Diagnosing, Prognosticating and Treating Collagenase-1 (Matrix Metalloproteinase-1) Related Diseases

Technology #j173

Degradation of the extracellular matrix is part of the pathological process associated with many diseases: e.g., joint destruction in arthritis, invasion and metastasis in cancer, bone dissolution in periodontitis, and plaque rupture in atherosclerosis. Most of this connective tissue degradation is accomplished by a family of enzymes called the Matrix Metalloproteinases, or MMPs, a family of enzymes that, collectively, degrade most matrix components. A sub-family of MMPs is the interstitial collagenases, enzymes that specifically degrade the stromal collagens, types I, II and III. Since these collagens are the most abundant protein in our body, the collagenases have a major role in connective tissue modeling and remodeling.

Of the three interstitial collagenases, MMP-1 (collagenase-1) is the most ubiquitously expressed. It is produced by a wide variety of normal cells, e.g., stromal fibroblasts, macrophages, endothelial cells, and epithelial cells, as well as by numerous tumors, suggesting a broad-based role for this collagenase in tumor biology. Normally, expression of MMP-1 by most cells is low, but is readily induced by phorbol esters, growth factors and inflammatory cytokines. In contrast, some tumors display constitutively high levels of MMP-1 expression, even in the absence of apparent external stimuli.

A genetic variation in the MMP-1 promoter can influence the level of MMP-1 transcription, and hence, the potential of this gene to mediate connective tissue degradation. This variation is a single nucleotide polymorphism (SNP) located at −1607 bp, where an insertion of a guanine base (G) creates the sequence, 5'-GGAT-3', the core binding site for members of the Ets family of transcription factors. We have demonstrated that the 2G DNA displays heightened MMP-1 transcription in both tumor cells and in normal fibroblasts, and the levels of MMP-1 expression may result from the presence of the 2G allele and from elevated expression of the transcription factors that bind to this site.

This SNP in the MMP-1 promoter is not a rare mutation or genetic variation found in a few tumor cells. Genotyping of 100 normal individuals indicated that the distribution of this SNP in the normal population is approximately: 30% = 1G homozygous; 30% = 2G homozygous; 40% = 1G/2G heterozygous. However, in tumor cells cultured in vitro, the incidence of the 2G allele rises to 62% (P = < 0.001), supporting the hypothesis that it correlates with aggressive tumors. This in vitro correlation has been confirmed in vivo, where patients with ovarian cancer had a significantly higher incidence of the 2G allele, compared to non-cancer controls, and expressed higher levels of MMP-1 protein.

The hypothesis is, therefore, that heightened MMP-1 expression results from the presence of (a) the 2G allele and (b) the appropriate transcription factors that bind to this site. In the absence of these factors, MMP-1 expression from the 2G allele is not necessarily increased compared to the 1G allele. The precise identity of the Ets family member(s) binding to this site is not known, and it is possible that several Ets proteins can function to drive transcription. Once the identity of these proteins is determined, they may become a target for therapeutic intervention to reduce MMP-1 expression in certain diseases.
Given the strong link between increased MMP-1 expression and the presence of the 2G allele, it is possible that a simple genetic analysis of this polymorphism may provide a useful and potentially important mechanism for predicting prognosis in certain diseases, such as cancer, arthritis, cardiovascular disease, and periodontitis. Inhibiting MMP-1 synthesis represents a new therapeutic approach of molecular medicine for the 21st century.

This technology is claimed in the issued United States Patent Nos. 7,033,756 and 7,473,774. We are seeking an industrial partner interested in its commercialization. (Ref: J17)