REVIEW

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Genetic patterns of metalloproteinases and their tissular inhibitors – clinicopathologic and prognostic significance in colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third most common cancer in men and second in women. Progression and invasion of colorectal cancer is a multistep process involving multiple interactions between the tumor and the surrounding stroma mediated by many proteins, among them metalloproteinases (MMPs) and tissular inhibitors of metalloproteinases (TIMPs). We aimed to review the correlations between the expression of the MMPs and TIMPs genes and the clinicopathologic variables of the CRC. Levels of MMPs genes expression in colorectal cancer correlate with the depth of invasion, hematogenous and lymphatic metastasis, poor differentiation, Duke's stage and prognosis. Levels of TIMP's genes expression correlate with better prognosis and longer survival. There are also some controversial data explained by the fact that most of the studies addressed one or few MMPs and/or TIMPs. The methods to assess the variance in gene expression were not always the same. The promoter regions of metalloproteinases present many polymorphisms and all have allele-specific effects on regulation of MMP gene transcription. Numerous studies on the association of these polymorphisms with cancer susceptibility have been carried out. Most of the studies addressed one or two polymorphisms and their implications. A meta-analysis is necessary to confirm significant correlations. The heterogenicity of the MMPs and TIMPs genetic patterns generated by different studies on colorectal cancer does not allow us to have an overall correlation with clinicopathologic variables and the prognosis of the disease. Studies that involve many MMPs, TIMPs polymorphisms and their tissular expression would be more valuable to better assess the role of those enzymes in the progression of the disease and may serve as a starting point for selective therapeutic approaches.

Keywords: matrix metalloproteinases, tissular inhibitors of metalloproteinases, genetic polymorphism.

Introduction

Colorectal cancer (CRC) is the third most common cancer in men (663 000 cases, 10% of the total) and the second in women (571 000 cases, 9.4% of the total) worldwide. Incidence rates vary 10-fold in both sexes worldwide, the highest rates being estimated in Australia/New Zealand and Western Europe, the lowest in Africa (except Southern Africa) and South-Central Asia, and are intermediate in Latin America [1].

Carcinogenesis of colorectal cancer is a complex multifactorial and multistep process. Progression and invasion of the tumor in the surrounding stroma is also a complex process involving many interactions mediated by different proteins. Remodeling of stromal components allows both progression of tumor but also angiogenesis. The most important factors that are involved in stromal remodeling, capable to create a pathway for the tumoral cells are the metalloproteinases [2, 3].

Matrix metalloproteinases (MMP) form a family of zinc dependent endopeptidases that degrade the extracellular matrix, but also non-matrix proteins [4]. There are 24 human MMPs known and classified based partly on their substrate specificity and partly on their cellular localization: collagenases (MMP-1, MMP-8, MMP-13, MMP-18), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10, MMP-11), matrilysins (MMP-7, MMP-26), membrane-type MMPs (MT-MMPs) (MMP-14, MMP-15, MMP-16, MMP-24, MMP-17, MMP-25) and others (MMP-12, MMP-19, MMP-20, MMP-21, MMP-23, MMP-27, MMP-28) [4–6].

Metalloproteinases functions are regulated by specific inhibitors, named tissue inhibitors of metalloproteinases (TIMP) [3]. There are only four TIMPs described so far [5] – TIMP-1, TIMP-2, TIMP-3 and TIMP-4.

Although all members of the TIMP family inhibit MMP's activity, there is a selective inhibition. For example, Lambert E *et al.* [7] and Baker AH *et al.* [8] consider that TIMP-1 is an inhibitor for all the MMPs except membrane-type MMPs and MMP-19 for which the effect is less important. TIMP-2 inhibits MMP's activity but promotes cell surface activation of pro-MMP-2 [7–9]. TIMP-3 presents a selective inhibition of members of the A Disintegrin And Metalloproteinase (ADAM) family of proteases, by a mechanism that appears to be distinct from that of MMP inhibition [10, 11]. TIMP-4 has received less attention compared to other members of its family probably, and therefore less

is known about it [9]. Pathological conditions occur when MMPs and TIMPs act independently [4].

Implication of metalloproteinases and their tissular inhibitors in colon cancer has been extensively studied also for clinical and therapeutical purpose.

The effects of MMPs and TIMPs gene expression levels in CRC

Different studies have shown that variations in DNA sequence and gene expression for an important number of MMP and TIMP genes may be associated to CRC, but many of them produced conflicting results. In analyzing these results it is important to consider the methods employed in measuring TIMPs and MMPs intermediate (mRNA) and final (protein) gene products. Among MMPs, MMP-1, -2, -3, -7, -9, -11, and -13 have been studied the most.

MMP-1, -2, -3, -7, and -9 gene expression levels are found significantly increased in CRC tumors when compared to normal mucosa or with adenoma [12–23].

MMP-1 expression was correlated with invasion, metastasis and prognosis [10, 24, 25]. MMP-1 gene expression pattern was associated with poor differentiation [12] advanced Dukes' stage, lymphatic invasion [12, 17], hematogenous metastasis [12] and shorter survival [23].

MMP-2 expression is increased in CRC with infiltrative rather than expansive growth pattern, and it has positive correlation with poor differentiation [26] and liver metastasis [27].

MMP-3 expression was found significantly lower in CRC with high microsatellite instability and better clinical outcome than CRC without microsatellite instability [28]. This led to the hypothesis that MMP3 may be implicated in tumor invasion, lymph node involvement and metastatic spread. Işlekel H *et al.* [15] observed that MMP-3 is associated with lymph node metastasis.

The expression of MMP-7 was shown to correlate with Dukes' stage and increased metastatic potential [29]. Higher levels of MMP-7 expression were found in liver metastases when compared with normal liver tissue [21]. MMP-7 correlates with poor differentiation [19], depth of invasion, lymphatic involvement [19], advanced Dukes' stage [19, 30], metastasis [30–32], and unfavorable survival [30]. The prognostic significance of MMP-7 was proven also in multivariate analysis [30, 31].

Zuzga DS *et al.* [33] concluded that the overexpression of MMP-9 in tumor cells was associated with metastatic progression of colorectal cancer. MMP-9 was found to be related to the presence of perineural invasion [15].

MMP-13 overexpression may predict a poor prognosis in patients with CRC [34].

However, there are a few reports showing inconsistent results on expression of MMPs in CRCs [5]. Roeb E *et al.* have reported that expression of MMP-3 and -13 is greater in CRC but MMP-1 expression is not [21]. Bodey B *et al.* have observed high expression levels for MMP-3 and -10 in colon cancers but not for MMP-13 [35].

Unlike other MMPs, MMP-19, -26, and -28 express in the normal intestine, but are down-regulated in colon cancer. Thus, it has been proposed that they play a prominent role in tissue homeostasis [36].

Expression of multiple MMPs and their inhibitors in CCR and liver metastases was investigated by Asano T *et al.* [37]. They found a significantly higher expression of MMP-1, -3, -7, -9, -10 and -11 in tumors compared to normal tissue. In the metastatic liver foci they demonstrated lower levels of MMP-1 and -11 and higher of TIMP-1 comparing with primary cancer. They also suggested that the lower expression of MMP-15 is an important risk factor for early recurrence of the disease.

In another study, the expression of MMP-9 was significantly higher and expression of TIMP-3 significantly lower in parenchyma of the carcinoma tissue from the patients who died during the follow up compared to survivors. Expression of TIMP-2 in stroma cells of carcinoma tissue was significantly lower in dead patients group as compared to the survivors [38].

Impact of MMPs and TIMPs polymorphisms in CRC

The promoter regions of MMP-1 and MMP-3 genes are all-polymorphic and have allele-specific effects on regulation of MMP gene transcription. The promoter region of MMP-1 contains a guanine insertion/deletion polymorphism at position _1607 relative to the transcriptional start site, with one allele having a single guanine nucleotide (1G) and the other having two (2G).

The promoter region of MMP-3 is characterized by a 5A/6A polymorphism located at nucleotide position _1171 relative to the transcriptional start site, with one allele having five adenosines (5A) and the other having six adenosines (6A) [50–52]. Concerning the other MMP-3 polymorphisms, four are in substantial linkage disequilibrium with the -1612 ins/delA (-1986 T/C, -1346 A/C, -376 G/C, and +802 A/G), except one (-709 A/G) which is not of proven functional importance [53].

In the MMP-7 gene promoter region, two SNPs (-181 A/G and -153 C/T) have been shown to modify the gene transcription activity [54]. Recently, both SNPs have been associated with CRC susceptibility and the -181 G/G genotype was linked to distant metastasis [55].

Numerous studies on the association of these polymorphisms with cancer susceptibility have been carried out. However, the results remain inconclusive.

Lièvre A *et al.* [56] tested the role of MMP polymorphisms in the early step of colorectal carcinogenesis, comparing patients with large adenomas, small adenomas and polyp-free controls. No association was observed between the polymorphisms and large adenomas when compared to polyp-free or small adenomas. Comparison between small adenomas and polyp-free controls revealed a significant association between MMP-3 -1612 ins/delA polymorphism and small adenomas. An increased risk was associated with the 6A/6A genotype. For MMPs polymorphisms

the best association was found for MMP-3.1 (1612 ins/delA)-MMP1.

Zinzindohoué F *et al.* [57] studied the role of MMP-1 -1607ins/delG and MMP-3 -1612 ins/delA promoter polymorphisms in colorectal cancer and found that patients with the -1607insG/-1607insG MMP-1 genotype had significantly worse specific survival than the others. MMP-1 -1607insG allele showed to be an independent poor prognostic factor after adjustment on stage, age, and the use of adjuvant chemotherapy. MMP-3 polymorphism was not associated with survival.

Hinoda Y *et al.* [58] explored the association of MMP-1 and MMP-3 promoter polymorphism with colorectal cancer risk in a Japanese population and found that the MMP-1 2G/2G genotype frequency was higher in colorectal cancer patients when compared to controls. This genotype is known to be associated with higher enzyme activity. MMP-3 6A/6A genotype was also detected at a higher frequency in the patients group. This genotype is known to be associated with less activity of the enzyme. The studied MMP-1 and MMP-3 polymorphic loci were in linkage disequilibrium and that 2G-6A haplotype was significantly increased in patients compared to controls.

Xu E *et al.* investigated [59] MMP-1 -1607 ins/delG (1G/2G) polymorphism and matrix MMP-3 -1612 ins/delA (5A/6A) polymorphism in colorectal cancer in Chinese population and found that the genotype frequencies nor allele frequencies of MMP1 and MMP3 polymorphisms showed significant difference from control subjects. The two single nucleotide polymorphisms of MMP1 and MMP3 were in a strong linkage disequilibrium, but no significant difference was found in haplotype distribution.

Elander N *et al.* [60] investigated MMP-1, -2, -3 and -9 promoter polymorphisms in colorectal cancer and found that the MMP-1 2G allele was significantly associated with CRC. No evident association was detected between CRC and MMP-2, -3 or -9 polymorphisms. The analysis of polymorphisms in the clinicopathological subgroups did not display any significant associations.

Ghilardi G *et al.* [61] investigated the impact of 2G insertion type polymorphism on invasion and metastasis of colorectal cancer (CRC) and found that the proportion of 2G homozygotes was higher in the CRC group than in the controls. The CRC group was divided in two groups: with and without developed metastasis. At the time of diagnosis, 2G homozygotes were more represented in the group with metastasis. The difference between patients and controls had no statistical significance.

Woo M *et al.* [62] investigated the association between the promoter and exon polymorphisms of genes of MMP-1, -3, -7, -9, plasminogen activator inhibitor-1 (PAI-1) and MMP-12 and the susceptibility of colorectal cancer. The homozygous MMP-1 -1607 dupG genotype was found significantly more frequent in CRC patients than in healthy controls. The frequency of MMP-1 -1607 dupG homozygotes was also higher in patients of less than or equal to 50 years of age, and in patients with 10 or more metastatic lymph nodes, compared with those of older age or with fewer lymph nodes. The frequency of MMP-9 -1562 C homozygotes was significantly higher in CRC patients than in healthy controls. The MMP- 7 -181A-MMP1-1607 dupG-MMP-3 -1171A-MMP-12 -82A and MMP-9 -1562C-90(CA)(20)+279Q haplotypes were significantly more frequent in CRC patients than in healthy controls. The frequency of PAI1-675 G homozygotes was significantly greater in patents over 50 years of age.

Xu E *et al.* [63] investigated whether the MMP-2 -1306C>T polymorphism contributed to the development and progression of CRC in the Chinese population. The results showed that the levels of MMP-2 mRNA expression in cell lines containing CC genotype were much higher compared with cell with CT genotype. The frequency of MMP-2 CC genotype was significantly higher in colorectal cancer patients when compared with controls. Colorectal cancers with CC genotype presented more frequent extension to serosal/adventitia layer of the colon or rectum than those with CT+TT genotypes.

In another study on Chinese population, Xu EP *et al.* [64] investigated whether the polymorphisms of MMP-2 and MMP-9 promoters contribute to the development and progression of colorectal cancer. They noticed a higher MMP-2 CC genotype frequency in CRC patients when compared with controls. The individuals with the CC genotype had an increased risk of developing colorectal cancer compared to those with CT+TT genotypes. Significant correlation was found between the depth of tumor invasion and MMP-2 -1306C/T polymorphism in colorectal cancer patients.

The same author [65] explored whether common genetic variants in MMP-2 (790T/G, -955A/C, -1575G/A) and MMP-9 (1562 C/T) are associated with the development and progression of CRC in a Chinese population. They found that the G/G genotype in the MMP-2 -1575G/A polymorphism was significantly increased in colorectal cancer patients compared to controls. In cases with serosal extension of the tumor, G/G genotype was more frequent than G/A+A/A genotypes.

Xing LL *et al.* [66] investigated the role of MMP-9 polymorphisms in colorectal cancer in a northeast Chinese population. The distribution of MMP-9 -1562C>T and 279 R>Q genotypes was not significantly associated with the risk of CRC. However, the risk of lymph node metastasis of CRC was increased in patients with the -1562T allele. The frequency of MMP-9 279RR + RQ genotype was higher than the QQ genotype among CRC patients younger than 60-year-old.

In a meta-analysis by Peng B *et al.* [67] suggested that MMP-1 -1607 1G/2G might be associated with colorectal, head and neck and renal cancer risk.

McColgan P and Sharma P [68] undertook a comprehensive genetic meta-analysis of all MMP genes investigated using an allelic-association case-control model in lung, breast and colorectal cancers. Twenty-five studies addressing five polymorphisms in four genes were analyzed among 30 651 individuals (15 328 cases and 15 253 controls). The MMP-1 nt-1607 poly-

morphism was significantly associated with CRC in both the dominant and recessive models. No association was found with MMP-2, -3 or -9 and colorectal cancer.

In spite of the fact that there is a vast amount of data on the MMPs expression and polymorphisms patterns correlated with the clinicopathologic variables and prognosis, most of the studies addressed one or few MMPs and/or TIMPs. That may explain the inherent controversies on the MMPs proteins results. Furthermore, the methods to assess the variance in gene expression were not always the same. There are some studies that addressed in the same time more MMPs and TIMPs. In our opinion, this is the ideal approach to understand the roles MMPs and TIMPs may play for CRC onset and progression. To exactly identify the origins of the MMPs, the immunostaining methods used to confirm the MMPs and TIMPs presence in tissue should be combined with microarray techniques for identifying mRNA of interest in laser-microdissected specimens.

Regarding the polymorphisms – there seems to be the same problem – most of the studies addressed one or two polymorphisms and their implications. A meta-analysis was necessary to confirm a correlation. It seems that more significant is to address in a single study as many as possible polymorphisms in correlation with the tissular expression.

The results of such studies may lead to the synthesis of MMP inhibitors directed towards a set of MMPs of certain polymorphisms and may explain why the therapeutic trials based on synthetic MMP inhibitors did not show any efficiency.

The heterogenicity of the MMPs and TIMPs genetic patterns generated by different studies on colorectal cancer does not allow us to have an overall correlation with clinicopathologic variables and the prognosis of the disease. Studies that involve many MMPs, TIMPs polymorphisms and their tissular expression would be more valuable to better assess the role of those enzymes in the progression of the disease and may serve as a starting point for selective therapeutic approaches.

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