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Commentary

Role of matrix metalloproteinases in physiological processes & disease

Proteases are enzymes that catalyze proteins by hydrolyzing peptide bonds that link the amino acids. Metzincins are a universally expressed family of multidomain zinc (II)-dependent endopeptidases[1,2], which includes metalloproteases such as matrix metalloproteinases (MMPs)[3]. A highly conserved motif containing 3 histidines that bind to zinc at the catalytic site and a conserved methionine that sits beneath the active site distinguishes the metzincin super family from others[4]. Metzincins, apart from participating in the digestion of proteins, tissue development, maintenance and remodelling, are also involved in highly specific cleavage events to activate or inactivate themselves or other proenzymes or active enzymes and bioactive peptides[5]. The MMPs dependence on metal ions as cofactors, their ability to degrade extracellular matrix and their specific evolutionary DNA sequence distinguish them from other endopeptidases[6].

High levels of MMPs are usually observed in disease state and pathological processes involved in connective tissue degradation such as inflammation[7]. Timely degradation of extracellular matrix (ECM) is an important feature of tissue repair and modelling and is precisely regulated under normal physiological conditions, but when dysregulated, it is the cause of many diseases such as cancer, fibrosis in pancreatitis, *etc*[8]. Various types of proteinases are known to be implicated in ECM degradation, however, the major enzymes are MMPs also known as matrixins[9].

Genes responsible for MMPs transcription are inducible and can also be activated by various chemicals such as phorbol esters. Transforming growth factor – beta (TGF-β), glucocorticoids and retinoic acid are some of the factors known to suppress the expression of matrix-metalloproteinase (*MMP)* genes. Activator proteins (AP) -1 and -2 sites, the polyomavirus enhancer-A binding protein-3 (PEA3) site, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*k*B) site, and the signal transducer and activator of transcription (STAT) site are some of the known key transcription binding sites involved in the regulation of *MMP* genes. MMP genes may also be induced through various signaling pathways (inflammatory cytokines like tumour necrosis factor and interleukin-1 indirectly influence the expression of *MMP* genes and trigger the ceramide signaling pathway). Finally and importantly, natural sequence variations in the promoter regions of the *MMP* genes may also modify the expression of the genes[7].

Plasma MMP levels, promoter polymorphisms and risk of pancreatitis

Several studies[10-12] have identified that plasma MMP-1, MMP-2, MMP-7 and MMP-9 levels may be susceptibility factor for chronic pancreatitis with higher levels associated with the pancreatitis group. Functional polymorphism of *MMP*-3 (5A/6A) was not associated with chronic pancreatitis (CP), however, higher levels of the protein were seen in the diseased group[13]. Another study[14] revealed a significant association of the MMP-1 -1607 1G/2G (rs1799750) gene promoter polymorphism with Indian CP. Polymorphisms in the promoter regions of MMP-2 (-1306 C>T, -735C>T), MMP-7 (-181 A>G) and MMP-9 (-1562 C>T) have been reported to be functional polymorphisms[15]. Shek *et al*[16] examined MMP and tissue inhibitor of metalloproteinase (TIMP) synthesis by transformed cultured pancreatic stellate cells and their regulation by TGF-β and concluded that pancreatic stellate cells expressed both mediators of matrix remodelling and the regulatory cytokine TGF- β 1 that, by autocrine inhibition of MMP-3 and MMP-9, may enhance fibrogenesis by reducing collagen degradation.

Future perspectives

The precise role of these proteins in various pathways and their role in carcinogenesis, other tumour related processes, fibrosis in pancreatitis *etc*., needs to be understood. There is a great potential in developing drugs that inhibit MMPs and studying the effects elicited by such drugs on critical aspects of pancreatitis and other important diseases. An interesting approach apart from synthetic MMPs inhibitor is the use of gene therapy aimed at delivering TIMPs at the site of the disease[17,18]. Moreover, there is a new field of non-catalytic targeting of MMPs via substrate-targeted inhibitors. There is also a possibility to regulate transcription, activation and inhibition of MMPs, which may help in designing newer strategies to block their unwanted activity in disease process.

The first generation of MMP inhibitor drugs was based on the structure of collagen molecule. The MMP inhibitors first tested in patients could not show good oral bioavailability[19]. Most MMP inhibitors are unable to target specific MMPs associated with specific pathological conditions, instead these inhibit multiple MMPs, some of which might have protective functions[20]. Therefore, the primary goal of MMP inhibitor design is selectivity. The targeting of specific MMPs is expected to improve efficacy and prevent side effects. Three dimensional (3D) structure analyses of MMPs could provide a source of insight of the structural relationships for selectivity.

In general, individual single nucleotide polymorphisms (SNPs) have limited value as predictors of complex multifactorial disease because of their modest effect on the phenotype. The ability to predict the susceptibility of a population to a disease increases tremendously with identification of newer susceptibility loci. SNPs in various genes have been identified for chronic pancreatitis namely *SPINK1*, chymotrypsin C (*CTRC*), calcium sensing receptor (*CASR*), trypsinogen gene (*PRSS1, 2* and *3*), cathepsin B (*CTSB*), serine protease inhibitor kazal type 1 (*SPINK1/PST1*), cystic fibrosis trans-membrane conductance regulator (*CFTR*) gene[21]. Most of these are in the pancreatic trypsin regulatory mechanism, however, many genetic factors outside this mechanism are being discovered for their role in pancreatitis namely claudin-2 (*CLDN2*), carboxypeptidase A1 (*CPA1*), *etc*. The study by Sri Manjari *et al*[22] in this issue looked at the association between a SNP in *MMP-7* gene (-181 *A/G*, rs11568818), serum levels of the protein and chronic pancreatitis. They report a significant association of the GG genotype with the disease, however, there is no significant difference in the serum levels of MMP-7 between patients and controls. Further, they suggest that there is a high risk of pancreatitis in alcoholics and those with the GG genotype. Finally, the polymorphisms identified in *MMP* genes with functional significance could add to the already existing markers for pancreatitis and could be used in the diagnostic workup for patients with pancreatitis.

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