Editorial

MMP7 Polymorphisms - A New Tool in Molecular Pathology to Understand Esophageal Cancer

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Esophageal cancer is one of the most aggressive malignant gastrointestinal tumors and the majority of esophageal cancers are squamous cell carcinoma (ESCC) or adenocarcinoma (AC). In the Asian population almost all cases of esophageal cancer are squamous cell cancers, whereas in the Western world adenocarcinoma occurs more often and its incidence has risen over recent decades (source: GLOBOCAN; http://globocan.iarc.fr). Patients with ESCC have a propensity to present with extensive local invasion and regional lymph node metastasis thereby leading to a worse prognosis than those with other digestive tract cancers even after curative surgical resection.[1] In the multi-step process of carcinogenesis, tumor invasion step requires the degradation or breakdown of the extracellular matrix (ECM) and connective tissue surrounding the tumor.[2] In this issue of the Saudi Journal of Gastroenterology, Malik and co-workers[3] assessed the association of MMP-7 (-181A>G) polymorphism with the esophageal cancer in the Kashmir Valley of India.

MMPs are a family of zinc-dependent proteolytic enzymes capable of degrading the ECM, and have been demonstrated to be involved in carcinoma invasion and metastasis by degrading the extracellular components.[4-6] MMP-7 is the smallest molecule of the MMPs. It can degrade laminin, type IV collagen, and entactin, which are the main components of the basement membrane, and activate other important MMPs (MMP-1, MMP-2, and MMP-9).[7,8] It can also inactivate α1-antitrypsin, which augments the serine protease activity, and thus activates MMPs indirectly.[9] MMP7 is overexpressed in a variety of epithelial and mesenchymal tumors, such as esophagus, colon, liver, renal, and pancreas. Its expression is correlated with tumor progression, metastasis, and unfavorable prognosis in the human esophageal carcinoma, colon, and gastric carcinoma.[10-12] On the other hand, MMP-7 was also found to contribute to early tumor development especially in tumors of gastrointestinal tract.[4,13] There are at least three regulatory mechanisms that may influence activities of MMPs - regulation of transcription, activation of latent MMPs, and inhibition of MMP function by tissue inhibitors of metalloproteinases. However, the most important step may be transcriptional regulation, since most MMP genes express only when active physiological or pathological tissue remodeling takes place.

Growing evidence indicates that natural sequence variations in promoters of the MMP genes may result in variable expression of MMPs in different individuals. These polymorphisms have been associated with susceptibility to some diseases including cancers.[14,15] In the promoter region of the MMP-7 gene, two single nucleotide polymorphisms (SNPs), an A to G transition at the -181 base pair position (-181A/G) and a C to T transition at the -153 base pair position (-153C/T), have been proved to be functional *in vitro* and may influence coronary artery dimensions.[16] Recently, the -181A/G SNP has been associated with increased risk of development and metastasis of colorectal cancer while the -153C/T polymorphism seems to be less involved in susceptibility to this tumor.[17] However, another study suggested MMP-7 -181A/G polymorphism might be a candidate marker for predicting individuals with a higher risk to develop ESCC, gastric carcinoma, and non small cell lung carcinoma.[18] Most recently, the author and his co-workers reported that the individual living in the Kashmir Valley carrying -181 GG genotype was associated with high risk of gastric cancer, indicating that common MMP-7 (-181A>G) genetic polymorphism may contribute to squamous cell gastric cancer susceptibility in the Kashmir valley.[19]

Malik and co-workers assessed the association of MMP-7 (-181A>G) polymorphism with the esophageal cancer in the Kashmir Valley of India. The investigators found that the individual carrying GG genotype had 2.17 fold increased risk to develop EC while the individual with A allele had 2.16 fold lower risk of EC. Moreover, the author and his colleagues found that GG genotype was associated with higher risk to develop ESCC, not adenocarcinoma of esophagus cancer while environmental factors (salted tea and smoking) did not modulate cancer risk by MMP-7 (−181A>G) genotype. All together, these data are very interesting and warrant further large-scale, case-controlled studies of MMP-7 (-181A>G) polymorphism as a biomarker to predict high-risk individuals

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for the development of EC. Treatment of esophageal carcinoma will evolve with the strides made in molecular diagnostics and targeted therapy. Commonly occurring SNPs should be meticulously studied in populations where there is paucity of such data, to learn more about the molecular signature of the tumors.

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