

The MMPs Genes Polymorphisms: Potential Role in Pharmacogenomics and Target Therapy

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The evidence that individual characteristics play an important role in physiological and pathological processes has resulted in the targeted study of genetic polymorphisms in the clinical setting. In this context, mediators that degrade the extracellular matrix (ECM), such as Matrix Metalloproteinases (MMPs) are focused in studies involving inflammatory and degenerative diseases, and principally the prognosis and metastasis of cancer [1].

MMPs have important roles in different physiological and pathological processes, as they regulate various cell processes such as angiogenesis, cell proliferation, apoptosis, alteration of cell motility, effects on the immune system and host defence, modulation of the bioactivity of chemokines [2,3], and connective tissue remodeling associated with cancer invasion and metastasis, cartilage destruction in arthritis, atherosclerotic plaque rupture, and the development of aneurysms [4].

In addition to a remarkably common 3-D structure [3,5], MMPs share a similar gene arrangement, suggesting that they arose by duplications of an ancestor gene. At least eight of the known human MMP genes (MMP-1, -3, -7, -8, -10, -12, -13 and -20) are clustered on chromosome 11 at 11q21-23. Other MMP genes are scattered among chromosomes 1, 8, 12, 14, 16, 20, and 22 [6].

Recently, naturally occurring sequence variation (DNA polymorphisms) has been detected in the promoter of several MMP genes, controlling gene transcription [3].

DNA polymorphism represents natural sequence variants (alleles), which may occur in more than one form. These appear in at least 1% of a population and are considered biologically normal, and have been estimated to occur on the average at one in every 1000 base pairs throughout the human genome [4,7].

Approximately 90% of DNA polymorphisms are single-nucleotide polymorphisms (SNPs) due to a single base substitution [8].

Apart from SNPs, there are minisatellite (0.1-20 kb long) and microsatellite (0.1 kb long) polymorphisms which result from variation in the number of tandem repeats of DNA sequence. The majority of microsatellite polymorphisms occur at di-nucleotide repeat sequences, such as (CA)_n repeats. Generally, SNPs are bi-allelic whereas microsatellite polymorphisms are multi-allelic [4].

Although the majority of DNA polymorphisms in MMPs genes are probably functionally neutral, a proportion of them can exert allele specific effects on the regulation of gene expression by altering the interaction between transcription factors and transcription-binding sites in the corresponding promoters, resulting in higher or lower transcriptional activity of the coded protein and having dual roles in disease [3,4], which may contribute to inter-individual differences in various biological phenotype traits, to increased susceptibility to the development of different pathologies and their prognosis [1], such as coronary heart disease, abdominal aortic aneurysm, and cancers

[4], likely through effects on the balance between the synthesis and degradation of extracellular matrix proteins and to differential response to pharmacological agents.

Many studies described in literature have suggested a correlations between single nucleotide polymorphisms of MMPs genes with several no cancer diseases and cancers [1], such as: lung cancer, head and neck cancer, renal cancer, esophageal cancer, colorectal cancer and breast cancer [9-12] (Table 1).

Furthermore, it is important to consider that MMP polymorphisms may not occur as independent events and could be associated with other polymorphisms in the genome, forming an haplotype [1,56]. Haplotypes are a combination of alleles at multiple loci that are transmitted together on the same chromosome. The interaction of different MMPs SNP induce an additive effect and increase the susceptibility to developing a disease, such as in the case of MMP-8, MMP-10, MMP-3 and MMP-14 polymorphism association in Ulcerative Colitis [57]. A previous study suggested that genetic variations in the MMP family, including MMP-1, -3, -8, -12 and -9, are associated with bladder cancer risk [56] whereas the haplotype +6727 C: +6767 G: +7096 T: +8153 G of MMP-14 gene might contribute to the prediction of susceptibility and pathological development of Oral Squamous Cell Carcinoma [58].

Also other studies suggested that the C(-1306)-C(-735) haplotype in the MMP-2 promoter contributes to risk of the occurrence and metastasis of esophageal squamous cell carcinoma by increasing expression of MMP-2 [22].

Haplotype effects may provide more complete and reliable information than single polymorphism analysis, which may contribute only partially to the MMP pathway [56].

Despite genomic studies coupled to functional analysis of promoter regions of MMP genes have already provided important information about the molecular mechanisms controlling their expression in health and disease these genetic approaches to MMP function are limited by poor methodology in many studies [1]. Further progress will depend

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Received January 23, 2012; Accepted January 24, 2012; Published January 26, 2012

Citation: Mannello F (2012) The MMPs Genes Polymorphisms: Potential Role in Pharmacogenomics and Target Therapy. J Pharmacogenom Pharmacoproteomics 3:e114. doi:10.4172/2153-0645.1000e114

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Gene	Polymorphisms	Promoter Activity	Associated pathology	
			Tumor disease	Non tumor disease
MMP1	-1607 1G/2G	Higher	↑ Risk: lung [13] and colorectal [14] cancer, renal cell carcinoma [15] Poor prognosis: breast [16] and ovarian [17] cancer, cutaneous malignant melanoma [18]	↑ Risk: idiopathic pulmonary fibrosis [19] Poor prognosis: cirrhosis [20]
MMP2	-1575 G/A	Lower	Breast cancer [21] (in vitro MCF-7 cells)	
	- 1306 C/T	Lower	↓ Risk: esophageal[22] and lung [23] cancer, gastric cardia adenocarcinoma [24], oral squamous cell carcinoma [25]	↓ Risk: lumbar disc disease [26]
	-735 C/T	Lower	↓ Risk: esophageal [22] and lung [23] cancer	
MMP3	-1171 5A/6A	Lower	↓ Risk: lung [27], breast [28] and oral [29] cancer	↑ Risk: atherosclerosis [30], myocardial infarction [31], aortic aneurysm [32] Poor prognosis: rheumatoid arthritis [33]
MMP7	-181 A/G	Higher	↑ Risk: gastric [34], cervical [35] and oral [36] cancer, esophageal squamous cell carcinoma and non-small cell lung carcinoma [37]	Poor prognosis: atherosclerosis [38]
MMP8	-799 C/T	Higher	Better prognosis: breast cancer [39]	↑Risk: preterm premature rupture of membrane (haplotype) [40]
	-381 A/G	Higher		↑Risk: preterm premature rupture of membrane (haplotype) [40]
	+17 C/T	Higher	↓ Risk: lung cancer [41]	↑Risk: preterm premature rupture of membrane (haplotype) [40]
MMP9	-1562 C/T	Higher	↑Risk: oral cancer [42,43]	↑Risk: atherosclerosis [44], abdominal aortic aneurysm [45], myocardial ischemia [46], schizophrenia [47], bipolar mood disorders [48,49], varicose vein [50]
	(CA) _n	Higher > 20	↑Risk: bladder cancer [51]	↑Risk: carotid atherosclerosis [52], multiple sclerosis [53]
	Microsatellite	CA repeats		Cerebral aneurysm [54], age-related macular degeneration [55]
MP12	-82 A/G	Lower	Poor prognosis: bladder cancer [51]	

Table 1: Functional polymorphism in MMPs promoters.

on improved methods, including larger sample sizes, genotyping of haplotypes rather than single-nucleotide polymorphisms, better matching of cases and controls and, importantly, replicating positive findings in a second independent population before publication [31] extend these regulatory studies on MMPs to other levels of control including those based on epigenetic or miRNA-mediated mechanisms to clarify the relevance of these alterations in complex diseases such as cancer [1].

Such genetic polymorphisms are important because they can be used as biomarkers that herald various diseases and thus facilitate early intervention in patients at high risk [3], indeed polymorphisms in MMP genes has been shown to influence therapy outcomes by altering signaling pathways. Advances in genome technology and their comprehensive and systematic deployment to elucidate the genomic basis of MMP differences promise to ultimately enhance the efficacy of chemotherapy while reducing its toxicity for the treatment of various cancers [59].

The MMPs genes polymorphisms in clinical medicine is gaining increasing attention in identifying genetic region or genes implicated in common complex diseases and traits such as Central Nervous System disorders, cancer and cardiovascular diseases [56]. A major application of SNP efforts is using small variations in genes sequences as markers for defining populations exhibiting a given phenotype. Thus

the major drivers for the SNP efforts in health care are defining genetic regions and targets for therapeutics, stratifying patient populations according to expression of SNP markers (and corresponding biological phenotype), and positioning drugs into the appropriate sub sectors of patient populations.

Harping on SNPs of MMPs promoters and better understanding the potential pharmacogenomics role, will give a fruitful return in the form of better understanding of complex diseases by deciphering metabolic pathways, reduction of drug toxicity, development of predictive genetic test and this will lead ultimately to the development of individualized medicine prescribing practices [60].

The impact of genetics on medicine will be even more widespread. The pharmacogenomics approach for predictive drug responsiveness will be standard practice for quite a number of disorders and drugs. New gene based “designer drugs” will be introduced in the market for diabetes mellitus, hypertension, mental illness and many other conditions. Improved diagnosis and treatment of cancer will likely be the most prominent clinical consequences of genetics. A vast amount of molecular information can be collected about the genetic basis of malignancy and on that basis every tumor will have a precise molecular fingerprint [61]. Cataloging the enzyme isoforms and their new cellular localization, the gene polymorphisms and the unexpected pathways involved [62], therapy will be individually targeted to that fingerprint

[63]. Many of the diseases can be identified where common variants in genes involved in drug metabolism [64] or drug action [65] are associated with the likelihood of a good or bad response [66].

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