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REVIEW

Matrix metalloproteinases and gastrointestinal cancers: Impacts of dietary antioxidants

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Abstract

The process of carcinogenesis is tightly regulated by antioxidant enzymes and matrix degrading enzymes, namely, matrix metalloproteinases (MMPs). Degradation of extracellular matrix (ECM) proteins like collagen, proteoglycan, laminin, elastin and fibronectin is considered to be the prerequisite for tumor invasion and metastasis. MMPs can degrade essentially all of the ECM components and, most MMPs also substantially contribute to angiogenesis, differentiation, proliferation and apoptosis. Hence, MMPs are important regulators of tumor growth both at the primary site and in distant metastases; thus the enzymes are considered as important targets for cancer therapy. The implications of MMPs in cancers are no longer mysterious; however, the mechanism of action is yet to be explained. Herein, our major interest is to clarify how MMPs are tied up with gastrointestinal cancers. Gastrointestinal cancer is a variety of cancer types, including the cancers of gastrointestinal tract and organs, *i.e.*, esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus. The activity of MMPs is regulated by its endogenous inhibitor tissue inhibitor of metalloproteinase (TIMP) which bind MMPs with a 1:1 stoichiometry. In addition, RECK (reversion including cysteine-rich protein with kazal motifs) is a membrane bound glycoprotein that inhibits MMP-2, -9 and -14. Moreover, α2-macroglobulin mediates the uptake of several MMPs thereby inhibit their activity. Cancerous conditions increase intrinsic reactive oxygen species (ROS) through mitochondrial dysfunction leading to altered protease/anti-protease balance. ROS, an index of oxidative stress is also involved in tumorigenesis by activation of different MAP kinase pathways including MMP induction. Oxidative stress is involved in cancer by changing the activity and expression of regulatory proteins especially MMPs. Epidemiological studies have shown that high intake of fruits that rich in antioxidants is associated with a lower cancer incidence. Evidence indicates that some antioxidants inhibit the growth of malignant cells by inducing apoptosis and inhibiting the activity of MMPs. This review is discussed in six subchapters, as follows.

Key words: Gastrointestinal cancer; Matrix metalloproteinase; Tissue inhibitor of matrix metalloproteinases; Reactive oxygen species; Antioxidants

Core tip: Matrix metalloproteinases (MMPs), a group of zinc dependent endopeptidases, substantially contribute to extra cellular remodelling, angiogenesis, cellular differentiation, proliferation and apoptosis. MMPs are also important regulators of tumor growth both at the primary site and in distant metastasis; thus the enzymes are considered as important targets for cancer therapy. This review describes the roles and regulation of different MMPs and their subsequent actions over different gastrointestinal cancers both in epigenetic and cellular level. Furthermore, this review summarizes the current state of knowledge of dietary antioxidants in preventing gastrointestinal cancer progression as well as mechanism of action.

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EPIDEMIOLOGY AND GENETIC BASIS OF GASTRIC CANCERS

As far the incidence rate is concerned, gastric cancer holds the fourth position among the most common cancers in men and fifth in women, from a worldwide perspective. The death rate goes hand to hand with lung cancer, the most frequent cancer globally[1]. Approximately, one million cases of gastric cancer were reported in the year 2008, which accounted for almost 8% of all cancerous incidents throughout the world[1]. Regions of Asia, eastern Europe, South America were highlighted in the reports as the most affected continents[2]. Carcinogenesis in the gastrointestinal tract, accounts for marked geographic variations in incidence and shows morphological heterogeneity. Histologically, gastric cancers are mainly of two types, diffuse and localized intestinal types. Poorly differentiated cancer cells, scattered within the stromal cells diagnosed as diffuse-type gastric cancer (DGC), whereas tubular gland like structures formed by the cancer cells having a few stromal components give rise to intestinal-type gastric cancer (IGC). Recognized as a familial disease many years ago, hereditary diffuse gastric cancer has now been identified as an autosomal dominant cancer susceptibility syndrome. This familial disease was probably most elegantly demonstrated in the family of Napoleon Bonaparte[3,4].

Chromosomal anomalies leading to gastrointestinal cancers

Aneuploidy of chromosomes 4, 8, 17 and 20 in gastric cancer were reported in several studies. Researchers have been trying to identify the precise stages known from Correa's pathway, where these chromosomal anomalies arise. Chromosome 4 and 20 were found to be amplified with the deletion of chromosome 17(p53) in multiple known progressive stages of carcinogenesis including normal gastric mucosa as well as metaplasia, dysplasia and cancer. A significant increase in the levels of aneuploidy was also reported with disease severity. Moreover, in some cases significant positive association was observed between chromosome 4 amplification and infection with *Helicobacter pylori* (*H. pylori*). In the same study, a similar kind of aneuploid condition was induced *in vitro* by exposing a human cell line to hydrogen peroxide suggesting that *H. pylori* induces gastric cancer with the help of reactive oxygen species (ROS) mediated chromosomal aneuploidy[5].

In 1988, Correa proposed the stages of human gastric cancer progression using several stages including gastritis, metaplasia, dysplasia, carcinoma, *etc.* In a study by Sugai *et al*[6] chromosomal allelic losses were tested of multiple cancer related chromosomal loci (1p, 3p, 4p, 5q, 8p, 9p, 13p, 17p, 18q and 22q). In addition, microsatellite instability (MSI) and overexpression of p53 protein were checked in all tumor samples. A prominent 3p allelic loss was observed in the cases of gastric phenotypes, whereas 5q allelic loss was highly associated to the intestinal phenotypes. Both loss of heterozygosity and microsatellite instability were observed in the genetic profiles of the mixed phenotypes. Allelic losses of 5q, 3p and 18q loci were consistent in intra-mucosal carcinomas and allelic losses of 17p, 1p and 9p were associated to submucosal carcinomas, all leading to loss of heterozygosity. MSI was observed only in 6 out of 31 cases of mixed phenotype gastric cancers, while p53 overexpression is observed in most of the cases of differentiated gastric carcinomas[6].

Specific gene mutations and their contributions

In most cases, the molecular expression of several biological markers show no link between the young ($\leqslant$ 45 years) and the aged ($\geqslant$ 45 years) patients, suggesting that early onset of gastric cancers possess different expression patterns of several important biomolecules[7]. Early onset gastric cancer patients may be more susceptible to the genetic factors but these individuals account for 10% or even less of all gastric cancer patients throughout the world[8,9]. Only10% of early onset gastric cancer cases belong to the inherited gastric cancer predisposition syndromes, but the genetic events taking place in the background of these remain largely unclear till date.

Development of tumors, often result from defects in several signaling pathways, including tyrosine phosphorylation, which occurs through the combined actions of protein tyrosine phosphatases (PTPs) and protein tyrosine kinases (PTKs). About 26% of colorectal cancers and a minute fraction of gastric cancers were reported to have mutations in the *PTP* genes. Mutated PTP originally are tumor suppressor genes, which regulate pathways associated with cell growth and differentiation. Wang *et al*[10] uncovered 83 such somatic mutations by mutational analysis of the six tyrosine phosphatase gene superfamily namely (PTPRF, PTPRG, PTPRT, PTPN3, PTPN13, and PTPN14). Production of truncated proteins lacking phosphatase activity was due to 15 mutations, which were nonsense, frame shift or splice site mutations. Reduced phosphatase activity was resulted in 5 missense mutations in PTPRT. Restoration of wild-type PTPRT expression in human cancer cells tended to cease cell growth[10].

Several studies reported the involvement of different biomolecules for the cause of gastric cancer. E-cadherin, p53, cycloxygenase-2 (COX-2), trefoil factor-1 (TFF-1), β-catenin, p16, c-myc, *etc.*, are some of the known molecules. Significant difference in the expression of these markers and some other molecules are found, namely c-jun, HuR, C/EBP-β, *etc.*, in early onset of gastric cancer, as well as regular gastric cancer patients. TFF-1 was overexpressed with a comparatively lower level of COX-2 in the early onset gastric cancer, whereas COX-2 overex-

pression and loss of TFF1 was found in regular cancers. Surprisingly, overexpression of COX-2, C/EBP-β in intestinal type gastric cancer was observed[7].

Risk factors for familial and non-familial gastrointestinal cancers

Gastrointestinal carcinomas like, esophageal adenocarcinoma, gastroesophageal junctional adenocarcinoma, *etc.*, often originate from Barrett's esophagus (BE), a chronic gastroesophageal reflux disease[11,12]. When BE and its associated diseases occur in families, they are collectively included within a syndrome named Familial Barrett's Esophagus, categorized as a complex genetic disease[13,14].

The onset of adenocarcinomas is thought to be determined by a combined effect of genetic variation and distinct environmental factors. Chak *et al*[15] determined the relationship between risk factors and the age of onset of these cancers. Family history of BE/cancer occurrence, gastroesophageal reflux symptoms, obesity (defined as body mass index > 30) and other risk factors were assessed in a total of 356 gastroesophageal adenocarcinoma patients. This study reports that both familial and non-familial cancers arise at similar ages, but obesity is associated with a comparatively earlier age of onset.

Appropriate clinical counseling based on the genetics of gastrointestinal cancers always depends on well substantiated data reflecting the risk factors existing through a family. The estimated risk of gastric cancer within a family, however, may differ widely from one another. A group of researchers from Sweden used the updated Swedish Family-Cancer Database to investigate the familial risks of gastric cancer in 5358 patients among the offspring and 36486 patients among the parents. In this investigation, 133 families were identified having one parent and one offspring recognized as patients of gastric cancer, whereas 20 families had two affected offspring. The standardized incidence ratio (SIR) for the families was 1.63, when the parents displayed gastric cancer and the same was 2.93 in the families where the siblings had the disease. Cancer in the corpus (main body of the stomach) was related to high sibling risk (SIR = 7.28). Whenever gastric cancer was diagnosed in the parents, the SIR for cancer in the cardia (the area joining stomach and esophagus) was 1.54. In most cases, upper stomach cancer did show a particular association to esophageal adenocarcinoma. Histological analysis revealed an increase of signet ring cells in cancers. Among the factors, giving rise to high sibling risk in the case of corpus cancer, *H. pylori* infection may be an important one. The association of upper stomach cancer and esophageal adenocarcinoma in families may also lead to important clues on the aetiology of both diseases[16].

Chromatin remodeling and epigenetic modifications as etiological factors

Various carcinogenic pathways and environmental factors may contribute to the aetiologies of gastric cancers[17]. Several genes as well as some of their mutations were identified in a study by exome sequencing of 22 gastric cancer samples. In this way, genes participating in chromatin remodeling were most commonly found to be mutated, leading to alterations in specific pathway. Protein deficiency of AT-rich interactive domain-containing protein 1A (ARID1A) were observed in 83% of gastric cancers with MSI, 73% of those with Epstein-Barr virus (EBV) infection and 11% of those that were not infected with EBV and microsatellite stable. A small division of the disease may arise due to *TP53* (gene encoding p53) mutations, as well as other genetic alterations and modified pathways. Occurrence of these mutations shows a negative correlation with mutations in *TP53*. The significance of chromatin remodeling is highlighted in the context of gastric cancers, which also reveal some new genomic landscapes[18].

Overexpression of claudin-4 (CLDN4), a protein involved in tight junctions is known to be associated to gastric cancers. Increased expression of CLDN4 on the membrane enhances the barrier like function of tight junctions which tends to prevent the migration and invasion of gastric cancer cells, without affecting cell growth. The epigenetic regulation of CLDN4 overexpression and its clinical significance as potential therapeutic targets was reported by Kwon *et al*[19]. DNA hypomethylation parallels to CLDN4 upregulation in both cancerous and non-cancerous gastric tissues. In normal gastric tissues, bivalent histone modifications often lead to repression of CLDN4 expression, whereas loss of repressive histone methylations results in upregulation of CLDN4 in gastric cancer cells[19].

Methylation level of long interspersed element-1 (LINE-1) is associated with esophagus gastric as well as colon cancer progression and prognosis[20]; this helps in assessing tumor heterogeneity and drug efficacy for the personalized treatment of patients with gastrointestinal cancers. Okada *et al*[21] documented that promoter methylation rate of seven genes *TP73*, *BLU*, *FSD1*, *BCL7A*, *MARK1*, *SCRN1*, and *NKX3.1* are higher in EBV-associated gastric carcinomas compare to EBV-negative gastric carcinoma signify the viral-mediated epigenetic alteration in cancer. Report suggested that *H. pyroli* infection induced promoter methylations of THBS1 and GATA-4 gene in the early stages of chronic gastritis and gastric cancer development[22]. Jin *et al*[23,24] reported the enhanced rate of promoter methylation of a transmembrane glycoprotein endoglin and Ras-related associated with diabetes gene in human ESCC. Also, TIMP-3 hypermethylation contributes to the downregulation TIMP-3 protein expression in ESCC and is associated with poor patient survival[25]. Poplineau *et al*[26] reported that a DNA hypomethylation agent enhanced upregulation of MMP-1 gene expression and triggered tumor cell invasion. In contrast, treatment with S-adenosylmethionine, a methyl donor, resulted in activation of TIMP-2 and significant downregulation of MMP-2 and MT1-MMP gene in colorectal cancer[27]. Prognostic values of promoter hypermethylation in patients with gastric cancer

Table 1 Major matrix metalloproteinases studied in cancer biology

Collagenase	Gelatinase	Stromolysin	Matrilysin	Membrane type MMPs	Others
MMP-1	MMP-2	MMP-3	MMP-7	MMP-14	MMP-12
MMP-8	MMP-9	MMP-10	MMP-26	MMP-15	MMP-20
MMP-13		MMP-11		MMP-16	MMP-28
MMP-18		MMP-19		MMP-17	
				MMP-24	
				MMP-25	

MMP: Matrix metalloproteinases.

documented that patients with higher stage of colorectal cancer possess a higher concentration of methylated APC, TIMP-3 and hMLH1 in the serum[28]. Wang *et al*[29] reported a frequent hypermethylation of RASSF1A gene promoter in gastric and colon cancer and predicted its utility as a diagnostic marker.

ELEVATED INDUCTION OF MMPS IN GASTROINTESTINAL CANCERS

The MMPs are comprised of a family of endopeptidases, which can cleave almost every component of the extra cellular matrix (ECM) proteins. It is documented that many non-ECM proteins can also be cleaved by selected MMPs. Structurally, they all have a zinc ion in the catalytic domain and their activity is dependent on divalent ions, mainly, Zn^{2+} and Ca^{2+}[30,31]. There are about 27 different MMPs discovered so far and they are subdivided in groups according to substrate specificity and structural integrity (Table 1). Induction and expression of MMPs are regulated at the level of transcription and translation, respectively. Further complexity of MMPs is the activation from zymogen to active enzyme and, secondly, the mRNA stability of few MMPs play critical role. ProMMPs are converted to active MMPs by intra-molecular cleavage of cysteine bridge between thiol group at the prodomain and Zn^{2+} near the catalytic site. The overall activity depends on the availability of the substrate as well as inhibitor in pericellular space, though a high concentration of MMPs exists near the plasma membrane.

Cancer progression can be explained in six major steps: self-support in growth signals; resistance to growth-inhibitory signals; reduced apoptosis; uncontrolled replication; sustained angiogenesis; and tissue invasion followed by metastasis[32]. Considerable evidence has demonstrated that disease progression in experimental animal models of cancer invasion and metastasis correlate with enhanced secretion of specific MMPs by tumor cells and/or stromal cells. Gastrointestinal cancer can be subdivided into different types, *e.g.*, cancers of upper digestive tract, esophageal cancer, gastric cancer, pancreatic cancer, liver cancer, gallbladder cancer and others like MALT lymphoma, gastrointestinal stromal tumors, cancer of the biliary tree, cancer of the lower digestive tract, colorectal and gastrointestinal carcinoid tumor.

Role of MMPs in esophageal and gastric cancer

Role of MMPs in gastrointestinal cancer has been well studied. IHC analysis of tumor biopsy samples suggest the expression of MMP-1 in 24% of oesophageal cancers, while MMP-2 and MMP-9 in 78% and 70% of samples respectively[33]. Similarly, studies revealed that MMP-13 is localized predominantly in tumor cells; and the presence of MMP-13 together with MT1-MMP is implicated in determining tumor aggressiveness of human oesophageal carcinomas. Etoh *et al*[34] found a significant correlation in survival period for subjects with the expression of MMP-13 and MT1-MMP in tumor tissue. Moreover, the activities of MMP-2, -3, -9, and -10 enzymes were detected in each of the 24 cancer cases. MMP overexpression was reported in tumors in comparison to normal tissue; having elevated levels of the activated form of MMP-3 and -10 in tumors. In addition, MMP-3 and -10 mRNA levels were significantly higher in tumors than paired normal tissues in both the stromal and epithelial component of tissues[35].

One of the important features of the malignant phenotype in both colorectal and gastric cancer is the overexpression of MMP-2 and -9 as well as activation of proMMP-2 to active MMP-2. Expression of MMP-2, -1 and -9 was found in 94%, 73% and 70% respectively in gastric specimens when studied in 74 patients. Conversely, MMP-3 was only present in 27% of tumors while MMP-1 and -9 were present mostly in all intestinal phenotypes of gastric cancer. In addition to MMPs, TIMP-1 and TIMP-2 were detected in approximately 50% of gastric tumors. Progression of gastric cancer is associated with MMP-13 expression along with its coexpression with MT1-MMP and/or MMP-2 that may have a synergistic effect in the progression of the disease[36]. The expression of TIMP-3 was significantly higher than that of MMP-3, and MMP-3/TIMP-3 was lower in gastric cancer tissue at the early stages (n = 18) than in that of the advanced stage group (n = 26) ($P < 0.05$)[37]. MMP-7 expression has been found to be prognostic marker for metastasis of gastric carcinoma because MMP-7 mRNA as well as protein was pronounced in aggressiveness carcinoma tissues.

Role of specific MMPs in colorectal cancer

The critical event in the process of cancer invasion and metastasis is the degradation of the ECM surrounding

the tumor tissue[38]. This ECM is degraded by the action of a set of proteases, in which several types of MMPs play major role, of which MMP-2 and -9 are most prominent. The basement membrane which prevents an invading epithelial tumor is mainly made up of type IV collagen, which is substrate of MMP-2 and -9. The event of basement membrane degradation promotes epithelial tumor invasion. Higher levels of MMP-1, -2, -3, -7, -9, -13, and MT1-MMP expression have been documented in human colorectal. Murray *et al*[33] demonstrated that MMP-1 in colorectal cancer specimens was linked to a poor prognosis of the disease. This study was later confirmed by performing IHC, FISH, and RT-PCR on 142 samples of colorectal carcinomas[39]. The latent form of MMP-2, *i.e.*, proMMP-2, is expressed in significant levels almost in all normal tissues. *MMP-2* acts as the 'house-keeping' gene due to its importance in normal cellular physiology. While active *MMP-2* is found in neoplastic tissues, it is lacking in most normal tissues. Parsons *et al*[40] in 1992, were the first who described the role of MMP-2 in colorectal cancer and the ratio of MMP-2 to proMMP-2 was 20 fold higher in colorectal cancer specimens in comparison to non-malignant biopsies as judged by gelatin zymography. Parsons *et al*[40] demonstrated increased expression of proMMP-9 in colorectal cancer. The increased activity of proMMP-9 from inflammatory cells may cause an early change in progression from adenoma to carcinoma, when colonic adenoma is compared to normal mucosa. Increased co-expression of MMP-3 and MMP-9 has been found in colorectal tumors. Co-expression of uPA with MMP-9 in colorectal cancers is responsible for the activation of plasminogen to plasmin[41]. Plasmin stimulates proMMP-3 to active MMP-3 which in turn promotes proMMP-9 to active MMP-9, thus, resulting in colorectal cancer progression[41]. Excess MMP-9 expression in colorectal cancer contributes to the inflammation related to neoplasms but not to aggressive tumors[42]. Low levels of microsatellite instability and poor prognosis is observed with increased expression of MMP-3 in colorectal cancer. Moreover 90% of colonic adenocarcinomas demonstrated high levels of MMP-7 expression. Studies on surgically resected colorectal cancer specimens elucidated the clinical importance of MMP-7 expression in this cancer type. It demonstrated that overexpression of MMP-7 in colorectal cancer (measured by IHC and in situ hybridization) directly relates to nodal or distant metastasis[43,44]. On the contrary, MMP-12 overexpression is associated with increased survival in colorectal cancer because of its influence as protective factor presumably by inhibiting tumor angiogenesis[43]. In fact, inhibition of tumor growth with upregulation of MMP-12, also known as macrophage metalloprotease, is well accepted. It was reported by Dong *et al*[45] that macrophages capable of producing MMP-12 in tumors that are responsible for increased production of angiostatin, an inhibitor of tumor neovascularization[45,46]. High expression of MMP-13 results in poor survival of colon cancer patients. Colorectal tumor biopsy specimens were examined for the identification of MMP-13 by Leeman *et al*[47]. MMP-13 was found in 91% of cases and was localized to cytosol of tumor tissues. Significantly higher activity of MMP-13 was observed in malignant than the non-malignant tissues. Moreover, plasmin, MT1-MMP and MMP-2 are key molecules in the production of active MMP-13. Active MMP-13 was found to be responsible for activation of MMP-9 during cancer progression[48].

MMPs polymorphism in tumor formation

Unlike classical oncogenes, MMPs are not upregulated by gene amplification or mutations. The increased MMP expression in tumours is mainly due to transcriptional changes rather than genetic alterations. The only two reported genetic alterations in cancer cells are translocation of the *MMP-23* gene in neuroblastoma[49] and amplification of the *MT5-MMP* gene[50]. Polymorphisms in MMP promoters also affect gene transcription and influence cancer susceptibility (Figure 1). The estimated number of single nucleotide polymorphisms (SNPs) in the human genome is 10 million, while only a small part of these polymorphisms are functionally relevant. The differences in allele transcription caused by polymorphisms in the MMP promoters are subtle compared with the overexpression that arises from the amplification of oncogenes. Most of the functional SNPs are located in the promoter region of the *MMP-1*,*-2*,*-3*,*-9* and *-7* genes that are associated with gastric cancer risk.

MMP1-1607 1G/2G polymorphism was found to be associated with gastric cancer risk as presence of extra guanine (2G) creates a binding site for Ets-1 transcription factor that enhances transcription of MMP-1. Bradbury *et al*[51] reported an elevated esophageal cancer risk in 1G/2G and 2G/2G carrier. MMP-1 protein expression is higher in tumors from gastric cancer patients who carry the 2G allele not 1G homozygotes[52]. Moreover, 2G homozygotes are more likely to develop invasive tumors. Dey *et al*[52] reported that MMP-1 promoter polymorphism is significantly associated with lower stomach tumor formation. MMP-1 -1607 1G/2G polymorphism is also involved with colon cancer risks.

MMP-2 polymorphism was investigated mainly in the promoter region, *e.g.*, MMP-2 -1306 C/T, -735 C/T, -790T/G, -955A/C, and -1575G/A in the context of gastrointestinal cancer risk[53]. Studies reported association of gastrointestinal cancer risk with -1306 C/T and -735 C/T polymorphic site worldwide. Price *et al*[54] characterized genetic variants in the human MMP-2 -1306 C/T allele-specific transcriptional regulation. The common C>T transition at -1306 disrupts a Sp1-type promoter site (CCACC box), leading to lower promoter activity with the T allele[54]. On the other hand, G to A substitution at the MMP-2 -1575 site reduces gene expression due to a reduction of estrogen receptor-α binding to A allele[55]. Fruh *et al*[56] found the presence of CC allele at MMP-2 -1306 position in *H. pylori* infected individuals which provide protection against esophagus adenocarcinoma. Studies also reported that presence of CC allele at

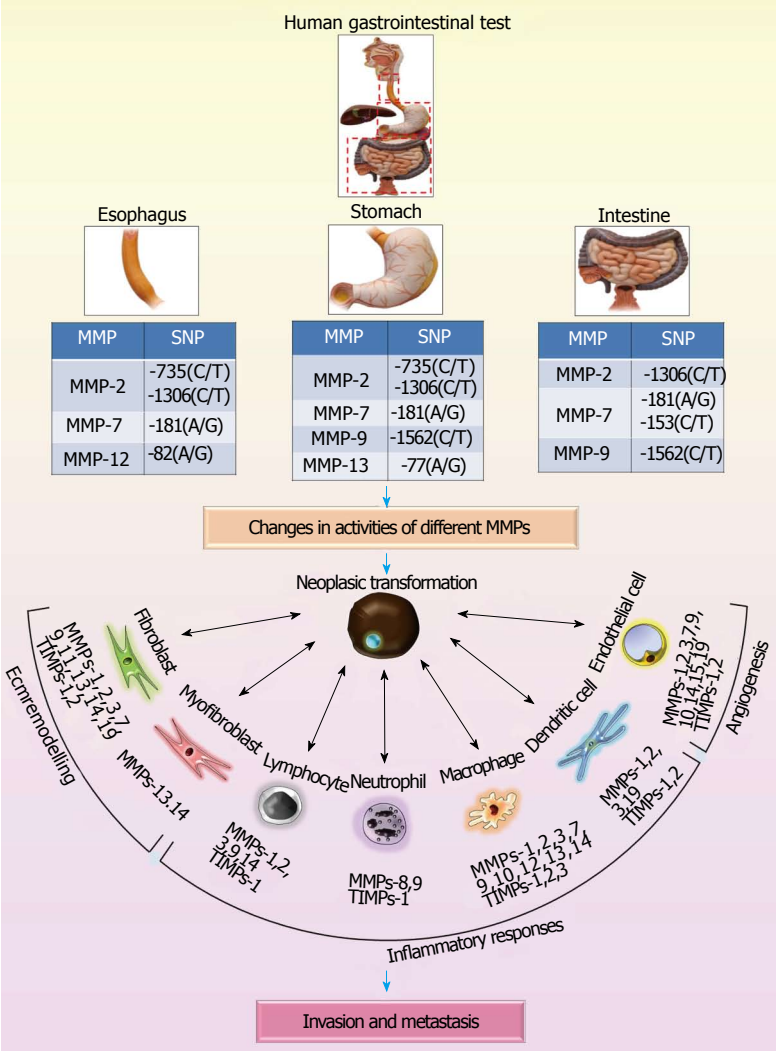

Figure 1 Matrix metalloproteinases polymorphism in gastrointestinal cancers. Single nucleotide polymorphism (SNP) for matrix metalloproteinases (MMP) genes in gastrointestinal organs (*e.g.*, esophagus, stomach and intestine) of human has been reported. These SNPs are involved in changing MMPs activities in neoplastic transformation of gastric tissues in cancer patients. In addition to cancerous cells, the secretion of MMPs by fibroblasts, myofibroblasts, lymphocytes, neutrophils, macrophages, dendritic cells and endothelial cells has been documented. Both MMPs and tissue inhibitor of metalloproteinases (TIMPs) are important in regulation of extracellular matrix (ECM) remodeling, inflammatory responses and angiogenesis for cancer invasion and metastasis.

-1306 site increases the risk of ESCC, although Chen *et al*[54,57] did not observe any positive association of MMP-2 -1306 C/T polymorphism with ESCC in Mongolian population suggests differences in genetic susceptibility between Han-ethnic Chinese and the Mongolian population. However, both positive and negative influences of MMP-2 -1306 C/T polymorphism with gastric cancer in Asian and Caucasian population were reported[58]. Studies were performed to evaluate the association of MMP-2 -1306 C/T polymorphism with colon cancer risk[59]. Langer *et al*[53,60] reported that presence of CC or CT genotype enhances the survival rate of colon cancer patients. There is also a significant association of MMP-2 -735 C/T polymorphism with esophageal cancer risks[54].

MMP-9 over expression is associated with almost all the hallmark steps of cancer progression that make MMP-9 an ideal candidate gene for genetic association studies. Functional polymorphisms, *e.g.*, MMP-9 promoter (-90CA(n), -1562C/T) as well as structural region (R279Q, P574R, R668Q) polymorphism were studied, assuming it might influence the *MMP-9* gene expression or protein activity. *MMP-9* polymorphism and gastrointestinal cancer risk is apparent in both Chinese and Caucasian populations[61,62]. In a hospital based case control study in Chinese population, *MMP-9* polymorphism in individual carrying RR genotype at P574R have increased risk of ESCC while R279Q and R668Q polymorphism has no association with cancer risk. In contrast Fang *et al*[63] reported that individuals having RR genotype at R279Q site have enhanced risk towards colon cancer. Tang *et al*[62] showed R279Q and P574R polymorphism were associated with lymph node metastasis of gastric cancer. Positive association of MMP-9 -1562 C/T polymorphism and colon cancer risk has been reported by Woo *et al*[61] in Korean population. Other studies reported a higher incident of lymph node metastasis in gastric and colon cancer patients having CC genotype at -1562 bp[64,65].

Association of SNPs in MMP-3 promoter and gastrointestinal cancer has been investigated in MMP-3 -1171 6A/5A site, since transcription repressor bind strongly with 6A allele leading to reduced gene expression. Bradbury *et al*[51] suggested a positive association of EA risk with 6A/5A or 5A/5A carrier. In addition, Zhang *et al*[64] found a higher ESCC risk among smokers having the 5A allele and reported that an elevated risk of lymph node metastasis in patients having 5A allele instead of the 6A allele. Interestingly, Dey *et al*[52] reported that the frequency of homozygotes for the 6A allele is lower in

gastric cancer patients than in controls of eastern Indian population[66]. On contrary, only one study performed in Japanese population that showed higher incidents of colon cancer in individuals having 6A/6A genotype.

Two common functional MMP-7 SNPs (-181A/G, -153C/T) are believed to control gene expression in several diseases, including gastrointestinal cancer[67-69]. MMP-7 up-regulation was significantly related to the promoter activity variation of the –181A/G alleles. Jormsjö *et al*[68] reported that the expression and promoter activity of the MMP7 -181G allele was higher in G over A and, attributed to the formation of a putative binding site (NGAAN) for a heat-shock transcription factor to G-allele. On the contrary, Richards *et al*[69] reported that elevated plasma MMP-7 level in AA genotype was governed by the G to A transition in -181 bp resulting in higher binding for the forkhead box A2 transcription factor to AA genotype. Studies reported a positive association of MMP-7 -181A/G polymorphism in esophagus, and gastric adenocarcinoma in Chinese population with an increased gastric cancer risk in G allele carrier[70]. However, in contrast, Kubbent *et al*[58] reported more AA and less AG in gastric cancer group. Moreover, MMP-7, -181 A/G and -153 C/T polymorphism is also significantly associated with colon cancer risk[71].

REGULATION OF MMPS IN GASTROINTESTINAL CANCER

An understanding of the MMP regulation in different cellular processes, *e.g.*, apoptosis, angiogenesis, invasion, metastasis as well as immune function is important for early prognosis and better therapeutics of gastrointestinal cancers. The regulation of MMPs goes awry at any or all cellular processes during cancer development[30]. The regulatory mechanisms shared among different cellular processes might control the invasive property of cells. The presence of MMP-1, -2, -3, -9, and MT1-MMP mRNA and protein in gastric and colorectal cancer tissues are evident from IHC and FISH assay. It is also known that MMPs are produced by inflammatory and fibroblast cells, in the vicinity of cancer cells. Among various signaling pathways, mitogen-activated protein kinases (MAPKs) pathways are important in the regulation of MMP induction as most of MMP promoters contain AP-1 and NFκB-binding sites, the downstream target of MAPK pathways. NFκB and AP-1 activity are significantly enhanced during cancer progression. JNK pathway induces MMP expression through activation as well as nuclear translocation of multiple transcription factors such as Jun D, ATF and most of the MMP promoter contain putative-binding sites for these DNA-binding proteins[72]. It is now conceivable that the function of MMPs is not only confined to invasion and metastasis steps of cancer but they also facilitate initial phases of cancer development. In cancer, special emphasis has been placed on the degradation of type IV collagen, a major protein component of basement membranes that can be cleaved by MMP-2 and -9. Disease progression in experimental animal models of cancer invasion and metastasis correlate with enhanced secretion of specific MMPs by tumor cells and/or stromal cells. Specific MMPs appear to have different functions depending on the stage of cancer and tissue type.

MMPs regulate apoptosis

MMPs especially, MMP-3, -7, -9 and -11 regulate apoptosis by degrading matrix protein. MMPs have both apoptotic and anti-apoptotic actions on endothelial and epithelial cells by cleaving adhesion molecule, *e.g.*, VE-cadherin[73], PECAM-1[74] and E-cadherin[75]. Detachment of adhesion molecules from the membrane is prerequisite for apoptosis to occur. Degradation of laminin by MMP-3 is another example of enhanced apoptosis in mammary epithelial cells possibly by degrading laminin[76]. MMP-7 releases the Fas ligand from the membrane which then induces apoptosis of neighboring cells, or decreases cancer-cell apoptosis, depending on the system[77]. MMPs might also negatively regulate cancer-cell growth, by means of activation of TGF-β or generation of pro-apoptotic molecules such as Fas ligand or TNF-α. By producing heparin-binding epidermal growth factor (HBEGF) from the latent form, *i.e.*, pro-HBEGF, MMP-7 promotes cell survival which is opposes the apoptosis *via* tyrosine kinase-mediated pathway. Moreover, MMP-11 also inhibits cancer cell apoptosis, as indicated by Wu *et al*[78], who showed that over expression of MMP-11 decreases spontaneous apoptosis in tumor xenografts. In contrast, MMP11-null mice show a higher rate of apoptosis compared to wild-type when challenged with cancer cells. MMP-11 inhibits apoptosis by the mechanism of releasing IGFs, known to can act as survival factors[79]. Although MMP-9 and -11 decrease cancer cell apoptosis, they increase apoptosis during development[78,80].

MMPs regulate angiogenesis

Angiogenesis, the formation of new capillaries from pre-existing vessels, is associated with several physiological processes as well as pathological conditions. Vascular endothelial growth factor (VEGF) is a mitogen for endothelial cells and is required for tumor-induced angiogenesis. The activation of MMPs is governed by VEGF and then activated MMPs degrade collagen and ECM proteins of basement membrane thereby aiding in the migration of endothelial cells. Cleavage of collagen type I allow endothelial cells to invade the tumor stroma during vessel formation and MMP promote the process by degrading collagen[81]. MMP-2, -9 and -14 directly regulate angiogenesis, and MMP-19 might also be important as it is expressed in blood vessel[82]. Furthermore, reduced MMP-2 expression resulted in decreased angiogenesis in cancer cells in chicken chorioallantoic membrane model. Tumor angiogenesis is significantly inhibited in mice deficient in MMP-2 in comparison with wild type mice[83]. Cleavage of collagen type IV by MMP-2 exposes a cryptic, αvβ3 integrin binding site within the collagen that

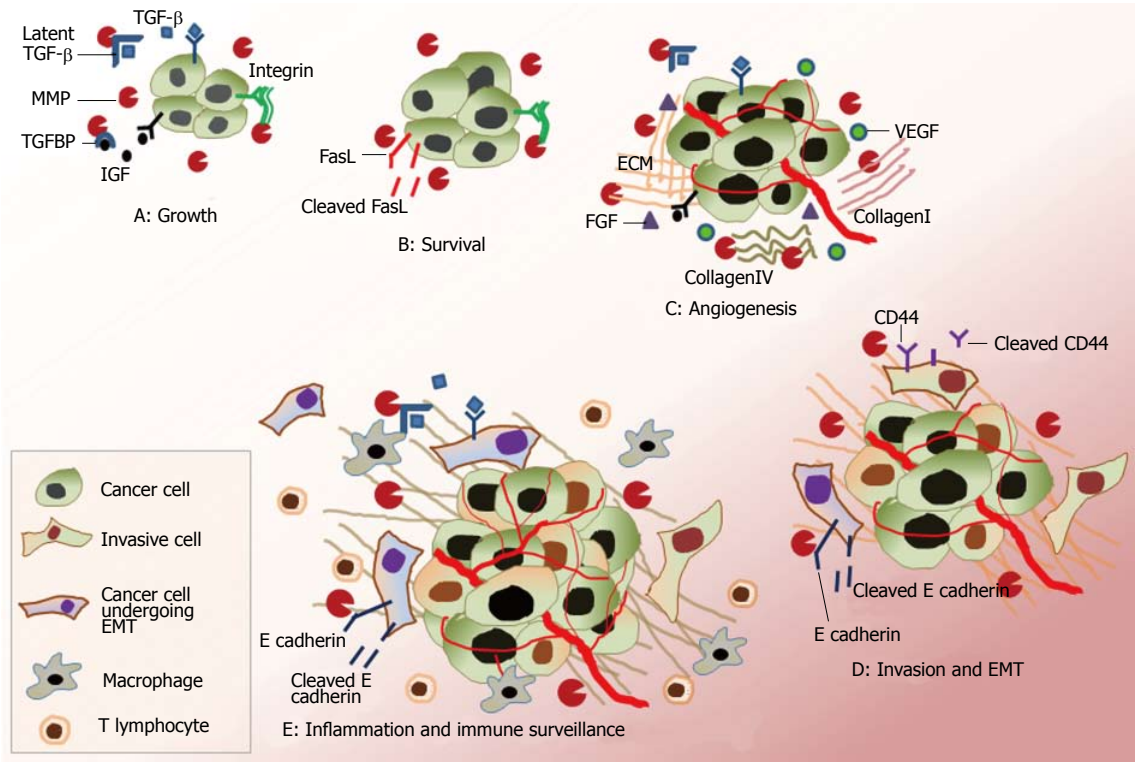

Figure 2 Roles of matrix metalloproteinases in cancer progression. The matrix metalloproteinases (MMPs) play complex but important roles during different stages of cancer progression. A and B: Growth and survival. MMP modulates cellular growth by cleaving different cellular components. It promotes cellular growth by releasing IGF from insulin growth factor-binding protein (IGF-BP). MMP-7 promotes cell survival by resisting apoptosis through cleaving Fas ligand (FasL). MMP modulates integrin signalling by regulating the extracellular matrix (ECM), which regulates growth. MMP activates transforming growth factor-β (TGF-β) from its latent TGF-β complex, which plays important roles in tumour development; C: Angiogenesis. MMP promotes angiogenesis through recruitment of VEGF, FGF. Angiogenesis is further promoted by degradation of extracellular component like collagen I, IV, fibrin, *etc*., which also act as pro-angiogenic factors; D: Invasion and epithelial to mesenchymal transition (EMT). MMP modulates invasion by degrading specific cellular components, including E-cadherin and CD-44. MMP is involved in mesenchymal transition through cleavage of E-cadherin and modulating TGF-β signaling. MMP-3 is directly involved in EMT, whereas MMP-9 has roles in differentiation; E: Inflammation and immune surveillance. MMPs also regulate immune reactions against the cancer cells. MMP-mediated TGF-β activation inhibits T lymphocyte proliferation. MMPs also modulate cancer-cell sensitivity to natural killer cells and leukocyte accumulation by cleaving different chemokines and cytokine families. VEGF: Vascular endothelial growth factor; FGF: Fibroblast growth factors.

helps in migration of endothelial cells both *in vitro* and *in vivo* model[84].

MMP-9 is a key player for pathological angiogenesis as revealed by experiments done in transgenic models of tumour progression, in the K14-HPV16 skin cancer model[85]. In contrast, the angiogenesis process is unaffected by MMP-2 in skin cancer. Both MMP-14 and MMP-9 null mice have impaired angiogenesis during development[86]. Cleavage of plasminogen by MMP-2, -3, -7, -9 and -12 generates angiostatin[87], and MMP-3, -9, -12, -13 and -20 are involved in the generation of endostatin, a C-terminal fragment of the basement membrane collagen type XVIII[45,88]. Both angiostatin and endostatin reduce endothelial cell proliferation[46]; endostatin also inhibits endothelial cell invasion by acting as an inhibitor of MMP-14 and -2[89]. By degrading fibrin matrix of blood vessels, MMP-14 promotes cell invasion and thus increase angiogenesis. In contrast, MMP-12 inhibits tumor angiogenesis by inhibiting endothelial cell invasion *via* a different pathway that mediated by urokinase-type plasminogen activator receptor.

MMPs regulate invasion and metastasis

One of the foremost and major steps in invasion is migration of cancer cells from the site of origin to the docking site. The cleavage of ECM is essential for detachment of cancerous cells from neighboring. Cleavage of laminin-5 by MMP-2 and -14 generates a cryptic site that facilitates cell migration[90]. This is supported by the fact of colocalization of laminin-5 and MMP-14 in human cancer specimen and abundance of degraded laminin in tumor tissues[91]. In addition, the main receptor for hyaluronan, CD44 is cleaved by MMP-14, thus, extracellular domain is released, thereby facilitating tissue invasion (Figure 2). Moreover, cell migration is hampered when the cleavage site is mutated[92]. In addition to binding to the ECM, CD44 also binds MMP-9, thereby localizing the enzyme to the cell surface that promotes tumor invasion and angiogenesis, as confirmed by overexpression of the extracellular domain of CD44 and suppression of tumor invasiveness[93]. Thus, cancer cell migration is regulated by cycles of MMP activity or localized MMP activity, not by continuously high activity. During metas-

tasis, cancer cells first cross the epithelial basement membrane and invade the surrounding stroma, followed by invasion to blood or lymphatic vessels; then extravasate to new tissues and establish growth of new proliferating cells in new tissues. The role of MMPs in metastasis was evidenced by *in vitro* invasion assays and *in vivo* xenograft metastasis assays. Overexpression of MMP-2, -3, -13 and -14 promotes invasion as documented through either optic nerve explants or cell culture in matrigel[94-96]. In addition, metastasis is reduced in the MMP-2 and MMP-9 null mice as compared with wild-type mice. There is no linear relationship between MMP-2 expression and cell invasion, rather cells expressing intermediate levels of active MMP-2 are the most invasive. The localization of specific MMPs to specialized surfaces on the cell membrane is necessary for their ability to promote invasion. Endothelial cell-adhesion molecule E-cadherin is associated with cancer progression, as it is cleaved by MMP-3 or -7[97]. The released fragment of E-cadherin promotes tumor cell invasion in a paracrine manner *in vitro*[98,99]. MMP-2, -9 and -14 are known to localize to invadopodia. Moreover, MMP-2 is recruited to invadopodia by either binding to α5β3 integrin[100] or by binding to MMP-14. MMP-14 is recruited to invadopodia by means of its transmembrane and cytoplasmic domains. Overexpression of MMP-14 increases the number of cancer cells in an experimental metastasis assay. Furthermore, the docking of cancer cells at the secondary site, the late events in the metastatic process also involves MMP activity.

MMPs and the immune responses to cancer

Inflammatory reactions by tumour-specific cytotoxic T lymphocytes, natural killer cells, neutrophils and macrophages are a key mechanism of cellular carcinoma[101]. The immune system is capable of recognizing and attacking cancer cells, while cancer cells somehow escape immune surveillance. MMPs are involved in the escape mechanisms. Although the immune response helps to delay tumour progression, chronic inflammation is also associated with various cancers including cancers those of gastric mucosa, large bowel, and liver[101]. In animal models, mast cells, neutrophils and macrophages are contributors to the progression of cancer. Inflammatory cells synthesize several MMPs, including -9, -12 and -14 and stimulate cancer progression. Indeed, MMP-9 null mice are less prone to skin cancer[85]. Especially, MMP-9 can cleave interleukin-2 receptor (IL-2R)-α and thereby suppress the proliferation of the T lymphocytes[102]. MMP-9 also can act on IL-8, and, thus increases the activity by several folds. MMP-2 cleaves the monocyte chemoattractant protein-3, and the cleaved fragment not only is inactivated but also becomes an antagonist to the receptors[103]. Furthermore, CXCL12 (also known as stromal-cell-derived factor 1) is cleaved and inactivated by MMP-1, -3, -9, -13 and -14[104]. CXCL12 is a ligand for the CXC chemokine receptor 4 (CXCR4) on leukocytes. Inhibition of the binding of CXCL12 to CXCR4 greatly reduces metastasis to lung and lymph nodes in breast cancer[105]. MMP-11 acts on α1-proteinase-inhibitor and the cleaved product altered sensitivity of tumor cells towards natural killer cells[106]. Moreover, few MMPs also activate TGF-β an important inhibitor of the T-lymphocyte response against tumors[107]. MMPs play indirect roles in proliferation of cancer cells by acting on growth factors that entangled into ECM (Figure 3). First, membrane-bound precursors of some growth factors, *e.g.*, TGF-β, are released by MMPs or ADAMs[107]. Second, degradation of growth factors by MMPs makes them available in pericellular space, *e.g.*, MMPs can cleave IGF-BP to release IGF[108]. Finally, cell proliferation by growth factors occurs through integrin signaling.

MAJOR IMPACT OF OXIDATIVE STRESS ON GASTROINTESTINAL DISEASES

For many years, researchers have recognized ROS only as causative factor in pathological processes, although the opinion has now changed. ROS were shown to meet the criteria for signalling molecules and they have significant roles in biological functions. This section deals with involvement of ROS in physiological and pathological processes and, subsequent responses in cancer cells under oxidative stress.

Generation of ROS in biological systems

ROS are often byproducts of mitochondrial function that are constantly generated and eliminated from physiological systems. ROS are oxygen containing reactive species, that may contain an unpaired electron, *e.g.*, superoxide radical ($O_2^{\cdot -}$), hydroxyl radical ($OH^{\cdot}$) and/or non-radical molecules, such as hydrogen peroxide (H_2O_2). $O_2^{\cdot -}$ are formed by chemical reduction of molecular oxygen, by electrons that escape from complex Ⅰ and Ⅲ of electron transport chain and $O_2^{\cdot -}$ is than dismutated to H_2O_2. Nearly 2% of molecular oxygen consumed during mitochondrial respiration ends up as $O_2^{\cdot -}$[109,110]. Apart from mitochondria, ROS can be generated from a family of trans-membrane proteins, known as NADPH oxidases (Nox). These enzymes catalyse NADPH dependent reduction of molecular oxygen to $O_2^{\cdot -}$[111].

Increased ROS generation can induce lipid peroxidation and protein oxidation, hampering normal cellular processes. In addition, ROS can target mitochondrial DNA (mDNA) more effectively due to its proximity and lack of protective histones and limited repair mechanism. mDNA does not contain any introns and encodes for 13 respiratory complexes essential for electron transport chain and oxidative phosphorylation. Mutation of mDNA results in aberrant mitochondrial proteins during ATP generation; this induces further ROS production. Moreover, ROS cause nuclear DNA damage through DNA oxidation (by formation of 8-oxo-G, 8-oxo-dG), which contributes to mutation[109].

Cancer cells are known to be metabolically active and require elevated amount of energy to support their functionality. To meet their ATP need, cancer cells exhibit an increased dependency to glycolysis which slows down

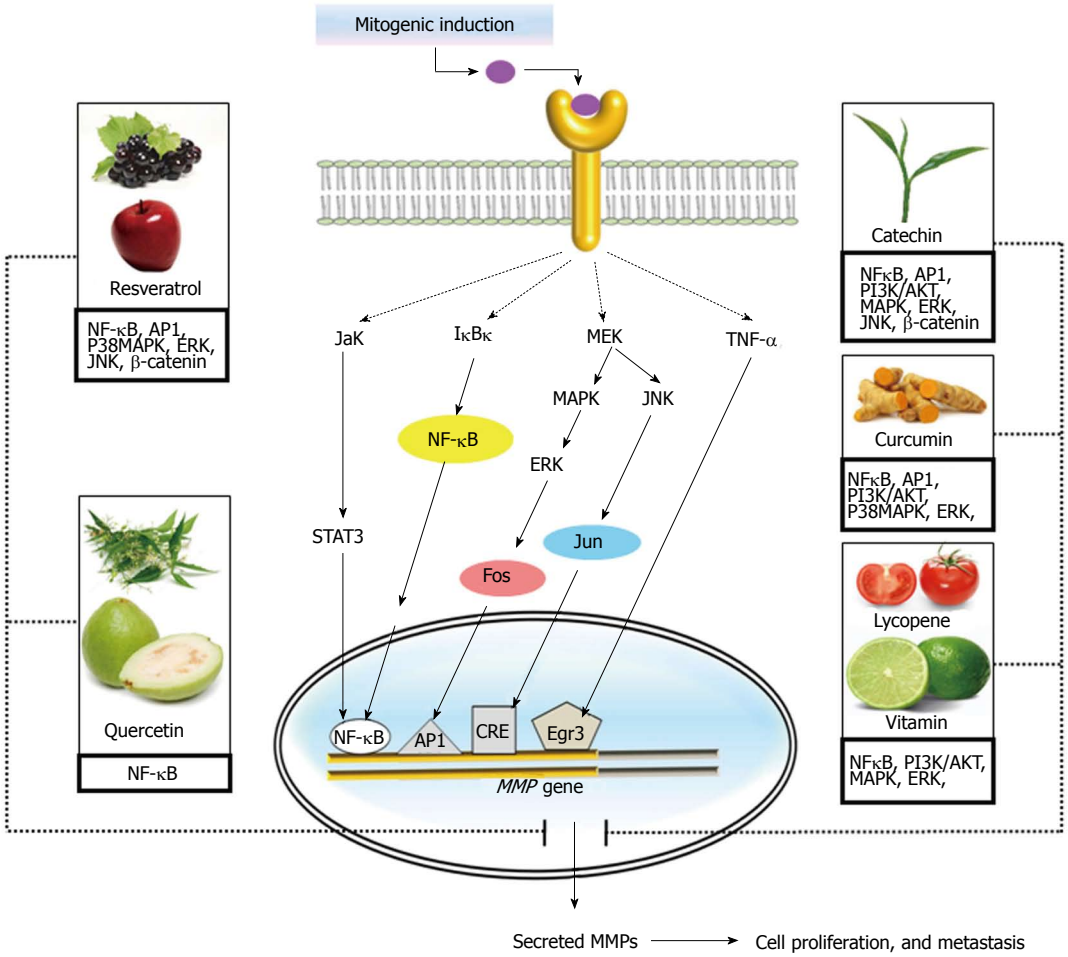

Figure 3 Role of dietary antioxidants in modulating matrix metalloproteinases action. Different ingredients in diet possess antioxidant activity. They act on various signalling pathways and transcription factors which modulate the synthesis and secretion of matrix metalloproteinases (MMPs). Therefore regulates MMP-dependent cellular processes, including proliferation and metastasis. TNF: Tumor necrosis factor; MAPK: Mitogen-activated protein kinases; MEK: Methyl ethyl ketone.

mitochondrial energy production. This phenomenon of stimulation of glycolysis in cancer cells that inhibit mitochondrial respiration, is known as "Crabtree effect"[112]. However, inhibition of glycolysis in tumor cells may result impairment of mitochondrial oxidative phosphorylation and subsequently associated with hypoxia and higher amounts of ROS generation and accumulation of ROS-mediated reaction products[113].

Oxidative stress and gastrointestinal diseases

Oxidative stress plays important roles in pathogenesis of gastro-intestinal diseases, which include mucosal damage, gastro-intestinal ulcers, and cancer. Although gastric ulcer can be generated by different factors, *e.g.*, non-steroidal anti-inflammatory drugs (NSAIDs), thermal stress, ethanol, and *H. pylori* infection, leading to oxidative damage through free radical generation (specially OH·) and subsequent apoptotic responses of gastric mucosa[114]. In addition, gastro-intestinal diseases are associated to increased oxidative stress and oxidants levels, such as glutathione, lipid peroxidation, myeloperoxidases, protein carbonyl, *etc*[115]. Furthermore, pathogens are directly involved in aggravating oxidative stress; for example, complete eradication of *H. pylori* is reported to attenuate oxidative stress in gastric mucosa[116].

Although certain types of gastro-intestinal inflammations, like ulcerative colitis, hepatitis, *H. pylori* infection, are more prone to develop cancer, the reasons are still not well elucidated. Inflammation and subsequent elevated oxidative stress might be the factors for aggravating chronic inflammation and inducing malignant transformation. Transgenic mice expressing hepatitis B protein in liver develop chronic hepatitis with elevated levels of 8-oxo-dG, leading to hepatocellular carcinoma[117]. It is well accepted that inflammation is always accompanied with elevated oxidative stress in cancer. Gastric cancer patients (with normal renal and hepatic functions) are found to have significantly increased lipid peroxidation levels[118]. Gastric carcinoma patients have significantly higher myeloperoxidase activity than controls, both before and after operation, although total antioxidant status was decreased post-operation[119]. Gastric cancers are also associated with augmented protein oxidation, although no differences are found in oxidative stress parameters and antioxidant enzyme activities between anti-*H. pylori* IgG positive and negative gastric cancer patients[120].

Cellular responses in cancer cells under oxidative stress

ROS, such as $O_2^{\cdot}$ and H_2O_2, have roles in proliferation and cellular growth that contribute to the development of cancer. Cancer cells also exhibit different cellular responses under oxidative stress, which include senescence, autophagy and apoptotic responses; although it is still not well understood, how these cellular pathways assume priority to become activated under particular conditions. H_2O_2 can directly modulate autophagic responses during nutritional starvation through Atg4 (autophagin-1) expression and accumulation of LC3-PE on the autophagosomal membrane[121]. In addition, ROS-induced autophagy is dependent on constitutive expression of Atg, baclin, hypoxia induced factor-1 (HIF-1) and BNIP3[122]. Mutations in *ATG* genes (like *ATG2B, ATG5, ATG9B,* and *ATG12*) are involved in gastric and colorectal carcinomas and may contribute to cancer development by deregulating the autophagy process. Moreover, increased autophagy (through upregulation of Atg5 and Atg7) is also involved in *in vitro* malignant transformation by K-Ras[123]. ROS and ROS-mediated signalling pathways are also involved in senescence responses. Overexpression of p21, along with increased ROS production, directly induces the senescence phenotype; while inhibition of p21-mediated ROS accumulation can rescue cells from senescence[124]. In addition, sub-lethal doses of H_2O_2 can induce senescence-like growth arrest at the G1 stage *via* up regulation of p53 and p21. Anti-apoptotic Bcl-2 family members antagonise ROS generation during apoptosis. Moreover, ROS generation is accompanied by cellular apoptosis due to lipid peroxidation and mitochondrial depolarization.

Increased ROS production in cancer cells is associated with constant activation of transcription factors including NFκB and AP-1. Moreover, a recent study found that activation of TLR4 promotes gastric cancer by increasing mitochondrial ROS generation through NFκB activation[125]. Oncogenic signals are involved in ROS generation that promote metastasis in gastric cancer[126]. The oncogene c-myc has been reported to develop genetic instability, DNA damage and mitigation of p53 function through ROS production[127]. RAS2 mutation promotes oxidative stress by restricting mitochondrial respiration into non-phosphorylating state. K-Ras is also involved in malignant transformation through ROS mediated JNK activation[123]. ROS and Rac1b are involved in MMP-3 mediated epithelial to mesenchymal transition (EMT). ROS also stimulate the expression of Snail and cause damage to DNA and subsequent genomic instability[128]. Reports have suggested a possible association of Nox and Nox-mediated ROS generation for carcinogenesis[111]. Nox1 is involved in *H. pylori*-induced gastric cancer and in angiogenic responses for tumour formation[129,130]. Nox2 is involved in phagocytosis; Nox4 controls cell survival in different cancers, including gastric, colon and pancreatic cancers[111,131]. Increased ROS can cause detachment of JNK associated glutathione-S-transferase (GST)-π and thus facilitates JNK activation. In addition, H_2O_2 mediated JNK activation also causes downregulation of JNK phosphatases[132]. Mice that have an inactive c-Jun that lacks JNK phosphorylation site or deficient in JNK displayed reduced tumor development[133,134]. Moreover, increased ROS productions in oncogenically transformed cells potentiate JNK and p38 MAP kinases activation[135].

Role of endogenous antioxidants during oxidative injury

Endogenous antioxidants are essential for maintenance and neutralization of perturbed oxidative free radical status. Superoxide dismutases (SOD) are important antioxidants, as Mn-dependent SOD (Mn-SOD) null mice cannot survive after birth[136]. Heterozygous Mn-SOD null mice can survive, however, show higher incidences of lymphomas and adenocarcinomas[137]. In addition, Zn-dependent SOD (Zn-SOD) knockdown mice develop hepatic cancer in late stages of life[138]. Mice lacking catalase also exhibit elevated cancer incidences[139]. Glutathione peroxidases (GPx) also have significant roles as antioxidants. Simultaneous knock out of GPx-1 and -2 in mice leads to gastrointestinal cancer[140].

Clinical publications have reported different levels of endogenous antioxidants in gastrointestinal cancers. GST, GPx and SOD activities are reported to be significantly elevated in colorectal cancers, than adjacent normal tissues[141]. Stomach adenocarcinoma and esophageal squamous cell carcinoma show significantly increased Mn-SOD expression as compared to noncancerous cells[142]. In clinical studies with gastric and colorectal cancer, GPx, SOD, glucose-6-phosphate dehydrogenase (G6PD), malonaldehyde and glutathione reductase were found elevated in the malignant phenotype[143]. However, because of the sustained oxidative stress conditions, these antioxidants are insufficient in cancer, eventually resulting in decreased antioxidant levels in several cancers[144]. Moreover, modulated expressions of Mn-SOD are reported due to mutations in the promoter region, abnormal methylation, loss of heterozygosity or mutation in the coding sequences[145]. These differential results of cellular antioxidant SOD cause metabolic chaos, due to different types and grades of malignancy[146].

DIETARY ANTIOXIDANTS AS A MODULATOR OF MMPs IN GASTROINTESTINAL CANCER

Human diet contains a mixture of oxidants and antioxidants substances. Dietary and endogenous antioxidants are important for cellular protection by reacting and/or eliminating oxidizing free radicals. The question of whether antioxidant supplements might protect against cancer has drawn much attention since the mid '80s and different antioxidants were extensively studied thereafter, although the results of the investigations are mixed and contradictory. Antioxidant and endogeneous redox enzymes act as the first-line defense against ROS in all

cellular compartments and also extracellularly. The most important of these enzymes include SOD, GPx, catalase and peroxiredoxins. The specific role of above enzymes in carcinogenesis is still unambiguous since their roles in ROS detoxification are well known. It is noteworthy that we do not yet fully understand the chemopreventive role of phytochemicals as antioxidants, or as modulators of other processes related to carcinogenesis. In this section, we highlight the effects of dietary antioxidants in prevention of cancers with particular emphasis on the regulation of MMPs activity.

Tea polyphenol and catechin

Tea, derived from the plant *Camellia sinensis*, is the most consumed beverage worldwide and it is grown in over 30 countries around the world, exclusively in the subtropical and tropical zones[147]. It is processed in different ways in different parts of the world to produce green, black, or Oolong tea. Both green and black teas have been studied for their health benefits, particularly for prevention and treatment of inflammatory diseases as well as cancer. Green tea is rich in polyphenolic substances, which include flavonoid, flavanols, and flavinidols all of which have antioxidant properties. The most common flavonal in tea is catechin. The most active and abundant catechin in green tea is epigallactocatechin-3-gallate (EGCG) that has been shown to inhibit cancer cell growth *in vitro* and *in vivo*. In black tea the major polyphenols are theaflavin and thearubigin.

During the last decade several epidemiological studies have linked tea consumption, especially green tea to a reduced risk of cancer in humans. Morse *et al*[148] documented the beneficial effects of the polyphenol fractions of green tea, the polyphenol fractions of black tea, *i.e.*, EGCG and theaflavins against N-nitrosomethylbenzylamine (NMBA)-induce esophageal cancer in rat. Wang *et al*[149] investigated both protective and therapeutic effects of green tea and black tea extract on esophageal tumorigenesis in rats. A population-based case-control study in Shanghai indicated that tea consumption was strongly associated with reduced colorectal cancer incident. Green tea polyphenol supplementation during the initiation or postinitiation period significantly lowered azoxymethane-induced tumor incidence in rats[150]. In addition, catechin and EGCG reduced colon tumor incidence in a 1, 2-dimethylhydrazine (DMH)-induced intestinal cancer.

Green tea polyphones were shown to prevent cancer cell proliferation and invasion. EGCG has been shown to inhibit NFκB activity in human colon cancer cells[151]. Several studies indicate that chemopreventive properties of EGCG can also mediated by inhibition of MMP induction. EGCG inhibited the PMA-induced cell invasiveness and MMP-9 expression in human gastric cancer adenocarcinoma (AGS) cells[152]. Fassina *et al*[152] documented that EGCG (25-100 μmol/L) inhibits the MMP-2 and -9 in endothelial cells. EGCG inhibited the activity and expression of MT1MMP, a protein responsible for the activation of MMP-2 as examined by Annabi *et al*[153]. Onoda *et al*[154] found that gastric cancer cell lines, *e.g.*, MKN-1, MKN-28, MKN-45, NUGC-3 and TMK-1 are sensitive to EGCG treatment with NUGC-3 being the most sensitive. Furthermore, EGCG suppresses Met signaling in HCT116 human colon cancer cells[155]. In another study, EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of VEGF and binding to its receptors. EGCG has been shown to affect MMP-2 and -9 activities both directly and indirectly in endothelial cells thereby inhibiting or delaying cancer invasion and metastasis. Concanavalin A-induced activation of MMP-2 and activity of MT1-MMP has been reduced by EGCG[156]. Catechin, another major component of tea, prevents vascular smooth muscle cell invasion by inhibiting MT1-MMP activity and MMP-2 expression[157]. Black tea polyphenols inhibit DMH-induced colorectal cancer by inhibiting MMP-7 induction *via* Wnt/β-catenin pathway[158]. Hwang *et al*[159] showed the apoptotic effect of EGCG in HT-29 colon cancer cells that was mediated by AMPK signaling. Hence, catechin and EGCG exert strong anticancer activity by targeting transcription factors like NFκB, and AP-1 which involve in the regulation of mainly MMP-2, -9 and -7 activities. Specifically, EGCG regulates angiogenesis and apoptosis *via* changing expression of VEGF, uPA, IGF-1, EGFR, cell cycle regulatory proteins and in turn affects NFκB, PI3-K/Akt, ERK, JNK, Ras/Raf/MAPK and AP-1 signaling pathways, thereby acting as chemopreventive agent[160].

Curcumin

Curcuma longa (Zingiberaceae family) rhizomes have been traditionally used in the south Asian countries for the treatment of a variety of inflammatory conditions and different diseases including carcinomas[161]. The pharmacological properties of curcumin are attributed mainly to the curcumin (diferuloylmethane)-(1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-hepadiene-3,5-dione) a hydrophobic polyphenol present in the rhizome. Curcumin is a potent antioxidant that acts as a free radical scavenger[162]. Curcumin possesses a wide range of pharmacological activities including anti-inflammatory, chemo-preventive, and antimicrobial and wound healing effects[162-164]. Curcumin which is also known as turmeric, has been shown to exhibit dose dependent chemo-preventive effects in several gastrointestinal cancers including colon, duodenal, stomach, esophageal and oral carcinogenesis[165,166]. *In vivo* and *in vitro* studies have demonstrated curcumin' s ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis and tumor growth[167]. These protective effects of curcumin are attributed mainly to its antioxidant properties and investigated for the purpose of developing novel drugs. It reduces carcinogen-induced tumorigenesis in the fore-stomach and N-ethyl-N'-nitro-nitrosoguanidine-induced duodenal tumors. Lower incidences of bowel cancer in Indians, possibly due to the use of turmeric during food preparation. The molecular basis of anti-carcinogenic and chemopreventive effects

of curcumin is targeted to transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators and cellular signaling molecules[166].

Koo *et al*[168] showed that curcumin and 5-fluorouracil (5-FU) additively inhibited the growth of gastric carcinoma cells. In another study, curcumin reversed the multidrug resistance of a human gastric carcinoma cell line[169]. Curcumin exhibited both preventive and therapeutic effects on the incidence and multiplicity of fore-stomach tumors induced by benzopyrene in mice[170]. A dietary supplementation of 0.15% curcumin reduces intestinal tumor formation in $Min^{-/-}$ mice by 63%. Curcumin induces apoptosis and prevents adenoma development in the intestinal tract in mice[171]. Tetrahydrocurcumin (THC) significantly decreases DMH-induced colon carcinogenesis[172]. Shpitz *et al*[173] showed that curcumin and celecoxib synergistically inhibit colorectal cancer progression in DMH-induced rat model. Several studies documented the inhibitory effects of curcumin on AOM-induced colon cancer[174]. Curcumin inhibits the expression of MMP-9 both *in vitro* and *in vivo* and thereby inhibits tumor invasion and metastasis. Bimonte *et al*[175] reported that curcumin inhibits the expression of MMP-9 in orthotopically implanted pancreatic tumors. Curcumin causes a significant reduction of tumor volume, and MMP-9 activity in a xenografted model[176]. Curcumin also reduces the expression of major MMPs *via* reduced NFκB activity and AP-1 transcription[176]. Lin *et al*[177] reported that curcumin inhibits SK-Hep-1 hepatocellular carcinoma cell invasion *via* suppression of MMP-9 secretion. Curcumin prevents human colon cancer, colo-205 cells migration through the inhibition of NFκB/p65 and downregulation of cyclooxygenase-2 and MMP-2 expression[178]. Lin *et al*[179] reported that curcumin inhibits SDF-1α-induced invasion of human esophageal carcinoma cells by down regulating MMP-2 promoter activity as well as suppressing the formation of lipid raft-associated Rac1/PI3K/Akt signaling complexes. In conclusion, curcumin appears to have a significant potential in the treatment of multiple diseases that are due to oxidative stress. Thus, various inflammatory pathways ultimately act on MMP transcription or expression during prevention of various types of cancer by curcumin.

Resveratrol

Resveratrol (trans-3,4',5-trihydroxystilbene), a non-flavonoid polyphenolic antioxidant, has attracted considerable attention due to its anti-oxidant, anti-cancer, and anti-inflammatory properties. It is in abundance in grapes and grape products such as wine, moderately abundant in blueberries, and sparsely abundant in other plants. Resveratrol is a scavenger of hydroxyl, superoxide, and other radicals and thus acts as a potent antioxidant. It protects against ROS-mediated lipid peroxidation in cell membranes and DNA damage. Resveratrol enhances the expression and/or the activity of drug metabolizing phase I/II enzymes such as Mn-SOD, GST, cytochrome P450 reductase, quinine oxidoreductase, NAD(P)H: quinone oxidoreductase (NQO1), quinone reductase (QR), heme oxygenase-1 (HO-1), glutamate cysteine ligase (GCL); thereby protecting against oxidative DNA damages[180]. Several studies demonstrated that resveratrol exhibits strong chemopreventive effects in various experimentally induced tumor models as well as inhibits proliferation and induces apoptosis of various cancerous or transformed cells. Oral or intra-peritoneal administration of resveratrol decreases expressions of COX-1, COX-2, and PGE2 reducing the number and size of esophageal tumors in N-nitrosomethylbenzylamine-induce rat tumor model[181]. Similarly, oral administration of resveratrol limits the formation of aberrant crypt foci and tumors in the colon of rats that are treated with chemical carcinogen, *i.e.*, 1,2-dimethylhydrazine (DMH) or azoxymethane. Resveratrol prevented the formation of colon tumors and reduced the formation of small intestinal tumors by 70% in $APC^{-/+}$ mice[182]. Resveratrol inhibits MMP-9 expression and invasion of human hepatocellular carcinoma cells. Resveratrol modulates all three MAP kinases namely ERK1/2, JNK, and p38 MAPK. Resveratrol impairs the expression of EMT-related genes (E-cadherin, N-cadherin, vimentin, MMP-2, and -9) in pancreatic cancer cells and inhibits proliferation, migration, and invasion[183]. Ji *et al*[184] demonstrated that resveratrol possesses chemopreventive effects in HCT116 CRC through inhibition of MMP-7 *via* Wnt/β-catenin signalling pathway. Weng *et al*[185] suggested that resveratrol and its related methoxy analogue MR-3 might exert anti-invasive activity against hepatoma cells through regulation of MMP-2 and -9 as well as TIMPs. Harikumar *et al*[186] reported that resveratrol can enhance chemopreventive activity of gemcitabine *in vitro* and *in vivo* mouse model of pancreatic cancer. In summary, anticancer activity of resveratrol is augmented by upregulation of TIMP and downregulation of MMP-9 expression.

Quercetin

Quercetin or 3,5,7,3',4'-tetrahydroxyflavone is a flavonoid found abundantly in plant-derived foods and has been shown to possess several health beneficial activities including anti-tumor, anti-inflammation and anti-proliferation; it has recently gained attention due to its potential anticancer activity. As an antioxidant it possesses the most potent ROS scavenging activity and provides protection against the development of variety of cancers by ameliorating ROS-mediated cellular damages[187]. Moreover, it reduces the level of oxidative enzymes, such as xanthine oxidase (XOD), lipoxygenase and NADPH oxidase, thereby preventing free radical-induced cellular damage[187]. *In vivo* studies have been performed to depict the chemopreventive properties of quercetin on different cancers. Volate *et al*[188] found that food supplementation of approximately 3% quercetin exerts significantly beneficial effects by decreasing precancerous lesions through induction of cellular. Dihal *et al*[189] reported that quercetin inhibits azoxymethane-induced colorectal carcinogenesis in F344 rats. Quercetin was found to be protective

against hepatocarcinoma that was generated by N-nitrosodiethylamine and, was accompanied by the maintenance of a correct intracellular oxidant/antioxidant status. Quercetin prevents 4-nitroquinoline 1-oxide-induced oral carcinogenesis during the initiation/post initiation phases of carcinogen treatment. A limited number of experiments were conducted to investigate the effects of quercetin in the regulation of MMP activity in gastrointestinal cancer. It has been found that quercetin supplementation did not alter MMP-2 or TIMP-2 gene transcription or plasma protein levels but TIMP-1 gene expression and plasma protein levels decreased significantly. Recently, Lai *et al*[190] reported that migration and invasion of SAS human oral cancer was inhibited by quercetin *via* downregulation of MMP-2 and -9 in a NFκB dependent pathway. They also showed significant reduction of the MMP-7, -10 protein levels by quercetin treatment.

Other promising dietary antioxidants

The roles of few more dietary antioxidants *e.g.*, melatonin, lycopene, retinoic acid, vitamin C and vitamin E in prevention of cancer through regulation of MMPs are discussed below. Melatonin is a naturally occurring antioxidant synthesized mainly by the pineal gland of vertebrates and also found in many edible plant products[191]. Recent research documents that consumption of tropical fruit enhances the serum melatonin level as well as raises the antioxidant capacity of blood serum[191,192]. Melatonin retards the development of cancer in different animal models and possesses strong anti-proliferative and pro-apoptotic effects in various cancer cells. Sharman *et al*[193] reported that long term exposure to dietary melatonin reduces tumor number and size in aged male mice. In addition, melatonin inhibits the growth of murine gastric carcinoma cells by upregulation of p21, Bax and down regulation of Bcl-2. Decreased expressions of melatonin receptor in various cancers also suggest the importance of melatonin signaling in cancer development[194]. Hong *et al*[195] reported that melatonin treatment induces apoptosis, autophagy, and senescence in human colorectal cancer cells. A few report suggested that melatonin prevents gastrointestinal cancer development by modulation of MMP functions. Melatonin induces apoptosis and reduces invasiveness of HepG2 cells *in vitro* through TIMP-1 upregulation and attenuation of MMP-9 activity *via* NFκB signal pathway[196]. Rudra *et al*[192] reported that melatonin reduces MMP-9 activity in AGS cell line and binds directly to its active site.

Two separate studies reported the chemo-preventive effects of lycopene in human colon cancer. Tang *et al*[197] evaluated the chemo-preventive effects of lycopene and fish oil in a mouse xenograft model of colon cancer. They found that inhibition of tumor growth and progression by the augmenting p21 (CIP1/WAF1) and p27 (Kip1) expression, and suppression of MMP-7, MMP-9, COX-2 and PGE2, PCNA, β-catenin, cyclin D1 and c-Myc proteins[197]. *In vitro* study by Lin *et al*[198] suggested the inhibitory effects of lycopene on tumor progression, where cell invasion was inhibited by down regulation of MMP-7 expression *via* blocking MAPK/ERK and PI3K/Akt signaling pathways. Adachi *et al*[199] reported that naturally occurring retinoid, all-trans retinoic acid (ATRA), 9-cis retinoic acid and 13-cis retinoic acid are helpful in the prevention and therapy of colon cancer. ATRA prevents tumor invasion in mice and inhibits *in vitro* invasion of colon cancer cells by down regulation of MMP-7 expression. Moreover, Park *et al*[200] reported that retinol reduces the invasive potential of retinoic acid resistance colon cancer cells by decreasing MMP-1,-2,-7,-9 expressions and activity. Retinol reduces the metastatic potential of colon cancer cells *via* down regulation of MMP induction in a retinoic acid receptor-independent mechanism. β-ionone, the derivative product of carotenoids, is the precursor of vitamin A also possesses anti-proliferative activity in cancer cells[201]. Liu *et al*[202] found that that γ-tocotrienol inhibit gastric cancer cell (SGC-7901) proliferation by reducing MMP-1 and -2 activity *via* modulating the expression of their inhibitor TIMP-1 and TIMP-2. Dietary supplementation of naturally occurring antioxidants, ascorbic acid reduces the size of colon xenograft cancer by downregulation of MMP-9 and VEGF in nude mice[203]. Vitamin E (γ-tocotrienol) effectively inhibits the growth of human gastric cancer in a xenograft mouse model. γ-tocotrienol inhibited the proliferation of gastric cancer cell lines, *via* inhibiting the NFκB mediated up-regulation of MMP-9 and VEGF[204].

CONCLUSION

The immense complexity of cancer disease is not yet fully characterized despite numerous advances in modern molecular biology. Complexity in cancer cells arise from heterogeneity of tumor microenvironment, inflammatory stimuli, immune responses, diet effects as well as intestinal micobiota. All these factors determine whether the fate of cancer cells undergo apoptosis or proliferation or even develop resistance to drugs. Cancer is a multifactorial disease, which varies from patient to patient. Even the complexity lies in a certain tumor cells that may refer to tumors with diverse genetics. In fact, every cancer types is unique. Hence, intramolecular heterogeneity poses another dimension during cancer progression. Significant intra-tumor heterogeneity is present in many patients, thus drug resistance may develop. Sequencing technology is used to monitor clonal dynamics of cancer cells. In this context, careful attention should be given to detect minor clones of clinical significance. Tumor heterogenity was documented by the Cancer Genome Atlas and the Cancer Genome Analysis projects.

In the future, personalised cancer medicine may be possible by accounting for both interpatient and intrapatient heterogeneity. Additionally, new therapeutic strategies are important for targeting cellular conditions like cellular senescence rather than targeting a particular biomolecule. Given the complexity of cancer, it is unlikely universal therapeutic strategy will be employed

for different cancer types and stages. The MMP family of enzymes occupies a major importance in the field of gastric cancer research. Literature in last two decades of MMP biochemistry and cancer biology supports the possibility of particular MMP in particular types of cancer, including gastrointestinal cancer. Both basic and applied research is needed to decipher the mechanisms of cancer progression and regulatory roles of particular MMP associated with different cancer types. Drug discovery efforts have uncovered pharmacological inhibitors of different MMPs. Specific MMP inhibitors at a specific dose would be an important achievement to treat particularly gastric cancer and to halt to the progression of these diseases.

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