Zn2+as cofactors. Its family members have similar structures and are generally composed of five domains with different functions:

A. The hydrophobic signal peptide sequences;

B. The prepeptide region, mainly used to maintain the stability of the zymogen. When the region is cut off by exogenous enzymes, MMPs zymogen is activated.

C. The catalytic active region, having zinc ion binding sites, crucial for the enzyme catalysis.

D. The hinge region rich in proline.

E. The carboxyl terminal region, related to the substrate specificity of the enzyme [1].

The enzyme catalytic active region and prepeptide region are highly conservative. MMPs members have their own characteristics based on the above structures. There is a certain substrate specificity among various MMPs, but it is not absolute. The same MMP can degrade multiple extracellular matrix components, while a certain extracellular matrix component can be degraded by multiple MMPs, but the degradation efficiency of different enzymes can be different. According to its different substrates and its different composition domains, MMPs is divided into collagenase (MMP-1-8, - 13, - 18) , gelatinase (MMP-2, -9), stromal lysin (MMP-3, -10, -11), matrix lytic factor (MMP-7, -26), membrane type matrix metalloproteinases (MT MMPs) (Type I transmembrane proteins: MMP-14, -15,-16,-24 Glycosylphosphatidylinositol anchored proteins: MMP-17, - 25), and other matrix metalloproteinases (MMP-12, -19, -20, -21, -22, -23, -27, -28) [2].

MMPs degrades extracellular matrix components and peptide hormones through hydrolysis and activates MMPs precursor molecules to participate in embryonic development, angiogenesis, tissue homeostasis, wound repair, inflammatory response and other important biological functions [1,3]. When parasites infect the host body, the host can produce MMPs, which plays a role in destroying its own physical barrier or organizational structure, regulating the development and outcome of parasitic diseases, participating in immune escape [4]. At the same time, MMPs produced by parasites can promote parasites to invade the host. As biological markers of parasites, MMPs produced by parasites can be used as diagnostic antigens of parasitic diseases and may also be used as candidate vaccines [5,6]. It can be seen that host MMPs and parasite MMPs play very important roles in parasitic diseases. When parasites infect the hosts, they can cause changes in MMPs of the hosts, and there are also MMPs in the parasites, but there are few studies on MMPs of the parasites.

At present, some MMPs from the parasites were found. Lam [5] reported when *Naegleria fowleri* infected the artificial basement membrane for 2 hours, the composite materials of the basement membrane were destroyed [5]. Through electron microscope scanning, the researcher found the *N. fowleri* trophozoites invaded the basement membrane. Western immunoblotting indicated the presence of the metalloproteinases MMP-2 (gelatinase A),

MMP-9 (gelatinase B) and MMP-14 [membrane type-1 matrix metalloproteinase (MT1-MMP)] in *N. fowleri*. Highly virulent mouse-passed amoebae expressed higher levels of MMPs than weakly virulent axially grown amoebae. When the basement membrane exited, the hydrolytic activity of *N. fowleri* MMPs increased. When the inhibitor 1,10-Phenanthroline was used, the activity of *N. fowleri* MMPs and the number of N.fowleri trophozoites entering the artificial basement membrane were significantly inhibited, indicating that the vitality and invasion of trophozoites are at least partially dependent on the hydrolytic activity of MMPs proteins in the parasites . The main surface glycoprotein GP63 of *Leishmania* is a 63000 M (r) zinc metalloproteinase, which exists on the promastigots and amastigotes of different species of *Leishmania* [6]. GP63 could degrade extracellular matrix, and Zn2+ enhanced its activity, while zinc chelating agent and α2 macroglobulin inhibited its protease activity. It is predicted that GP63 is a precursor protein, and the NH2 terminal contains a precursor region related to the regulation of protease activity, which needs to be activated to give full play to protease activity. GP63 was recombined by baculovirus expression system. When it was incubated with HgCl2, the enzyme activity of GP63 was significantly enhanced. Host cell proteins, such as SHP-1, Synaptotagmin XI, VAMP8, and Syntaxin-5 are bona fide GP63 substrates [7]. SjSte24p is a monoexonic gene constantly expressed in the *Schistosoma japonicum* from cercariae to adult stages [8].

The expressed recombinant SjSte24p protein showed a proteolytic activity, which was inhibited by EDTA, activated by Zn2+. A metalloproteinase property of Taenia *solium metacestode* (TsMP) showed high specificity and proteolytic activity, which prefered host extracellular matrix proteins like collagen and fibronectin as degradable substrates [9]. A protein of *Onchocerca volvulus* (named Ov-AST-1) is identified as a member of the astacin family of zinc endopeptidases in excretory-secretory worm products [10]. The recombinant Ov-AST-1 protein in baculovirus-infected insect cells exhibited MMP enzymatic activity. Ov-AST-1 is also considered as a candidate of vaccine for intervention filarial infections. Janwan used a recombinant MMP protein from *Gnathostoma spinigerum* as antigen, through Western Blotting (WB) and dot enzyme linked immunosorbent assay (Dot ELISA) to examine the serum of patients with echinococcosis, finding that the sensitivity reached 100%, the specificity of WB run up to 94.7%, and the Dot ELISA was 96.1%, which indicates that MMP protein can be used as diagnostic antigen of echinocandinostoma disease [11]. We had cloned a gene named CEMMP62 from *Caenorhabditis elegans*, the putative 62-kDa protein that contains 579 residues with MMP-conserved catalytic domain known as ZnMc-MMP and shows high identities with MMPs from Homo sapiens [12]. Western blot analysis revealed that sera from BALB/c mice immunized by recombinant protein could recognize excretory-secretary (ES) antigens from *A. cantonensis* third-stage larvae (L3). The results implies that protocol CEMMP62 has homologous proteins which exist in *A. cantonensis*. Recently, we have added ES from *Angiostrongylus cantonensis* larva to the gel containing collagen and found obvious collagen hydrolytic bands. After adding Ca2+, their hydrolytic activity increased. We predict they are matrix metalloproteinase -like substances, and the follow-up work is in progress.

To sum up, in parasitic infection, MMPs of the hosts and MMPs of the parasites play important roles in the occurrence and development of parasitic diseases. However, at present, the study mainly focuses on the MMPs of the hosts infected with some protozoan and worms. It is worth noting that, compared with the study of MMPs of the hosts, the study on the related functions of MMPs of the parasites is still relatively scarce, and whether there is an interaction between MMPs of the hosts and MMPs of the parasites needs to be explored. Several MMPs deriving from protozoan and worms have been found. Some of them have certain homology and some of them have high specificity, but they are quite different from the MMPs of the hosts. The important role of MMPs in the occurrence and development of tumors being considered [13], can the use of these MMPs deriving from protozoan and worms to immunize animals inhibit the activity of MMPs in animals, thus playing a role in the prevention and treatment of tumors?

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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