Single Nucleotide Polymorphisms in MMP Genes and Susceptibility to Growth, Invasion, Progression, and Metastasis of Cancer

Taghvaei Somayye¹*, Saremi Leila² and Motovalibashi Majid³*

¹Department of Medical Biotechnology, National Institute of Genetic Engineering and Biotechnology, Iran
²Department of Biology, Islamic Azad University, Iran
³Department of Biology, Isfahan University, Iran

Abstract

The growth and progression of cancer are complex multi-step processes that require transformed cells to be colonized to distant locations. Degradation of Extracellular Matrix (ECM) and basement membrane by Matrix Metalloproteinases (MMPs) are key steps in these processes. Invasion and metastasis are symptoms of cancer malignancy.

A family of enzymes called MMPs involves in cancer initiation and progression. Because, their main function is digestion of the ECM, as well as they are participating in physiological processes such as wound healing, bone absorption, and the development of mammary glands in various pathological conditions such as cancer. Tumor cells can use the digestive ability of MMPs. MMPs also are stimulating the growth of the metastatic tumor cells after the occurrence of the metastasis. Therefore, MMPs can act as an oncogene. Increasing evidence suggests natural Single Nucleotide Polymorphisms (SNPs) in MMP genes especially in the promoter are leading to their variant expression, in different individuals by changing susceptibility to diseases including acute myocardial infarction, rheumatoid arthritis, multiple sclerosis, and cancer. In this review, the role of MMPs in cancer (invasion, metastasis, angiogenesis) will be discussed and the many studies of the relation of SNPs in MMP genes will be illustrated.

Keywords: MMPs; Cancer; SNPs; Oncogene; Metastasis

Introduction

Cancer is a mechanism of cell destruction that is necessary for the growth and maintenance of a multicellular organism. Number of cancer mortalities and new cases in Iran and worldwide in 2020 showed in Figure 1. Indefinite proliferation, failure in response to growth inhibitory signals, and resistance to apoptosis and immune system are the main features of tumor cells. Some other attributes of these cells include separation from the base membranes, lack of gap and tight junctions with neighboring cells, migration through extracellular matrix, entry, and survival in blood or lymph circulation, and proliferation within vessel walls or after the exit of a vessel in the secondary site(s) [1].

The tumor environmental factors that inhibit tumor progression are components of ECM, basement membranes, oxygen-active species, limited availability of oxygen and nutrients, and immune system [2]. The tumor environment can be affected by stimulation of angiogenesis using active stromal fibroblasts, production of proteolytic enzymes, and change of extracellular matrix, and eventually, leads to tumor progression [3].

The Matrix Metalloproteinase (MMP) family is common in several characteristics: ability of decomposition at least a component of the basement membrane, action in the physiologic pH, activation with two Zn⁺⁺ ions, inactivation by metal chelators and tissue metalloproteinase, and secretion as zymogene, and activation [4,5]. Since the role of the MMPs in invasion and metastasis of tumors is important, then very much attention has been attracted to them as one of the cancer therapeutic targets. MMP inhibitors have also evolved able to inhibit angiogenesis using active stromal fibroblasts, production of proteolytic enzymes, and change of extracellular matrix, and eventually, leads to tumor progression [3].

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led to the identification of MMP genes, therefore this review is an overview of concepts of cancer, the role of MMPs, and their Single Nucleotide Polymorphisms (SNPs) in the stages of cancer including angiogenesis, invasion, and metastasis. As those results of researches were approved. It should be noted that this review tries to recapitulate the most genetic variations in MMP genes.

**MMPs**

MMPs are a family of calcium and Zinc dependent endopeptidases and were produced from the reproduction of an ancestral gene and evolutionary branching [9]. Most of the MMP genes are placed on various chromosomes, but the MMP1-3-7-8-10-12-13-20, and 27 are located at position 11q22.2-22.3. The MMP family is classified into gelatinases (MMP-2 and MMP-9), collagenses (MMP-1, MMP-8, MMP-13, and MMP-18), matrixins (MMP-7, and MMP-26), stromelysins (MMP-3, MMP-10, and MMP-11), membrane-type MMPs (MMP-14, MMP-15, MMP-16, MMP-24, MMP-17, and MMP-25), and others (MMP-12, MMP-19, MMP-20, MMP-21, MMP-23, MMP-27, and MMP-28) [10].

The MMP substrates include growth factors, binding proteins, their receptors, cell adhesion molecules, chemokines, cytokines, apoptotic ligands, angiogenic factors, chemokine molecules, proteinase inhibitors, and clotting factors [11,12]. The MMPs are involved in the physiological and pathological processes including embryonic development, ovulation, wound healing, heart failure, arthritis, atherosclerosis, periodontal disease, bone changes, and especially cancer [13,14]. Most MMPs expression in tissues is often low and induces during ECM changes, which may increase cell proliferation, invasion, and metastasis by stimulating angiogenesis or cancer progression. Therefore, it is not surprising that increased MMPs levels were observed in numerous cancers [15,16]. Membrane tissue 1-matrix metalloproteinase (MT1-MMP) is involved in the physiological and pathological changes of the ECM, cell migration, invasion, activation of MMP-2, MMP-13, and MT4-MMP, and activation of growth factors particularly Vessel Endothelial Growth Factor (VEGF), tumor growth, enlargement of blood vessels, and lung metastasis. Expression of MT4-MMP in breast cancer, prostate cancer, and gliomas cancer has been identified. Initial studies have shown the role of MT1-MMP and MT4-MMP in the initial growth and the metastasis of cancer (lung) [17].

Several *in vitro* studies have been demonstrated that cleavage of particular substrates by MMPs can directly affect tumor growth. These substrates contain pro-forms of growth factors as Transforming Growth Factor (TGF)-β and inhibitory proteins of growth factor as Insulin-like Growth Factor Binding Proteins (IGFBPs) which one of those has been indicated *in vivo* to have a relationship with tumor growth [18]. Different research results are showing single nucleotide polymorphisms in MMP genes especially, MMP-1, 2, 3, 7, 8, 9, 12, 13, 14, 15, 17, 20 relate to susceptibility, invasion, and metastasis of different cancers such as breast, gastric, lung, ovarian, stomach, gallbladder, ovarian, colorectal, oral, renal, salivary, prostate, tongue, endometrial, esophageal, nasopharyngeal, melanoma, thyroid, pancreatic cancers, and etc. that is indicating a striking role of MMPs in cancer.

**Structure of MMPs:** MMP proteins consists of at least three homologous domains. The first domain is a signal peptide required for protein secretion. The second domain is propeptidase domain that comprises a consensus cysteine-switch sequence and is responsible for the activation of MMP enzymes. The third domain is the catalytic domain containing the consensus sequence of zinc-binding and is needed for the proteolytic action. The amino-terminal signal peptide is composed of 17-29 amino acids which is necessary for targeting the enzyme to the endoplasmic reticulum and Golgi complex for the later...
excretion out of the cell [19].

**Regulation of MMPs:** The catalytic activity of MMPs is controlled at four main levels, including gene expression through transcriptional and post-transcriptional mechanisms, extracellular localization and cell or tissue type of MMP release, zymogen activation by pro-domain removal, and inhibition by specific and non-specific inhibitors, e.g. Tissue Inhibitors of Matrix metalloproteinases (TIMPs) and a 2-macroglobulin, respectively [20]. Active MMPs can regulate the global proteolytic potential by degradation of inhibitors or inactivation of other proteases and activation of zymogen [21].

MMP-7 is capable cleavage of the cell surface non-matrix substrates such as F as ligand, E-cadherin, and Tumor Necrosis Factor (TNF), which are key players in signal transduction, cell-cell adhesion, and apoptosis [22]. MMP-7 also cleavages IGFBP and Heparin Binding-Epidermal Growth Factor (HB-EGF) which their effects result inmitogenic increase and cell disorganization and cause epithelial to mesenchymal change and cancer progression [23].

At transcriptional level, the MMP expression is performed by multiple mechanisms [24]. While its regulation is carried out by transcription factors, including basic Fibroblast Growth Factor (bFGF), Epidermal Growth Factor (EGF), Tumor Growth Factor (TGF), cytokines (IL-4, and IL-10), steroid hormones, the cell-cell, cell-matrix interactions, oncogenes, and tumor promoters [25].

MMPs are involved in the early stages of tumor growth, regulating the of cell growth, apoptosis, and the vessel formation through a diverse group of receptors other than components of the ECM including growth factors binding proteins, pro-growth factors, tyrosine kinase receptors, cell attachment molecules, and other proteinases [26-29]. MMPs in cancer tissues unlike normal tissues are increased and, in most cases, they are associated with poor survival. The role of MMPs in invasion and metastasis first reported in melanoma, and the tumor cells have been recognized as source of MMPs. However, increasing evidences has been indicated that most of the normal cells express MMPs [30]. Tumor inflammatory cells and stromal fibroblasts in tumor tissue induce the production of MMPs from the surrounding cells by producing of cytokines and proteins [31]. Stromal cells have also been suggested to express MMPs [32].

**Angiogenesis**

Angiogenesis includes the growth of endothelial cells and digestion of vascular endothelial old basement membrane, the formation of a cavity, penetration and migration, proliferation, and maturation of endothelial cells for formation of a capillary bed. Studies have established the expression of MMPs in this capillary network. Several growth factors can promote MMPs, which are containing cytokines and growth factors, with the activation of zymogen forms, and VEGF, through stimulation of neovascularization [33-35].

Angiogenesis is beginning with the releasing of factors eg VEGF, bFGF, and TNF from inflammatory cells, mast cells, macrophages, and tumor cells. After binding to specific receptors on cell surfaces and endothelial cell activation are leading to the induction of cell proliferation, enhanced expression of cell adhesion molecules (e.g. integrin), MMPs secretion, and enhanced migration and invasion. It has also observed an imbalance between proangiogenic and antiangiogenic factors in some early malignant cancers, even before the malignant status [36].

VEGF, akey angiogenic driver, not only stimulates proliferation and migration of endothelial cells but also activates passive MMPs. VEGF also activates MMPs and affects the activity of TIMPs, for instance, the activation of MMP-2 and MMP-9 by MMP-7 [27] and the activation of MMP-1, 8, 9, 13 by MMP-3 [37].

Tumor metastasis is essential to angiogenesis, and without this process, the tumor can grow only 1 mm to 2 mm³. Besides, tumors with higher angiogenic cells have higher ability of metastasis and invasion. MMP-13 also increases the bioavailability of VEGF. MMP-3, and MMP-7 increase cell proliferation and angiogenesis by separation of HB-EGF. MMP-9 also enhances invasion and angiogenesis with the activation of TGF-β. MMP-9 and MMP-13, because of the release of VEGF from the ECM, are the main factors in the promotion of tumor angiogenesis. With the production of inhibitors such as endostatin, angiotin, and neostatin, MMPs can prevent angiogenesis and most MMPs have opposite functions in tumorigenesis [38,39].

**Invasion**

Degradation of the ECM and the basement membranes by cancer cells are main processes in the invasion. Three types of enzymes namely MMPs, serine proteinases, and cysteine proteinases degrade efficiently the ECM. MMPs with malignant phenotypes are joined because invitro evidences have shown that malignant tumors can degrade collagen and MMPs have this character [36].

Invasion allows cancer cells to enter the blood stream or lymph system, to reach distant organs and form secondary tumors. Invasion and metastasis not only occur in cancer but also happen during fetal development and in non-cancerous diseases [40]. The ability of tumor cells for detachment from tumor and migration depends on the differentiation degree and lack of adhesion of cell-cell is a characteristic of malignant tumors. Obstruction of differentiation and lack of cell-cell adhesion by E-cadherin lead to releasing tumor cells to invasion and metastasis and the inhibition of tumor migration is the main stage in the inhibiting metastasis [41]. Tumor invasion is regulated by specific chemokines and many cancers, including, breast, ovarian, prostate, kidney, brain, lung, and thyroid cancers are expressing chemokine receptor to stimulate tumor cell adhesion and to increase endothelial cell growth understress [42]. As well as chemokine scan cause to the secretion of MMPs. Invasion is also increased by separation of E-cadherin by MMP-3 and MMP-7 (MMP-3, 7, 9, and 19) and MMPs are digesting each of the six IGFBP and are increasing their bio-availability and tumor growth [22]. The decreased invasive capacity of tumor cells was observed when the endogenous inhibitors of MMPs known as TIMPs were expressed [18].

**Metastasis**

Metastasis is the final step in the progression of metastatic tumors from normal to a malignant state. The limiting step of the metastasis rate is being called growth in the organ [43]. Metastasis is in charge of 90% of human cancer mortality [44]. Clinical observations have been shown that distant metastasis can occur many years after primary tumor resection [45].

Each step of metastasis is necessary, and by an interaction between the tumor cells, the host, and environment is regulated. The formation of the metastasis depends on the invasion of the tumor cells to the surrounding tissues and the formation of the metastatic tumors in the distant organs. Although a large number of cells isolate from the primary tumor and enter to vessel system, their small percentage succeed in making metastasis and the number of metastatic colonies depends on the number of cells that entered blood or lymph circulation
Degradation of the ECM by the MMPs not only may facilitate the metastasis but also may cause the cell growth by releasing the growth factors. Many genes participate in the metastasis and seem the regulation of the expression of these genes that functionally participate in the metastasis can occur in a tissue-specific method with different regulatory genes such as oncogenes and tumor suppressor genes that multiple stages of the specific metastatic phenotype are inducing [48]. Several reports have shown the high expression of MMPs in many cancers compared with normal tissues.

MMP8 reduces metastasis by increasing the cellular adhesion, and the relation of its expression with the reduction of incidence of breast cancer was observed [49]. The high expression of anti-apoptotic effectors such as BCL2, and BCL-XL, and the lack of initial factors of apoptosis path way result in resistance to apoptosis and elevation of metastatic potential. When expressing, metastasis inhibitor genes can inhibit exclusively metastasis but have no effect on other processes, and reduction of their expression through transcription inactivation and Loss of Heterozygosity (LOH) in the tumor cells have been found [2].

**Anti-cancer therapies targeting MMPs**

TIMPs indicated ability to prevent the function of MMPs and represented selectivity for anti-cancer therapies. TIMP-1 can prevent angiogenesis by the destructive action of MMPs. However, these biological molecules have a restricted half-life when experimented in vivo to validate their act as a pharmaceutical factor. Establishing this fact, studies are now centralized on gaining an alternative solution to minimize the role of MMPs in cancer progression [36].

**SNPs of MMP genes and cancer**

Sequence variations including SNPs in the promoter region and the coding region of MMP genes result in their variable expression in different people. SNPs are variations in DNA which were observed in more than one percent of the population of the world. SNPs may change the structure and function of protein through single nucleotide substitution in the coding region of the gene and also the gene expression through changes in the coding and regulatory regions [50]. The study of polymorphisms helps to identify people at risk of disease and to define medical purposes.

The relation of MMP-1 (collagenase-1) with different cancers has been investigated and displayed. A link was shown between 1G/2G (-1607) polymorphism and Colorectal Cancer (CRC) by Kouchkan et al. in Iran and Hinoda et al. in Japan [51,52], hematogenous metastasis of CRC by Sunami et al. in Japan [53], lung cancer by Zhu et al. in United States, Liu et al. and Ma et al. in China, and Scherf et al. in Germany [30,54-56], and breast cancer by Przy et al. in Poland, Padala et al. in India, Hughes et al. in United Kingdom, Hojiati et al. and BALKHI et al. in Iran [57-61]. Zhou et al. and HSIAO et al. did not also find any relation for breast cancer in China and Taiwan, respectively [62,63]. The positive relation of 1G/2G (-1607) polymorphism with cancer has also been demonstrated in melanoma by Ye et al. in United Kingdom, glioma by KAWAL et al. in India, and ovarian cancer by LI et al. in China and KANAMORI et al. in Japan [64-67]. No relation was shown in ovarian cancer by Ju et al. in Korea [68]. Other cancers include gastric cancer by DEVULAPALLI et al. in India [69], gall bladder cancer by Yan et al. in China [70], oral cancer by LI et al. in China [71], tongue cancer by Shimizu et al. in Japan [72], Prostate cancer by Liao et al. in Taiwan [73], and no relation with prostate cancer by WENG et al. in China [74]. The study by NIKFARJAM et al. also found no relation with gallbladder cancer in Iran [75], and the study by TAO et al. found protective effect of this polymorphism with gall bladder cancer in China [76]. BALIKOWSKA et al. [77], also demonstrated no relation of this polymorphism with lung, colon, and breast cancers in Polish population. Other studies include the carcinogenesis effect of 1G/2G (-1607) polymorphism in endometrial cancer by NISHIOKA et al. in Japan [78], nasopharyngeal cancer by NAR et al. in Tunisia and KONDO et al. in Taiwan [79,80], Esophageal cancer by BRADBURY et al. in United States [81], and renal cell carcinoma by HIRATA et al. in Japan [82].

Positive relations of MPP2-1306 G/T polymorphism were also showed in cancers: head and neck by FANG et al. in China [83], prostate by SRIVASTAVA et al. in India [84], breast by HABEL et al. in Tunisia, SLATTERY et al. in United States, and GRIEU et al. in Australia [85-87], ovarian by ZHU et al. in China [88], prostate by WENG et al. in China [74], Gastric cardia adenocarcinoma by MIAO et al. in China [89], hepatocellular carcinoma recurrence by WU et al. in China [90], Progression and invasion of CRC by BANDAY et al. in Kashmiri population, XU et al. in China, HESHAM MAHMOUD et al. in Saudi population, KANG et al. in Korea [20,27,91-93], susceptibility to lung cancer by Yu et al. in China [94], Salivary gland cancer by RADUNOVIC et al. in Serbia [95], T-cell Acute Lymphoblastic Leukemia by LIN et al. in China [96], Esophageal cancer by YU et al. in China [97], and gall bladder cancer by YAN et al. in China and SRIVASTAVA et al. in India [70,98]. In the while, TAO et al. [76], showed protection in Asian population (China) for MMP-2. -1306 C/T did not show relation in cancers: oral (by Li et al. in China) [71], colorectal (by KANG et al. in Korea) [93], gastric (by KUBBEN et al. in NETHERLANDS) [99], prostate(by ADADI et al. in Iran) [100], laryngeal carcinoma (by LIUKEVIČIUS et al. in Lithuania) [101], and breast (by ZHOU et al. in China) [62]. This polymorphism also significantly protective showed effect in breast cancer by ZHOU et al. in China [102].

The carcinogenesis effect of MPP2-735 C/T polymorphism was seen in head and neck carcinoma by HOJIHOSEINI et al. in Iran [103], cardia adenocarcinoma, esophageal squamous cell carcinoma by LI et al. in North China [8], and cervical cancer by ZHANG et al. in China [104]. C-1306-C-735 haplotype in the MMP-2 promoter contributes to the risk of the occurrence and metastasis of esophageal squamous cell carcinoma through increasing expression of MMP-2 which was indicated by YU et al. in China [97]. Also, ZHOU et al. [105], showed that C-1306 or C-735 containing haplotypes increase lung cancer risk in China. In the study by DOFARA et al. [106], T-1306 and T-735 polymorphisms associated with reduced risk of breast cancer in China, Mexico, and Tunisia. RADUNOVIC et al. [95], also showed MMP-2-1575 G/Apolymorphism has minor importance for salivary cancer in Serbia, and HABEL et al. [107], showed which MMP2 (promoter) variants: rs243864 (-790 G/A), rs243865 (-1306 C/T), rs243866 (-1575 G/A), and rs2285053 (-735 C/T) also have protective effect in Tunisian women. KIANI et al. [9], also showed MMP-2-1575 G/A polymorphism increases prostate cancer risk in patients with diabetes or in individual smokers in Iran.

Results of the various researches in the world wide have shown -1171 5A/6A MMP-3 polymorphism significantly associates with esophageal squamous cell carcinoma in China [37], lung cancer...
in Lebanon and China [108,109], breast cancer risk in Italy [110], growth and metastasis of breast cancer in South India, Italy, Egypt, and Iran [58, 110–112], CRC in Japan and Iran [52,112], and lymphatic metastasis in esophageal squamous cell carcinoma in China [37]. No association was also found in the studies in other worldwide regions in gastric cardiac adenocarcinoma (China) [37], Ovarian (China) [66], Gallbladder (North India) [113], Breast cancer (China) [62], laryngeal carcinoma (Lithuania) [101], and oral (China) cancers [71].

The studies also reported the relationship of the -181 A/G MMP7 polymorphism with susceptibility to metastasis of breast cancer by Beeghly-Fadiel et al. in China [114], Prostate cancer by Balikowska et al. in Poland [115], Ovarian cancer by Li et al. and Zhu et al. in China [66,88], Gastric cancer by Kubben et al. in Netherlands and Alakus et al. in Germany [99,116], and glioma by Kawal et al. in India [65]. But this polymorphism protected gallbladder cancer in the Asian population (China) [76], and had no association with bladder cancer in the polish population [117], and with breast, lung, and colon cancers in the Polish population [77]. Other studies also include association of -181 A/G MMP7 polymorphism with CRC in Kashmiri and Taiwanese populations [20,118], no association with CRC in a Chinese population [83], and association with CRC in the study by Motovall-Bashiet al. in Iran [119]. MMP-7 rs11225297 is in high linkage disequilibrium with MMP-8 rs11225395 and was significantly associated with breast cancer survival in a large two-stage survival study among Chinese women [120].

These four SNPs of MMP-8 including rs11225395, rs1940475, rs1892886, and rs1276284 have been shown a positive relationship with lymphatic metastasis of breast cancer in Chinese population [121]. Despite these positive reports of MMPs in cancer, the protective effect of +17C/GMMP8 polymorphism displayed in cancer such as lung cancer by González-Arriagl et al. in Northern Spain [122] and no relation in bladder cancer in the Polish population were found by Wieczorek et al. [117]. MMP-8 -799 C/T polymorphism increased ovarian cancer risk in China [88], cancer risk in non-Asian populations [123], and had inhibitory effect on breast cancer metastasis by in Belgümet al. [124].

The relation of the (-1562) C/TMMP9 polymorphism in different studies were showed especially with susceptibility and metastasis of breast cancer in Iran, Invasion and development of breast cancer in Iran [125], and breast cancer development in Iran [125-127]. MMP-9C-1562T polymorphism al one and in combination with MMP-2 C-735T polymorphism increased the risk of breast cancer Taiwanese population [128] and in other world regions were reported that presence of T allele is in relation with CRC metastasis (Kashmiri, Korean, Taiwanese and North Chinese populations) [20,93,128-130], Tumor progression and malignant phenotype of gastric cancer (Japanese and Chinese populations) [131-133], Susceptibility to prostate cancer (Tunisian population) [134], Invasion and metastasis of breast cancer (North East London population) [59], Breast cancer risk (British population) [135,136], and tumor growth and breast malignancy (Polish population) [57]. Other cancers with association with positive association with C-1562T polymorphism included salivary gland cancer in Serbia [95], Cervical cancer in China [104], and no association with lung cancer in China and France [137,138], Breast cancer [139] and CRC in Sweden [140], NSCLC in China [141], Papillary thyroid carcinoma in Serbia [142], and T-cell Acute Lymphoblastic Leukemia in China [96]. While, the relation did not find by Roche et al. in South Brazil and Beeghly-Fadiel et al. [143,144], in China breast cancer. MMP-9 rs3918242 (-1562 C/T), but not rs3787268 (A/G, intron) and rs17576(Q279R) polymorphisms may be risk factor for breast cancer in China [145]. Also, the Q279R and the R574PMMP-9 coding polymorphisms were associated to metastasis of lung cancer in China [146]. 279Q, 574R, and 668R alleles of MMP-9 were related to metastasis of melanoma in United States [147] and CA microsatellite polymorphism was associated to the invasion of bladder cancer in China [70]. While, Yang et al. [148], have been shown that P574R and R668Q polymorphisms did not associate with CRC in Chinese population.

The relation of -82A/GMMP12 polymorphism was showed with the invasion of the gallbladder by Kader et al. in United States [149], Ovarian cancer risk by Zhu et al. and Liu et al. in China [88,150], and CRC by Van Nguyen et al. in Southeastern Sweden [151]. As well as, the association of -1082A/GMMP-12 polymorphism with NSCLC was showed in United States [50].

In a few studies, the effect of haplotype was surveyed, Bradbury et al. [81], showed which 82G-5A-2A haplotype cause to increased risk of esophageal cancer in United States and Su et al. [50], showed which 1G-5A-82A-1082A (MMP-1-MMP-3-MMP-12-MMP-12) haplotype may be associated with a higher risk of lung cancer in United States.

-77 A/G MMP-13 was associated with NSCLC by Li et al. in China [141] but, it was not associated with CRC by Van Nguyen et al. in Southeastern Sweden [151], and also with breast, colon, and lung cancers in the Polish population [77]. As well as, -82A/GMMP12 and -77 A/G MMP-13 associations with developing ESCC and GCA were found in the North China by Li et al. [8].

The +6767 and +7096 polymorphic genotypes and haplotype -165 T: +221 T: +6727 C: +6767 G:+7096 T: +8153 G of MMP-14 gene contributed in the risk and pathological development of hepatocellular carcinoma in Taiwan [152].

MMP-20 rs2292730, rs12278250, 9787933 showed the positive relations with ovarian cancer in China [88], but rs738791, rs738792, rs2267029, rs28382575, and rs131451 did not show associations with uterine cervical cancer in Taiwanese population [153].

Conclusion

The tumor progression is a multi step process that involves complex molecular events such as separation of the tumor cells from a primary tumor, invasion to surrounding tissues, and formation of metastatic tumors [26]. Collagentype IV is a major component of the basement membrane and the first barrier that is decomposed by the tumor cells with the expression of MMP-2 and MMP-9 [154]. The tumor and the stromal cells can produce MMP-9. MMPs with the initiation of carcinogenes is and an increase in angiogenesis in the primary site and the metastatic site can stimulate tumor progression. Since angiogenesis is requires to the progression of the primary tumor and invasion to the surrounding tissues, therefore MMPs with the formation of the hole in the ECM and creation of progression pathway of de novo capillaries have an important role in the development of angiogenesis. Several studies have shown, MMPs expression is increasing in endothelial cells adjacent to tumor cells [155].

Invasion and metastasis by conversion epithelial cadherins to mesenchymal are regulated. So that, over expression of E-cad in epithelial carcinoma associates with cancer progression. But N-cad, which normally is expressing in neuronal and mesenchymal tissues, is increasing during tumor invasion that is indicating a change of...
epithelial to mesenchymal. R-cad is another cadherin. The studies were demonstrated the reduction of R-cad and E-cad, but increased expression of N-cad in metastatic breast cancer [156]. Metastasis is defined by the endpoints, which are metastatic failures and have been discovered in the special organs away from the primary tumor. While sometimes the steps by which the formation of metastasis is inhibited other than those observed.

Invasion, the movement of tumor cells and their penetration to near tissues has the a central role in the metastasis, and destruction of adhesive joints are increasing the mobility and separation of the tumorcells, which are leading to metastasis [157]. Studies with MMPs synthetic inhibitors were showed a more protected role of MMPs in invasion, andmetastasis. So that, British biotech inhibitor batimastate (BB-94), (a synthetic MMP inhibitor) metastatic melanoma, breast carcinoma and colon and colorectal tumor cells and breast tumor cells reduced. Also, combinational therapy with specific inhibitors of gelatinase A and cytotoxic agentshas been decrease invasion and metastasisof lung carcinoma.

Also, transfection of gelatinase A CDNA in bladder cancer cells increased the region of lung metastasis, increased expression of MT-MMP, and increased survival of carcinoma cells of mice. Several degrading proteases of ECM in addition to its activators, inhibitors, and their receptors are increasing in cancer cells [41].

MMPIs are no directly killed cancer cells but angiogenesis, invasion, and metastasis processes are targeting. There are evidences that TIMPs in the cells having receptor have growth stimulatory effects. However, factors such as the relative concentration of MMPs and specific TIMPs and extracellular environment may affect the reply of the tumor cells to TIMPs expression. However, the MMPs relate to metastasis and there is no doubt that they are the main participants of the metastasis process [158,159].

The Human Genome Project has been identified millions of SNP that are attractive biomarkers in diagnosis, treatment, screening, staging, or grading [109]. New evidences showed that sequence variations including SNP in the promoter and the coding region of the MMP genes result in variable expression in different people and change of their susceptibility to cancer. MMP1, 2, 3, 7, 8, 9, 12, 13, 14, and 20 were shown to contribute in cancer such as breast, lung, CRC, ovarian, gallbladder, gastric, renal, oral, head and neck, cervical, endometrial, esophageal, nasopharyngeal, laryngeal, leukemia, salivary, prostate, tongue, thyroid, pancreatic cancers, hepatocellular carcinoma, melanoma, glioma, and etc in different populations.

Viewed differences between stated risks are presumably due to the differences in genetic context, sample size of the studied population, and environment. The main features of cancer cells can include proliferation, invasion to surrounding tissues, and migration to distant organs, which are leading to sporadic metastasis, the main cause of cancer deaths. Then, MMPs are attractive targets for cancer therapy and the development of new inhibitors with, less toxic and more effective, accompanied by conventional combinational factors is the main focus of cancer therapy researches. As well, the study of clinicopathological may help to identify populations at high risk and provide attractive targets for targeted therapies because, in the majority of studies, the relation of SNPs of MMP genes with clinicopathological characters such as smoking status, age, gender, stage, and grade of tumor were showed.

References


