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The Clinical Aspects of Epilysin (MMP28)

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Background

Gastric cancer (gastric carcinoma) cells have been found to have higher levels of a mutated form of the matrix metallo-proteinase Epilysin (MMP-28). The study of metalloproteinases like epilysin focuses on structurally similar enzymes that include a metal core. These proteins play important roles in breaking down other material found in the spaces between individual cells including other proteins, growth factors.

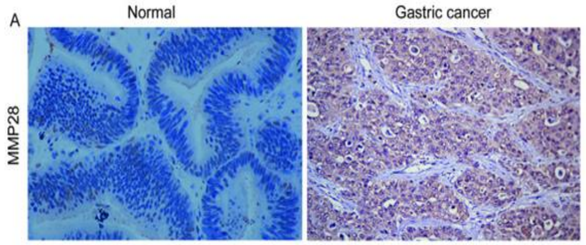

Figure 1: Overexpression of MMP28 protein in gastric cancer is correlated with tumor aggressiveness and poorer prognosis (Jian, et al. 2016).

Introduction

Epilysin is one of the members of the matrixmetalloproteinase (MMP) family. Epilysin has been shown to be expressed in many human tissues such as testes, lung, intestine, heart, brain, and keratinocytes in skin. The protein is made up of 520 amino-acids which include a signal peptide, a prodomain with an unusual cysteine-switch region followed by the furin cleavage site, a catalytic domain, a hinge-region and a hemopexin domain (see Figure 5).

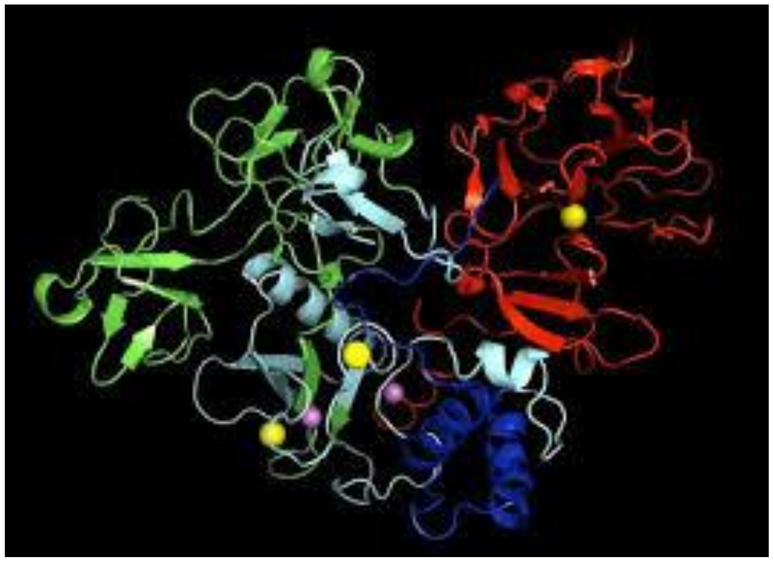

Figure 2: Three-dimensional structure of Epilysin (MMP28). Sites indicated in yellow are zinc ions (Kalluri, R, et al. 2009).

Epilysin is responsible for restructuring of the basement membrane and adhesive proteins between karyocytes to supply newly formed cells. In different cancer tissues, increased expression of mutant epilysin results in activation of tumor growth factors that promote cell division and growth while also promoting stable and irreversible epithelial to mesenchymal transition (EMT) accompanied by loss of cell surface adhesion.

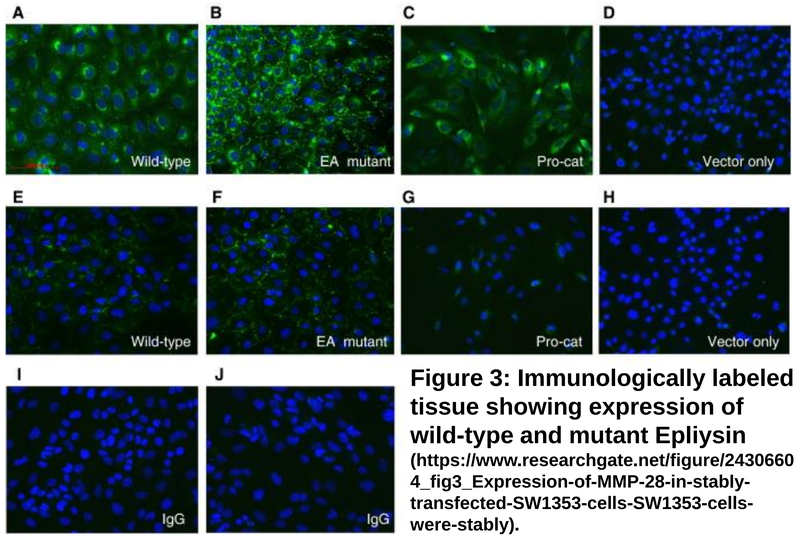

Figure 3: Immunologically labeled tissue showing expression of wild-type and mutant Epliysin (https://www.researchgate.net/figure/243066604_fig3_Expression-of-MMP-28-in-stably-transfected-SW1353-cells-SW1353-cells-were-stably).

Figure 4: Amino acid sequence of Epilysin (MMP-28). Mutations occur mostly on the N-terminus and represent a signal peptide and prodomain (Smart BLAST. (n.d.). Retrieved April 01, 2016, from http://blast.st-va.ncbi.nlm.nih.gov/blast/smartblast/smartBlast.cgi).

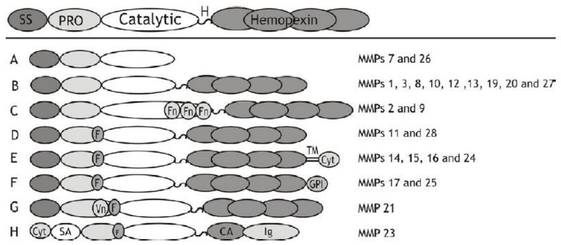

Figure 5: Homologous architecture of the MMP protein family. Abbreviations: SS, signal sequence; PRO, propeptide; Catalytic, catalytic domain; H, hinge region; Hemopexin, hemopexin domain; Fn, fibronectin type II inserts; F, furin-cleavage site; TM, transmembrane domain; Cyt, cytoplasmic domain; GPI, glycosylphosphatidyl inositol anchoring domain; Vn, vitronectin-like sequence; CA, cysteine array; Ig, immunoglobulin-like domain (Illman, 2007).

Epithelial to mesenchymal transition is a fundamental biological process where epithelial cells lose their polarity and adopt morphology appropriate for migration (and, if carcinoma, metastasis). The second type of EMT which occurs in the epithelial tissues is mediated by inflammatory cell and fibroblast which release a variety of inflammatory signals which lead to organ fibrosis, the thickening and scarring of connective tissues. Therefore epithelial cells are important precursors for fibroblasts that begin during the course of organ fibrosis. Matrix metallo-proteinases degrade the extra-cellular membrane and release bioactive fragments and growth factors (including tumor growth factors), fundamental for tumor genesis.

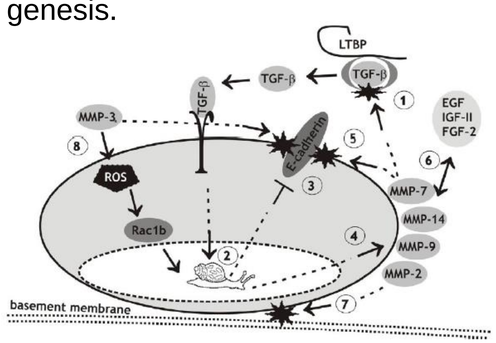

Figure 6: MMPs affect EMT. MMPs can contribute to EMT by different actions. MMPs release and activate ECM-bound latent TGF-β (1). MMPs also release other growth factors from the ECM that facilitate the induction of EMT and also regulate the expression of the MMPs themselves (6) (Illman, 2007).

References

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