Chapter 10
The Role of Inflammation in Gastric Cancer

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Abstract Gastric cancer, despite its declining incidence rate, is still the second cause of cancer-related death worldwide, killing 750,000 people each year and remaining the second common type of cancer. The best examples of inflammation-associated cancer in human beings may be gastric cancer. Understanding the molecular mechanism of the inflammation in gastric carcinogenesis is important for developing new strategies against gastric cancer.

10.1 Introduction

Cancer is a major public health problem. Every year almost 1 million new cases of gastric cancers are presented and there are about 750,000 deaths caused by gastric cancer. It ranks second in terms of cancer-related deaths after lung and bronchus cancer (Hussain and Harris 2007; Jemal et al. 2011). Although chemotherapy improves life expectancy, complete resection of gastric cancer (R0) via gastrectomy remains insufficient and more than 80 % of patients with advanced gastric cancer die of the recurrent disease within 1 year after diagnosis (Group et al. 2010; Gomceli et al. 2012).

The choice of treatment generally depends on the tumor's size, tumor location, stage of disease, and general health status of patient. Treatment of the gastric cancer consists of surgery, chemotherapy, radiotherapy, and also targeted therapy. Surgery is a common treatment of all stages of gastric cancer. The aim of surgery is to remove as completely as possible all grossly visible tumor tissue and to obtain histologically free surgical margins. Total and subtotal gastrectomy are used for R0 resection. If the tumor is blocking the stomach but the cancer

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cannot be completely removed by standard surgery, endoluminal stent placement, endoluminal laser therapy, and gastrojejunostomy are used in palliative surgical procedures. Generally, 3 cycles of chemotherapy regimen are used before and after surgery. Each cycle lasts 3 weeks. The most commonly used drug combinations for gastric cancer are ECF and ECX. ECF contains the drugs epirubicin, cisplatin, and fluorouracil, and ECX contains epirubicin, cisplatin, and capecitabine. Targeted therapy is an another type of treatment of gastric cancer. A drug called trastuzumab has led to significant gains in overall survival if the stomach cancer cells have too much HER2 protein (Misleh et al. 2013).

10.2 Inflammatory Signaling Pathways

Cell proliferation, differentiation, and function are principally arranged with a broad signaling network mediated by stimulative/inhibitory hormones, neurotransmitters, various cytokines, and growth factors. The interactions between cells are the most important factors that keep the balance of this network which can influence cell proliferation in positive or negative ways, as well as these interactions induce a series of differentiated responses in appropriate target cells. When these networks are inappropriately regulated, neoplastic cells may occur with its autonomy of unrestrained growth and may harm the organism even the causes are disappeared (Fedi et al. 2000).

Inflammation is one of the predominant manifestations of innate and adaptive immune systems that different and also alternative inflammatory mechanisms play a part in remodeling of tissue and re-establishment of tissue homeostasis in consequence of infection or injury by exogenous or endogenous means. All pro-inflammatory responses are accompanied by anti-inflammatory responses as a non-homogenous result that depend on type of the pathogen or tissue damage, the genotype of the host, and also discrepancies between the tissue involved. Any disturbance in tissue homeostasis activates the innate immune cells that are first line of defense which quickly migrate into the injured tissue after vasodilatation and in response to chemokine gradients, classically described as the inflammatory stage of wound healing (Velnar et al. 2009). The innate immune system cells are composed of macrophages, mast cells, dendritic cells (DC), and natural killer cells (NK), etc., that regulates the inflammatory response by releasing excessive growth hormones, cytokines, chemokines, matrix-remodeling proteases, reactive oxygen, and nitrogen species on behalf of taking control of the inflammatory process (Coussens and Werb 2002; Nathan 2002). These cells also promote healing by releasing cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, interleukin (IL)-6 that achieves cell survival, activate stem cells and promote epithelial proliferation. Also, the correlation between tumor-associated macrophage abundance and poor prognosis has been shown (Nowicki et al. 1996). Furthermore, macrophage-deficient mice display reduced progression of tumors to a more malignant phenotype (Bromberg and Wang 2009). NK and DC also play a key role in providing a link between adaptive and innate immune response, and both have

crucial roles in maintaining the antigen-specific immunity (de Visser et al. 2006). Th1 response and its accompanying mediators interferon (IFN)-γ are not only necessary for *Helicobacter*-induced inflammation but also for the development of atrophy or metaplasia and spasmolytic polypeptide-expressing metaplasia (SPEM); however, a Th2 response and its mediators (i.e., IL-4) appear to be protective. The presence of a Th1, rather than a Th2, immune response is also associated with better survival in gastric cancer patients (Marshall and Warren 1984).The host response to the inflammation is a key factor takes role within inflammation process leading to carcinogenesis which includes the steps of initiation, promotion, and progression (Kinzler and Vogelstein 1996).

In addition, inappropriate and steady regulation of the immune components may be a cause of chronic inflammation by generating an initiative microenvironment that alters normal cellular homeostasis and advances the stepwise accumulation of genetic and epigenetic alterations of various proto-oncogenes and tumor suppressor genes on behalf of cancer development. These genetic and epigenetic changes include point mutations, deletions, duplications, recombinations, methylation of various tumor-related genes through various mechanisms (Chiba et al. 2012) and also include altered microRNAs expression (Zhang et al. 2008). Although, multiple signaling pathways including increased inflammatory cytokine production, abnormal apoptosis, inappropriate cell proliferation/differentiation, and epithelial transformation are triggering causes of these alterations. The fact is that biology of cell division, differentiation, and apoptosis is exceedingly similar in both normal and cancer cells (Ooi et al. 2009).

Some of the earliest observations in cancer biology as well as recent advances in molecular analyses contribute to our knowledge about the multistep process of gastric carcinogenesis (Yokozaki et al. 1997; Balkwill and Mantovani 2001; Gutierrez-Gonzalez and Wright 2008). Ooi et al. (2009) mentioned in a study that among 70 % of GC patients, three oncogenic pathways are deregulated, which are demonstrated as: proliferation/stem cell pathway (40 % of GCs), NF-κB pathway (46 % of GCs), and Wnt/b-catenin pathway (39 % of GCs). Nuclear factor (NF)-κB and STAT3 pathways have emerged as key regulators of the release of these pro-inflammatory cytokines, and important mediators of both tumor proliferation and persistence of chronic inflammation. The activation of these pathways results in further cytokine release (Yang 2007; Rius et al. 2008; Guilford et al. 1998). Several studies suggest that association between gastric carcinogenesis and cytokine overexpression, especially IL-1, IL-6, TNF which are also regulated by the NF-κB, showed such a clinical correlation with NF-κB signaling pathway upregulation in gastric cancer cells more than benign disorders such as gastritis (Yin et al. 2013). STAT3 drive in gastric cancer initiation and progression through its activation by cytokines, IL-6 family ligands are expressed in the stomach that IL-6 and IL-11 provide a basis in tumorigenesis (Giraud et al. 2012).

The gastrointestinal tract has rapid epithelial turnover and exposure to injury by infections and dietary toxins. These conditions create very high cancer prevalence. Intestinalization of gastric units, which is called “IM”; phenotypic antralization of fundic units, which is called “spasmolytic polypeptide-expressing metaplasia

(SPEM)"; and the development directly from the stem/progenitor cell zone are three pathways that have been described for gastric carcinogenesis (Fox and Wang 2007; Hoffmann 2008; Slack 1986).

Stem cell activation is a remarkable step in obtaining the tissue repair and self-renewal. Despite the main disadvantages of addressing the response of human immune system in the clinical researches remain obscure, these studies implicate that only a subset of cancer stem cells (CSCs) propagate the tumor (Vries et al. 2010), while the frequency of CSCs greatly increases to possibly more than 25 % of all tumor cells (Shmelkov et al. 2008; Quintana et al. 2008; Kelly et al. 2007). Several signaling pathways such as, Wnt/β-catenin pathway, take role in assuring the homeostasis and maintain the balance of gastric epithelia between progenitor and stem cells (Lickert et al. 2001; Katoh 2007). Additionally, Wnt signaling pathway is described as important steps of tissue repair and stem cell self-renewal in chronic tissue injury-related carcinogenesis (Beachy et al. 2004). It has been shown in a study that Wnt pathway in association with other inflammatory signaling pathways initiates the gastric progenitor cells through the metaplasia-carcinoma sequence in rat gastric mucosa (Oshima et al. 2006). In another mouse model, activated macrophages in the inflamed or *Helicobacter pylori*-infected gastric mucosa express TNF-α, which stimulate the surrounding cells to promote Wnt/β-catenin signaling activity in multistep pathogenesis of inflammation leading to gastric cancer (Oguma et al. 2008).

Cyclooxygenases (COX) are the key enzymes that convert and array of fatty acid substrates into pro-inflammatory prostanoids. There are 2 types of COX genes, type 1 is a physiologic gene that constitutively expressed in many tissues and responsible for the synthesis of prostanoids involved in protection of the gastrointestinal mucosa and for production of the pro-aggregatory prostanoid thromboxane by the platelets. In the contrary, type 2 COX gene is usually undetectable in most tissues. COX-2 is an inducible gene and activated by several stimulus like hormones, pro-inflammatory cytokines, growth factors, and tumor promoters. Also COX-2 has been related to inflammation, reproduction, and carcinogenesis (Taketo 1998; Dannenberg et al. 2001).

Although the subsequent pathways are different, chronic inflammation is the first step in both the intestinal and the diffuse type of gastric cancer. While the intestinal type has a sequence of multifocal atrophic gastritis, IM, and dysplasia, which advances to carcinoma, the diffuse type tends to be primarily genetic in origin (Correa 1995; Nardone et al. 2004). The progress from IM to gastric cancer has a wide range of molecular alterations affecting transcription factors, such as CDX1 and CDX2, telomerases, microsatellite instability, mutations of p53 protein, overexpression of COX-2, cyclin D2, and decreased expression of p27 (Muller et al. 2001). The next step is gastric dysplasia. During the progression of normal tissue through the metaplasia-dysplasia sequence, there are mutations in genes including *p53*, also loss of heterozygosity of the adenomatous polyposis coli gene, overexpression of the anti-apoptotic gene *bcl-2,* and a mixture of polyploidy and aneuploidy (Muller et al. 2001).

As described above, several signaling pathways take place in gastric carcinogenesis, and detection of the form and complexity of interactions between these

oncogenic pathways may be helpful in the immediate future to taxonomize the individual gastric cancers into biologically and clinically relevant subgroups (Ooi et al. 2009).

Aside cytokines, members of the nuclear hormone receptor superfamily, which are ligand-activated transcription factors and members, peroxisome proliferator-activated receptors (PPARs) are assigned in multiple tasks. PPARγ, in particular, is involved in the control of inflammation and glucose metabolism and participates in the processes of cellular proliferation, differentiation, and apoptosis. It has been clearly demonstrated that gastric cancer cell lines express PPARγ and PPARγ is implicated in *H. pylori*-related gastric carcinogenesis (Morita et al. 2001; Konturek et al. 2003). PPARγ ligands, especially troglitazone, induce growth inhibition of gastric cancer cell lines, and that PPARγ agonists may have potential in a cancer therapeutic role (Sato et al. 2000). In addition, a study suggested that on the effect of PPARγ agonists, PPARγ antagonists also inhibit the gastric cancer cell lines growth which explains that PPARγ may effect gastric carcinogenesis through a PPARγ-independent pathway (Ma et al. 2009).

10.3 Role of Inflammation in Gastric Cancer

About 150 years ago Rudolph Virchow distinguished that inflammatory cells are existed in tumor tissues suggesting that chronic inflammation played a role in carcinogenesis. Since then it has been established that 25 % of all cancer types related with chronic inflammation (Hussain and Harris 2007). After identifying chronic atrophic gastritis and discover of *H. pylori*, gastric carcinoma has taken place in one of the cancers caused by chronic inflammation.

Over 100 years several studies have been conducted on gastric cancer and its relationship with atrophic gastritis and intestinal metaplasia. There has been a significant progress through the understanding of the development of gastric cancers, after in 1937, Magnus concluded that *the presence of intestinal epithelium in the stomach is the result of the faulty regeneration of surface epithelium in a mucosa repeatedly damaged by gastritis and that it is, in fact, an example of metaplasia resulting form chronic irritation*, and in 1955, Morson suggested that gastric carcinoma has arose from the areas of intestinal metaplasia (Morson 1955; Magnus 1937). Interest in *H. pylori* as a cause of cancer began after the pioneering discoveries of Marshall and Warren in 1983. *H. pylori* infection is the most common bacterial infection worldwide, almost 80 % of the population in developing countries are infected with *H. pylori* (Pounder and Ng 1995). *H. pylori* is a gram-negative spiral-shaped rod that usually acquired in infancy. It has four to six flagella that settle beneath the mucus layer of stomach. This is a defensive mechanism which protects bacteria from low gastric pH. Another defensive mechanism is its highly active urease enzyme which is capable of dividing urea into ammonia and bicarbonate, creating a non-acid microenvironment. *H. pylori* has various virulence factors such as its screw-like shape, lipopolysaccharide, vacuolating cytotoxin

A (VacA), cytotoxin-associated gene A (CagA), and its pathogenicity island (cagPAI). In recent years, there have been some studies about cagA and cagPAI and their relationship with gastric adenocarcinomas (Yamaoka 2010).

After the discovery of *H. pylori* in the late 1980s and 1990s, many researches have been achieved on its effects over the gastric mucosa and linkage to multistep pathogenesis of atrophic gastritis, intestinal metaplasia, and finally gastric cancer sequence (Correa 1988). The pattern of gastritis has also been shown to correlate strongly with the risk of gastric adenocarcinoma. The presence of antral-predominant gastritis, the most common form, confers a higher risk of developing peptic ulcers whereas corpus predominant gastritis and multifocal atrophic gastritis lead to a higher risk of developing gastric ulcers and subsequent gastric cancer. Pathogens that insist a long-term infection, such as *H. pylori,* can lead to the chronic production of pro-tumorigenic cytokines (Grivennikov et al. 2010). The response to *H. pylori* infection and the subsequent pattern of gastritis depends on the genotype of the patients and in particular genetic polymorphisms of IL-1 beta which is an inflammatory mediator triggered by *H. pylori* infection (Milne et al. 2009). *H. pylori* is the most important risk factor that causes chronic gastritis, peptic ulcus, non-cardia adenocarcinomas, and mucosa-associated lymphoid tissue (MALT) lymphoma. Although most of the infected individuals are asymptomatic, 10–15 % of them develop peptic ulcus and only 1 % of them develop gastric malignancy (Ernst et al. 2006). *H. pylori* has been classified by the World Health Organization as a class one carcinogen in 1994 (Hoggart et al. 2002). However, gastric cancer is not prevented by *H. pylori* eradication in all patients. This can be speculated that prevention of *H. pylori*-associated carcinogenesis only benefits those in whom the malignant process has not begun. Understanding the mechanism of inflammation and cancer may provide a powerful tool for understanding cancer development and prognosis.

Also other pathogen-associated inflammatory responses leading to gastric cancer has been identified, especially Epstein–Barr virus (EBV) that has been accounted for 10 % of the total GC cases (Ushiku et al. 2007). As well as Shin et al. (2006) revealed a rare agent human papilloma virus called the John Cunningham virus (JCV), and JCV T-Ag (oncogenic transforming antigen) has been isolated in 21 out of 37 GC (57 %) patients. Besides, other studies has already been concluded that JCV T-Ag DNA sequences are even presented in 80–90 % of colorectal cancers (Dyson et al. 1990; Bollag et al. 1989).

In the literature, association between parasitic infections and gastric cancer has also been described. Toxocariasis infestation-related multiple liver and pulmonary metastatic nodules have been documented in the follow-up of three gastric cancer patients which are fully regressed after anti-biotherapy (Park et al. 2012). In another patient diagnosed as gastric cancer showed Microfilaria infestation in a sample of supraclavicular lymphoid tissue aspiration cytology in the background of malignant cells thought as transmigration along with metastatic emboli in an immunosuppressed state (Kumar 2010). Although, underlying mechanisms of existence of these pathogens, associated malignancy has to be clarified.

Other etiologic factors in gastric cancer are shown in Table 10.1 (Gomceli et al. 2012).

Table 10.1 Etiologic factors in gastric cancer

Genetic factors	Environmental factors	Other factors
Sex	*Helicobacter pylori*	Gastric adenomas
Familial adenomatous polyposis	Epstein–Barr virus	Barrett's esophagus
Hereditary non-polyposis colorectal cancer (Lynch 2)	Nitrites	Hamartomas
Genetic diffuse gastric cancer (E-cadherin–CDH 1 mutation)	Excess alcohol ingestion	Menetrier's disease
Genetic polymorphisms for pro- and anti-inflammatory cytokines	High intake of salted, pickled, or smoked foods	Chronic atrophic gastritis
Polymorphisms for cell receptors of innate immune response	Low intake of fiber, fruits, and vegetables	Gastric metaplasia
Peutz–Jeghers syndrome	Antioxidant consumption (especially ascorbic acid, carotenoids, folates, and tocopherols)	Pernicious anemia
	Tobacco smoking (adenocarcinoma of cardia)	Benign gastric ulcers
		Fundic gland polyps
		Hyperplastic polyps
		Gastric biopsy revealing high-grade dysplasia
		History of subtotal gastrectomy (>20 year)

Adapted from Gomceli et al. (2012)

10.4 Role of Inflammatory Molecules in Gastric Cancer: Evidence from In Vitro Studies

Inflammatory cytokines are the remarkable determinants cell survival and death. IL-1 and IL-6 activate nuclear factor-κB (NF-κB) and STAT3 pro-survival transcription factors to induce cell survival and tumor development, where as other cytokines such as Fas ligand and TNF-related apoptosis-inducing ligand (TRAIL) induce apoptotic cell death (Kuraishy et al. 2011). It is now well accepted that if the host-mediated anti-tumor activity is incapable of forming immune response via several defending mechanisms, tumor cells undergo immune escape and grow rapidly. Dunn et al. (2004) suggested as in "cancer immunosurveillance" theory that cytokines have dual roles, while such cytokines especially TNF, TRAIL, FasL, and TWEAK are inducing the apoptotic cell death, the other cytokines such as type I interferon (IFN) and TGF-β limit the proliferation of epithelial cells. TNF-α, especially in combination with IFN-γ, were originally described for their anti-tumoral activity, a cytotoxic action against tumor cells by regulating the immune response, host defense and gene expression. It is demonstrated in a study that IFN-γ regulates apoptosis by soluble TNF-R released by IFN-gamma in the injured gastric epithelial cell line induced by TNF (Furuta et al. 2002). IL-12 and IL-18 both

allow proliferation of T cells and potent production of IFN-γ, which may lead to a direct anti-proliferative and pro-apoptotic effect on the tumor cells as well as anti-tumor activity (Ye et al. 2007). In a study, IL-18 enhance the proliferation of gastric cancer lines via NF-κB signaling pathway in a dose-dependent manner, where as L-18-pretreated gastric cancer cells, which were cultured with cytokine-activated peripheral blood killer lymphocytes, showed less secretion of IFN-γ or perforin, anti-tumor products of killer lymphocytes, resulting in a decreased susceptibility of cancer cells to killer lymphocytes (Majima et al. 2006). Despite cytokines, several in vitro studies have found that PPARγ activation results in cell cycle arrest and/or apoptosis of gastric cancer cells (Takahashi et al. 1999). Cytokines produced in response to injury have enormous effects on cell survival contributing to tumor initiation, growth, progression, and metastasis, which is yet to be elucidated.

Chronic inflammation plays an important role in tumorigenesis and macrophages are a key player in generating the chronic inflammation microenvironment by being activated persistently until leading to continuous tissue damage (Macarthur et al. 2004). In the acute phase of inflammation, the release of endogenous reactive oxygen (ROS) and nitrogen species (NOS) (O_2^-, H_2O_2, NO, OH, $ONOO^-$, HOCl) from such innate immune cells as macrophages together with other leukocytes contributes a fight back to infection and pathogens (Maeda and Akaike 1998; Leach et al. 1987). However, sustained generation of ROS and NOS may alter proliferating cells via forming a tumorigenic microenvironment that generated in several pathways. Continuous deleterious ROS and NOS exposure triggers amplification of inflammatory cytokine production that stimulates signal transductors, angiogenic factors, and oncogene overexpression and post-translational modification of tumor suppressor genes and also causes direct DNA damage by inhibition of DNA repair in proliferating cells (Federico et al. 2007).

ROS and NOS secretion is under control of pro-inflammatory cytokines through the activation of protein kinases signaling that accumulates the production of free radicals such as hydroxyl radical (OH•), superoxide (O_2^-•), nitric oxide (NO•), and peroxynitrite ($ONOO^-$).

TNF-α induces ROS production in neutrophils, tumor cells, and also endothelial cells via a ceramide-dependent signaling pathway (Corda et al. 2001), while TNF-α, IL-1β, interferon-γ (IFN-γ) stimulates the expression of inducible nitric oxide synthase in inflammatory and epithelial cells. In addition, in an increased cellular oxidative stress process, TNF-α induced excessive production of reactive oxygen species, influence its cytotoxic effects on tumor cells, and arrangement of gene expression (Goossens et al. 1995; Schutze et al. 1992).

TNF-α and IL-1β also induce the formation of $ONOO^-$, which formed by a reaction of NO• with superoxide, is a constitutive producer of IL-8. IL-8 is a potent pro-inflammatory chemokine derived from monocytes, macrophages, and endothelial cells that promote adhesion, migration, invasion, and chemoresistance of gastric cancer cells (Zouki et al. 2001; Kuai et al. 2012). When ROS levels are significantly increased, oxidatively altered nucleic acids (Demple and Harrison 1994) cause DNA damage including strand breaks, intrastrand adducts, and DNA protein cross-links (Valko et al. 2005). In addition, ROS mediates the formation of

8-oxo-7,8-dihydro-20-deoxyguanosine (Inoue and Kawanishi 1995), and *8-nitroguanine* (Yermilov et al. 1995; Akaike et al. 2003), which are considered to be potential biomarkers of oxidative stress (Evans et al. 2004), in relation to cancer-associated inflammation (Valko et al. 2006, 2007). 8-hydroxydeoxyguanine basically alters the nucleotide string by leading to guanine(G)/cytosine(C) to thymine(T)/adenine(A) transversions which are also observed in vivo in the ras gene (Bos 1988) and the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*K-RAS*) and *TP53* tumor suppressor gene in lung and liver cancers (Takahashi et al. 1989; Hsu et al. 1991).

In an another study, chronic gastritis as a precancerous lesion of gastric cancer, is characterized by the accumulation of oxidative DNA damage that *H. pylori* infection is the major determinant for DNA adduct formation (Farinati et al. 1998). *H. pylori*-infected stomach arranges the microenvironment for the activated neutrophils to provide the ROS or NOS production besides that *H. pylori* itself also produces ROS (Handa et al. 2010).

NO• has a crucial role in inflammation and its functional heterogeneity, between preneoplastic and antineoplastic functions is the remarkable status in the field of cancer biology. NO• and nitric oxide synthase (NOS), *especially overexpression of NOS2*, both have an impact on the post-translational modification of tumor suppressor genes such as p53 and Rb during chronic inflammation (Ying et al. 2005; Hofseth et al. 2003). NO• mediated p53 accumulation and post-translational modification promote gastric cancer progression in association with advanced tumors even with metastasis thereby causing cellular growth arrest, inducing apoptosis and oncogenic mutations in the p53 gene (Rajnakova et al. 2001).

However, *c-MYC oncogene* activation generates sufficient ROS to produce DNA strand breaks, activate p53 pathway in the absence of apoptosis, and cause DNA damage before the S phase in association with ROS induction in normal human fibroblasts (Vafa et al. 2002). Thus, activated oncogenes induce genomic instability in consequence of DNA damage in both precancerous lesions and cancers (Halazonetis et al. 2008)

However, a tumorigenic microenvironment, formed by an unresolved inflammation on account of any deleterious effects of unrestrained release of mediators that already exacerbated by such immune cells, mesenchymal cells, and epithelial cells, contributes to tumor initiation and/or initial tumoral progression. Cytokines are the putative regulators of the inflammation with pro- and anti-inflammatory functions, where INF-γ, TNF, IL-1α/β, IL-6, and chemokines are known to be the major cytokines important for inflammation and cancer development (El-Omar et al. 2000; Ben-Neriah and Karin 2011; Kuraishy et al. 2011).

TNF-α has an important role in both anti-tumoral activity and tumorigenesis with a diversity of response in the chronic inflammation, which ranges between tissue recovery and tissue destruction. TNF-α, produced by malignant cells, leukocytes, and other cells in tumor microenvironments, acts primarily through membrane-bound homotrimeric receptors TNRFI and TNRFII in autocrine and paracrine ways (Locksley et al. 2001). Despite locally high dose of TNF-α exposure destroys the tumor vasculature and causes tumor necrosis, sustained production of TNF-α may facilitate

tissue remodeling and stromal development linking to tumor growth and spread as an endogenous tumor promoter (Balkwill and Joffroy 2010). TNF-α can also promote the angiogenesis by inducing a range of angiogenic factors, thymidine phosphorylase, and matrix metalloproteinases (MMPs) (Balkwill and Mantovani 2001; Leek et al. 1998; Balkwill and Joffroy 2010; Aggarwal 2003). In addition, TNF-α has a vital role in DNA damage with the help of other inflammatory cytokines, IFN-γ, and IL-1β, by upregulating iNOS and NO• production which causes direct damage of DNA and inhibits the DNA repair (Jaiswal et al. 2000). Besides that, TNF-α implicates other chemokines via regulating a tumorigenic signaling network, in inflammatory processes leading to tumorigenesis (Balkwill and Joffroy 2010).

Thus, TNF-α secures its position as a major mediator of inflammation-associated carcinogenesis, by contributing a tumorigenic microenvironment via inducing several cytokines, angiogenic factors, and MMPs that cause DNA damage and promote tumor growth and tumor metastasis in the survival of tumor cells through a tumorigenic signaling pathway, NF-κB (Balkwill and Joffroy 2010). NF-κB is a transcription factor, and NF-κB-regulated genes provide several products that inhibit apoptosis and enhance cell cycle progression, angiogenesis, and metastasis, in consequence of forming the IKK complexes which pro-inflammatory cytokines and microbial infections are being stimulated (Karin and Greten 2005; Karin 2006; Luo et al. 2005). Soutto et al. (2011) demonstrated that Trefoil factor 1(TFF1, a tumor suppressor gene) knockout mice leads to activation of IKK complex-regulated NF-κB transcription factors, and hence, NF-κB-mediated inflammatory response causes a multistep carcinogenesis cascade in the progression of gastric carcinogenesis with the help of TNF-α-mediated NF-κB activation through the TNF receptor 1 (TNFR1)/IκB kinase (IKK) pathway. In an another study, Mochizuki et al., also showed that by using a green fluorescent protein (GFP)-tagged human gastric cancer cell line, TNF-α-pretreated mice group exhibits an early progression of peritoneal metastasis which is more significant than the non-pretreated group (Mochizuki et al. 2004). It is still a controversial manner that gastric cancer patients show a significant increase in TNF-α levels.

TNF-α and IL-1β are essential in the initiation of chronic inflammation. Recent works have shown that IL-1β overexpression, in the absence of *H. pylori* infection, is sufficient to cause gastric cancer. In addition, IL-1β is one of the essential pro-inflammatory cytokines modulated during *H. pylori* infection that directs the mucosa toward atrophy, metaplasia, and neoplastic transformation (El-Omar et al. 2000; El-Omar 2001; Pollard 2004). Beales (2002) demonstrated in a study that IL-1β stimulates the proliferation of gastric cancer cell lines via tyrosine kinase-dependent signaling pathway and autocrine stimulation of GM-CSF contributes to this stimulation in a dose-dependent manner. Similar to findings for IL-1β, Uefuji et al. (2005) demonstrated that IL-1α mRNA expression levels were relevant to COX-2 positive cancer cell lines, that exogenous supplement of IL-1α enhances both IL-1α and COX-2 mRNA expression levels which indicates IL-1α-COX-2 pathway might be involved in tumor progression by regulating cancer cell proliferation. Several researchers have demonstrated that IL-1α enhances angiogenesis and vascular endothelial cell proliferation in gastric cancer cell lines (Ma et al. 2008; Furuya et al. 2000).

Recently, direct evidence has also linked IL-6 to inflammation-mediated tumor initiation and proliferation in colon cancer (Bromberg and Wang 2009). IL-6 plays an important role in stimulation of tumor growth and tumor metastasis including the steps of tumor cells invasion of the stroma, intravasation of blood vessels and circulation in the blood. In an in vitro study designed with several gastric cancer cell lines demonstrated that such gastric cancer cell lines expressed IL-6 mRNA, which was an indicator of gastric cancer cell growth, even anti-IL-6 antibody inhibited this process (Ito et al. 1997). In cancer cells, IL-6 expression that leads to tumor invasion and metastasis in gastric cancer may act as in autocrine and paracrine ways. IL-6 can be secreted from cancer cells which combines with IL-6 receptors on the surface of cancer cells, directly promote the cancer cell mitogenic activity in an autocrine pathway (Ashizawa et al. 2005). IL-6 also stimulates cancer cells to produce hepatocyte growth factor (HGF), which combines with the HGF receptor (c-met) expressed on cancer cells, through a paracrine pathway that HGF induces cancer cells to move to the metastatic site by promoting and accelerating invasion as well as lymph node and/or hepatic metastasis (Ashizawa et al. 2005). In addition, it is documented that IL-6, is an important effector of TNF-α and IL-1β actions in vivo (Gangopadhyay et al. 1998). IL-6 promotes the adhesion of cancer cells and endothelial cells via overexpressing the intercellular adhesion molecules such as ICAM, VCAM, and E-selectin in association with TNF-α and IL-1β (Gangopadhyay et al. 1998). IL-6 acts on cancer cells directly via the Janus Kinase (JNK)/signal transducer and activator of transcription 3 pathways (Ashizawa et al. 2005) and may also inhibit DC maturation and, together with the NF-κB-activating cytokines IL-1 and TNF may promote tumor progression. IL-6 can regulate VEGF and angiogenesis in gastric cancer, as demonstrated in another study that increasing dose and duration of IL-6-stimulated gastric cancer cell lines produces significant amount of vascular endothelial growth factor (VEGF) in vivo and in vitro (Huang et al. 2004).

IL-10 and transforming growth factor (TGF)-β are known for not only their effects oversuppressing the host anti-tumor immunity and anti-inflammatory actions, but also are central regulator of regulatory T cell (Treg) which can inhibit immune responses mediated by CD4(+) and CD8(+) cells (Tsujimoto et al. 2010). TGF-β1 expression demonstrated as a clinical prognostic marker and putative angiogenic factor in gastric carcinogenesis that has already been suggested in a study that TGF-β1 expression stimulates angiogenesis via promoting indirectly by VEGF upregulation (Saito et al. 1999).

10.5 Role of Inflammatory Molecules in Gastric Cancer: Evidence from In Vivo Studies

IL-1β, IL-6, IL-8, and TNF-α mRNA expression levels were significantly elevated in *H. pylori*-positive mucosa compared with *H. pylori*-negative mucosa. In *H. pylori*-positive gastric mucosa, IL-1β, IL-6, and IL-8 mRNA expression levels correlated significantly with activity and chronic inflammation scores, and TNF-α mRNA

expression levels correlated with chronic inflammation scores. There was a negative association between IL-6 and IL-8 mRNA expression and intestinal metaplasia scores IL-6 and TNF-α mRNA expression levels increased with the severity of atrophic gastritis, while pro-inflammatory cytokine mRNA expression levels were lower in the mucosa with intestinal metaplasia compared to mucosa with extended atrophic gastritis (Isomoto et al. 2012).

Individual differences in the intensity of the inflammatory response (which affects the maintenance, severity, and outcome of *H. pylori* infection) may contribute to gastric mucosa transformation. Moreover, the impact of gene polymorphisms on the activity of key inflammatory molecules is relatively well known.

Previous studies on the association between IL-1 genetic polymorphisms and the risk of gastric cancer have produced controversial results. In a meta-analysis, authors observed that the IL-1B–511T carrier, as well as the IL-1RN*2 carriers, are associated with an increased risk of developing of gastric cancer, markedly the intestinal type. IL-1RN*2 carrier increased the risk of developing gastric cancer among Caucasian. However, the IL-1B–31C and +3954T genotypes are not associated with an increased risk of developing gastric cancer (Wang et al. 2007).

In contrast, these polymorphisms are not consistently related to the risks of esophageal or gastric cardia cancers (El-Omar et al. 2003).

A number of studies have shown that cyclooxygenase-2 (COX-2) gene polymorphisms were associated with gastric cancer. However, the results from different research groups have not been consistent. At present, two polymorphisms in COX-2 have been reported. The promoter region polymorphic variant of −1195G>A and −765G>C has been demonstrated to have a functional effect on COX-2 transcription, which may cause gastric cancer (Pereira et al. 2009; Zhang et al. 2005).

Several studies have examined the association of polymorphisms in tumor necrosis factor-A gene (TNF-A) with gastric cancer risk. However, the meta-analysis of these studies have shown that TNF-A-308AA genotype was associated with a increased risk of gastric cancer, whereas other polymorphisms are not (Gorouhi et al. 2008).

Polymorphisms in the 5′-flanking region of IL-10 at positions −1082 A/G, −819T/C, and −592A/C have been suggested to be associated with gastric cancer risk in different populations (El-Omar et al. 2003; de Oliveira et al. 2012). IL-10-592 AA is a factor of protection against the development of this neoplasm in Asians, but not among Caucasians and Latinos, indicating differences in the genetic background of Asians and other ethnicities (Zhu et al. 2011).

IL-17A has a crucial role in the gastric inflammation and carcinogenesis. Genetic polymorphisms of IL-17A may be involved in methylation-related carcinogenesis in the stomach (Tahara et al. 2010). Similarly, it also indicates that IL8, and maybe IL4R, variants may modify the risk for gastric cancer (Crusius et al. 2008).

Few studies have done combined analysis of different polymorphisms in gastric cancer. El-Omar et al. (2003) analyzed 11 polymorphisms of the IL-1B, IL-1RN, IL-4, IL-6, IL-10, and TNF-A cytokine genes and showed that the risk for non-cardia gastric cancer increased progressively with the number of pro-inflammatory genotypes to 27.3 for three or four polymorphisms. This finding is probably due to

an additive effect of the pro-inflammatory profiles of these gene polymorphisms, resulting in an exacerbated immune response. Several studies have demonstrated that the Pro12Ala polymorphism is associated with the high risk of gastric adenocarcinoma (Xu et al. 2010; Lee et al. 2012).

TNF-α-857T carrier showed significantly better overall survival than patients with CC genotype. Gastric cancer patients who have both IL-1β-31 CC and IL-1β-511 TT genotypes and have at least one of the protective genotypes (IL-1β-31 CC, IL-1β-511 TT, TNF-α-857 T carrier) were also associated with better survival. IL-1β-31CC, IL-1β-511TT genotype, and TNF-α-857T carrier may have protective effect against gastric cancer progression (Tahara et al. 2011). Percentages of Tc17 cells in gastric tumors are associated with survival times of patients (Zhuang et al. 2012). Overexpression of TNF-α, IL-6, IL-8, IL-10, IL-18, and IL-33 correlates with several poor prognostic factors such as depth of invasion, distant metastasis, and advanced stage (stage III/IV).

Despite the several studies concluded, the correlation between high serum levels of TNF-α is a prognostic marker in advanced gastric cancer (stage III and IV) patients (Forones et al. 2001; Macri et al. 2006), Wu et al. (1998) suggest that TNF-α value was not an independent prognostic indicator and the role of TNF-α in gastric cancer remains obscure. Gastric cancer patients show different biologic behavior in each of the cases depending on host inflammatory immune conditions. For example, TNF-α gene polymorphism, which is located in the promoter of TNFA gene, effects the prognosis and survival of the patients in such protective and progressive ways (Tahara et al. 2011; Hong et al. 2013). Several studies manifest that IL-6 serum level increase is a significant marker in correlation with tumor size, tumor stage, and metastasis in gastric cancer patients as well as indicator of gastric cancer progression (Ikeguchi et al. 2009; Ashizawa et al. 2005).

On the other hand, low serum levels of IL-12 have been associated with more advanced stages of gastric and colorectal carcinomas and tended to be associated with lymph node metastasis and carcinoembryonic antigen (CEA)-positive tumors greater than 5 cm in diameter (Kawabata et al. 2001; Wu et al. 1998; Nakayama et al. 2000; Sun et al. 2011; Szaflarska et al. 2009). IL-18, previously known as interferon-γ-inducing factor, found elevated in patients with gastric carcinoma stage 2 or 3 (Kawabata et al. 2001).

Also, COX-2 expression is associated with intestinal histologic subtype, proximal location, large tumor size, and advanced stage (Thiel et al. 2011).

Although there are several studies about relation between gastric cancer prognosis and inflammation markers, none of these markers are used in clinical practice.

10.6 Inhibitors of Inflammation for the Prevention and Treatment of Gastric Cancer

Chemoprevention of gastric carcinoma may be divided into three titles: eradication of *H. pylori*, cyclooxygenase inhibitors which directly effects inflammation, and dietary supplements.

Eradication of *H. pylori* for prevention from gastric adenocarcinoma still keeps its uncertainty. But there is a truth that eradication reduces the rates of precancerous lesion such as atrophic gastritis and intestinal metaplasia (Mera et al. 2005). Recent studies state that early eradication of *H. pylori* seems to reduce gastric cancer risk (Fuccio et al. 2009). The key point of eradication is "timing." If the malignant process has begun, eradication therapy loses its significance. Recent long-term studies about the patients with high risk of gastric carcinoma or with patients after endoscopic resection of early gastric carcinoma showed that the eradication therapy did not reduce the risk of development of primary or metachronous gastric cancer (Wong et al. 2004; Maehata et al. 2012). A double-blind randomized study in China showed that gastric cancer still occurred after successful eradication of *H. pylori* and that *H. pylori* eradication did not lead to significant decrease in the incidence of gastric cancer. In the high-risk region of China, 1630 healthy carriers of *H. pylori* were followed for 7.5 years. During the follow-up, the development of gastric cancer was observed in 7 subjects from the *H. pylori* eradication therapy group and 11 subjects from the placebo group, with no significant difference between the two groups. In the subgroup analysis without precancerous lesions (atrophy, intestinal metaplasia, and dysplasia), the incidence of gastric cancer was significantly lower in the *H. pylori* eradication therapy group than in the placebo group (Wong et al. 2004). This study suggested that the preventive effect of *H. pylori* eradication for gastric cancer is sufficient only in patients without an atrophic change (Kato and Asaka 2012).

Right after the study which defines miRNA expression patterns in *H. pylori*-infected gastric mucosa before and after eradication (Matsushima et al. 2011), Shiotani made similar study with patients who underwent endoscopic gastric resection with control biopsies before and 1 year after the eradication therapy (Shiotani et al. 2012). In *H. pylori*-infected mucosa, eradication therapy works as a decreasing factor for vast majority of miRNA which expressed during the *H. pylori*-associated gastritis. But on the other hand, Shiotani underlined that eradication therapy did not improve the abnormal expression of many oncogenic miRNAs in intestinal metaplastic glands or in the gastric mucosa of the high-risk group for gastric cancer (Kato and Asaka 2012).

Several epidemiologic studies have suggested that long-term and regular use of NSAIDs, aspirin in particular, reduce mortality from gastrointestinal metaplasias (Ristimaki et al. 1997). As a result, cyclooxygenase enzyme (COX) is to be thought of a potential therapeutic target in cancer prevention and treatment (Thiel et al. 2011). Firstly, COX-2 inhibitors were tried for prevention therapy of colorectal polyps and cancer; then, recent studies showed that NSAIDs and specific COX-2 inhibitors can play role in prevention of gastric cancer.

In a large prospective cohort study in 2009, Abnet et al. found that regular use of aspirin, or non-aspirin NSAIDs, may reduce the risk of non-cardia gastric cancer. In this study, they reached 2078248 person-years of follow-up in total (mean follow-up is 6.7 years). They found that reported use of aspirin or non-aspirin NSAIDs was associated with a significant 36 % reduction in the risk of non-cardia gastric cancer (Abnet et al. 2009).

Except from NSAIDs, there are several published articles about selective COX-2 inhibitors. In animal models, a study with reflux-induced gastric adenocarcinoma in

Wistar rats that underwent gastrojejunostomy stated that celecoxib has an inhibiting effect on reflux-induced gastric carcinogenesis (Rocha et al. 2009).

In a human trial, patients with gastric preneoplastic lesion, who taken *H. pylori* eradication therapy, received either celecoxib or placebo for 3 months, and a significant improvement in precancerous lesions was observed who received celecoxib for placebo (Zhang et al. 2009). In an another study, etodolac was used as a selective COX-2 inhibitor to demonstrate the preventive effects on cancer development in extensive metaplastic gastritis (Yanaoka et al. 2010). These results strongly suggest that chemoprevention of cancer in the metaplastic stomach is possible by controlling COX-2 expression.

In light of these findings, there is a high probability that in near future, gastric cancer will be prevented by COX inhibition.

There are various studies about diet, nutrition, dietary supplements, and their relation with gastric cancer and also its prevention. According to The World Cancer Research Fund and the American Institute for Cancer Research, non-starchy vegetables and fruits probably protect against stomach cancer. Salt and also salt-preserved foods are probably the causes of this cancer (Wiseman 2008). A prospective study with 10-year follow-up of the Japan Public Health Center study cohort suggested that consumption of vegetables and fruits is associated with diminished gastric cancer risk (Kobayashi et al. 2002). Current epidemiologic and human trial evidence generally indicates that antioxidant foods or supplements provide little protection against gastrointestinal cancers (Jayaprakash and Marshall 2011).

10.7 Conclusions and Future Directions

Gastric cancer is a major health problem in worldwide. Understanding of the mechanism inflammation and cancer may provide a powerful tool for understanding cancer development and prognosis. CSC hypothesis has received more and more attention in last 10 years. This hypothesis will change our daily practice in several types of cancer including gastric cancer. An in-depth understanding of the relation between stem cell and inflammation can lead to development of new drugs and markers that can be used in routine practice.

References

Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A (2009) Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br J Cancer 100(3):551–557. doi:10.1038/sj.bjc.6604880

Aggarwal BB (2003) Signalling pathways of the TNF superfamily: a double-edged sword. Nat Rev Immunol 3(9):745–756. doi:10.1038/nri1184

Akaike T, Okamoto S, Sawa T, Yoshitake J, Tamura F, Ichimori K, Miyazaki K, Sasamoto K, Maeda H (2003) 8-nitroguanosine formation in viral pneumonia and its implication for pathogenesis. Proc Nat Acad Sci USA 100(2):685–690. doi:10.1073/pnas.0235623100

Ashizawa T, Okada R, Suzuki Y, Takagi M, Yamazaki T, Sumi T, Aoki T, Ohnuma S, Aoki T (2005) Clinical significance of interleukin-6 (IL-6) in the spread of gastric cancer: role of IL-6 as a prognostic factor. Gastric Cancer (Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association) 8(2):124–131. doi:10.1007/s10120-005-0315-x

Balkwill F, Joffroy C (2010) TNF: a tumor-suppressing factor or a tumor-promoting factor? Future Oncol 6(12):1833–1836. doi:10.2217/fon.10.155

Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357(9255):539–545. doi:10.1016/S0140-6736(00)04046-0

Beachy PA, Karhadkar SS, Berman DM (2004) Tissue repair and stem cell renewal in carcinogenesis. Nature 432(7015):324–331. doi:10.1038/nature03100

Beales IL (2002) Effect of interlukin-1beta on proliferation of gastric epithelial cells in culture. BMC Gastroenterol 2:7

Ben-Neriah Y, Karin M (2011) Inflammation meets cancer, with NF-kappaB as the matchmaker. Nat Immunol 12(8):715–723. doi:10.1038/ni.2060

Bollag B, Chuke WF, Frisque RJ (1989) Hybrid genomes of the polyomaviruses JC virus, BK virus, and simian virus 40: identification of sequences important for efficient transformation. J Virol 63(2):863–872

Bos JL (1988) The ras gene family and human carcinogenesis. Mutat Res 195(3):255–271

Bromberg J, Wang TC (2009) Inflammation and cancer: IL-6 and STAT3 complete the link. Cancer Cell 15(2):79–80. doi:10.1016/j.ccr.2009.01.009

Chiba T, Marusawa H, Ushijima T (2012) Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation. Gastroenterology 143(3):550–563. doi:10.1053/j.gastro.2012.07.009

Corda S, Laplace C, Vicaut E, Duranteau J (2001) Rapid reactive oxygen species production by mitochondria in endothelial cells exposed to tumor necrosis factor-alpha is mediated by ceramide. Am J Respir Cell Mol Biol 24(6):762–768

Correa P (1988) A human model of gastric carcinogenesis. Cancer Res 48(13):3554–3560

Correa P (1995) *Helicobacter pylori* and gastric carcinogenesis. Am J Surg Pathol 19 (Suppl 1):S37–S43

Coussens LM, Werb Z (2002) Inflammation and cancer. Nature 420(6917):860–867. doi:10.1038/nature01322

Crusius JB, Canzian F, Capella G, Pena AS, Pera G, Sala N, Agudo A, Rico F, Del Giudice G, Palli D, Plebani M, Boeing H, Bueno-de-Mesquita HB, Carneiro F, Pala V, Save VE, Vineis P, Tumino R, Panico S, Berglund G, Manjer J, Stenling R, Hallmans G, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen N, Key TJ, Binghan S, Caldas C, Linseisen J, Kaaks R, Overvad K, Tjonneland A, Buchner FC, Peeters PH, Numans ME, Clavel-Chapelon F, Trichopoulou A, Lund E, Jenab M, Rinaldi S, Ferrari P, Riboli E, Gonzalez CA (2008) Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EURGAST). Ann Oncol (Official Journal of the European Society for Medical Oncology/ESMO) 19(11):1894–1902. doi:10.1093/annonc/mdn400

Dannenberg AJ, Altorki NK, Boyle JO, Dang C, Howe LR, Weksler BB, Subbaramaiah K (2001) Cyclo-oxygenase 2: a pharmacological target for the prevention of cancer. Lancet Oncol 2(9):544–551. doi:10.1016/S1470-2045(01)00488-0

de Oliveira JG, Rossi AF, Nizato DM, Miyasaki K, Silva AE (2012) Profiles of gene polymorphisms in cytokines and toll-like receptors with higher risk for gastric cancer. Dig Dis Sci. doi:10.1007/s10620-012-2460-5

de Visser KE, Eichten A, Coussens LM (2006) Paradoxical roles of the immune system during cancer development. Nat Rev Cancer 6(1):24–37. doi:10.1038/nrc1782

Demple B, Harrison L (1994) Repair of oxidative damage to DNA: enzymology and biology. Annu Rev Biochem 63:915–948. doi:10.1146/annurev.bi.63.070194.004411

Dunn GP, Old LJ, Schreiber RD (2004) The immunobiology of cancer immunosurveillance and immunoediting. Immunity 21(2):137–148. doi:10.1016/j.immuni.2004.07.017

Dyson N, Bernards R, Friend SH, Gooding LR, Hassell JA, Major EO, Pipas JM, Vandyke T, Harlow E (1990) Large T antigens of many polyomaviruses are able to form complexes with the retinoblastoma protein. J Virol 64(3):1353–1356

El-Omar EM (2001) The importance of interleukin 1beta in *Helicobacter pylori* associated disease. Gut 48(6):743–747

El-Omar EM, Carrington M, Chow WH, McColl KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS (2000) Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 404(6776):398–402. doi:10.1038/35006081

El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, Schoenberg JB, Stanford JL, Mayne ST, Goedert J, Blot WJ, Fraumeni JF Jr, Chow WH (2003) Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 124(5):1193–1201

Ernst PB, Peura DA, Crowe SE (2006) The translation of *Helicobacter pylori* basic research to patient care. Gastroenterology 130(1):188–206; quiz 212–183. doi:10.1053/j.gastro.2005.06.032

Evans MD, Dizdaroglu M, Cooke MS (2004) Oxidative DNA damage and disease: induction, repair and significance. Mutat Res 567(1):1–61. doi:10.1016/j.mrrev.2003.11.001

Farinati F, Cardin R, Degan P, Rugge M, Mario FD, Bonvicini P, Naccarato R (1998) Oxidative DNA damage accumulation in gastric carcinogenesis. Gut 42(3):351–356

Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C (2007) Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer 121(11):2381–2386. doi:10.1002/ijc.23192

Fedi P, Kimmelman A, Aaronson SA (2000) Growth factor signal transduction in cancer. In: Bast RC Jr, Kufe DW, Pollock RE et al (ed) Holland-Frei cancer medicine, 5th edn. BC Decker, Hamilton (ON). http://www.ncbi.nlm.nih.gov/books/NBK20800

Forones NM, Mandowsky SV, Lourenco LG (2001) Serum levels of interleukin-2 and tumor necrosis factor-alpha correlate to tumor progression in gastric cancer. Hepatogastroenterology 48(40):1199–1201

Fox JG, Wang TC (2007) Inflammation, atrophy, and gastric cancer. J Clin Investig 117(1):60–69. doi:10.1172/JCI30111

Fuccio L, Zagari RM, Eusebi LH, Laterza L, Cennamo V, Ceroni L, Grilli D, Bazzoli F (2009) Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? Ann Intern Med 151(2):121–128

Furuta S, Goto H, Niwa Y, Ohmiya N, Kamiya K, Oguri A, Hayakawa T, Mori N (2002) Interferon-gamma regulates apoptosis by releasing soluble tumor necrosis factor receptors in a gastric epithelial cell line. J Gastroenterol Hepatol 17(12):1283–1290

Furuya Y, Ichikura T, Mochizuki H, Shinomiya N (2000) Relationship between interleukin-1-alpha concentration in tumors and cell growth in gastric cancer, determined using flow cytometry. Gastric Cancer (Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association) 3(2):86–90

Gangopadhyay A, Lazure DA, Thomas P (1998) Adhesion of colorectal carcinoma cells to the endothelium is mediated by cytokines from CEA stimulated Kupffer cells. Clin Exp Metastasis 16(8):703–712

Giraud AS, Menheniott TR, Judd LM (2012) Targeting STAT3 in gastric cancer. Expert Opin Ther Targets 16(9):889–901. doi:10.1517/14728222.2012.709238

Gomceli I, Demiriz B, Tez M (2012) Gastric carcinogenesis. World J Gastroenterol 18(37):5164–5170. doi:10.3748/wjg.v18.i37.5164

Goossens V, Grooten J, De Vos K, Fiers W (1995) Direct evidence for tumor necrosis factor-induced mitochondrial reactive oxygen intermediates and their involvement in cytotoxicity. Proc Natl Acad Sci USA 92(18):8115–8119

Gorouhi F, Islami F, Bahrami H, Kamangar F (2008) Tumour-necrosis factor-A polymorphisms and gastric cancer risk: a meta-analysis. Br J Cancer 98(8):1443–1451. doi:10.1038/sj.bjc.6604277

Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140(6):883–899. doi:10.1016/j.cell.2010.01.025

Group G, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Van Cutsem E, Buyse M (2010) Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 303(17):1729–1737. doi:10.1001/jama.2010.534

Guilford P, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE (1998) E-cadherin germline mutations in familial gastric cancer. Nature 392(6674):402–405. doi:10.1038/32918

Gutierrez-Gonzalez L, Wright NA (2008) Biology of intestinal metaplasia in 2008: more than a simple phenotypic alteration. Digestive and Liver Disease (Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver) 40(7):510–522. doi:10.1016/j.dld.2008.02.029

Halazonetis TD, Gorgoulis VG, Bartek J (2008) An oncogene-induced DNA damage model for cancer development. Science 319(5868):1352–1355. doi:10.1126/science.1140735

Handa O, Naito Y, Yoshikawa T (2010) *Helicobacter pylori*: a ROS-inducing bacterial species in the stomach. Inflam Res (Official Journal of the European Histamine Research Society [et al]) 59(12):997–1003. doi:10.1007/s00011-010-0245-x

Hoffmann W (2008) Regeneration of the gastric mucosa and its glands from stem cells. Curr Med Chem 15(29):3133–3144

Hofseth LJ, Saito S, Hussain SP, Espey MG, Miranda KM, Araki Y, Jhappan C, Higashimoto Y, He P, Linke SP, Quezado MM, Zurer I, Rotter V, Wink DA, Appella E, Harris CC (2003) Nitric oxide-induced cellular stress and p53 activation in chronic inflammation. Proc Natl Acad Sci USA 100(1):143–148. doi:10.1073/pnas.0237083100

Hoggart K, Lees L, Davies A (2002) Researching human geography. Hodder Arnold

Hong Y, Ge Z, Jing C, Shi J, Dong X, Zhou F, Wang M, Zhang Z, Gong W (2013) Functional promoter −308G>A variant in tumor necrosis factor alpha gene is associated with risk and progression of gastric cancer in a Chinese population. PLoS ONE 8(1):e50856. doi:10.1371/journal.pone.0050856

Hsu IC, Metcalf RA, Sun T, Welsh JA, Wang NJ, Harris CC (1991) Mutational hotspot in the p53 gene in human hepatocellular carcinomas. Nature 350(6317):427–428. doi:10.1038/350427a0

Huang SP, Wu MS, Shun CT, Wang HP, Lin MT, Kuo ML, Lin JT (2004) Interleukin-6 increases vascular endothelial growth factor and angiogenesis in gastric carcinoma. J Biomed Sci 11(4):517–527. doi:10.1159/000077902

Hussain SP, Harris CC (2007) Inflammation and cancer: an ancient link with novel potentials. Int J Cancer 121(11):2373–2380. doi:10.1002/ijc.23173

Ikeguchi M, Hatada T, Yamamoto M, Miyake T, Matsunaga T, Fukumoto Y, Yamada Y, Fukuda K, Saito H, Tatebe S (2009) Serum interleukin-6 and -10 levels in patients with gastric cancer. Gastric Cancer (Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association) 12(2):95–100. doi:10.1007/s10120-009-0509-8

Inoue S, Kawanishi S (1995) Oxidative DNA damage induced by simultaneous generation of nitric oxide and superoxide. FEBS Lett 371(1):86–88

Isomoto H, Matsushima K, Inoue N, Hayashi T, Nakayama T, Kunizaki M, Hidaka S, Nakayama M, Hisatsune J, Nakashima M, Nagayasu T, Nakao K, Hirayama T (2012) Interweaving microRNAs and proinflammatory cytokines in gastric mucosa with reference to *H. pylori* infection. J Clin Immunol 32(2):290–299. doi:10.1007/s10875-011-9626-3

Ito R, Yasui W, Kuniyasu H, Yokozaki H, Tahara E (1997) Expression of interleukin-6 and its effect on the cell growth of gastric carcinoma cell lines. Jpn J Cancer Res: Gann 88(10):953–958

Jaiswal M, LaRusso NF, Burgart LJ, Gores GJ (2000) Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 60(1):184–190

Jayaprakash V, Marshall JR (2011) Selenium and other antioxidants for chemoprevention of gastrointestinal cancers. Best Pract Res Clin Gastroenterol 25(4–5):507–518. doi:10.1016/j.bpg.2011.09.006

Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61(2):69–90. doi:10.3322/caac.20107

Karin M (2006) NF-kappaB and cancer: mechanisms and targets. Mol Carcinog 45(6):355–361. doi:10.1002/mc.20217
Karin M, Greten FR (2005) NF-kappaB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol 5(10):749–759. doi:10.1038/nri1703
Kato M, Asaka M (2012) Recent development of gastric cancer prevention. Jpn J Clin Oncol 42(11):987–994. doi:10.1093/jjco/hys151
Katoh M (2007) Networking of WNT, FGF, Notch, BMP, and Hedgehog signaling pathways during carcinogenesis. Stem Cell Rev 3(1):30–38
Kawabata T, Ichikura T, Majima T, Seki S, Chochi K, Takayama E, Hiraide H, Mochizuki H (2001) Preoperative serum interleukin-18 level as a postoperative prognostic marker in patients with gastric carcinoma. Cancer 92(8):2050–2055
Kelly PN, Dakic A, Adams JM, Nutt SL, Strasser A (2007) Tumor growth need not be driven by rare cancer stem cells. Science 317(5836):337. doi:10.1126/science.1142596
Kinzler KW, Vogelstein B (1996) Lessons from hereditary colorectal cancer. Cell 87(2):159–170
Kobayashi M, Tsubono Y, Sasazuki S, Sasaki S, Tsugane S, Group JS (2002) Vegetables, fruit and risk of gastric cancer in Japan: a 10-year follow-up of the JPHC Study Cohort I. Int J Cancer 102(1):39–44. doi:10.1002/ijc.10659
Konturek PC, Kania J, Konturek JW, Nikiforuk A, Konturek SJ, Hahn EG (2003) *H. pylori* infection, atrophic gastritis, cytokines, gastrin, COX-2, PPAR gamma and impaired apoptosis in gastric carcinogenesis. Med Sci Monit: Int Med J Exp Clin Res 9(7):SR53–SR66
Kuai WX, Wang Q, Yang XZ, Zhao Y, Yu R, Tang XJ (2012) Interleukin-8 associates with adhesion, migration, invasion and chemosensitivity of human gastric cancer cells. World J Gastroenterol 18(9):979–985. doi:10.3748/wjg.v18.i9.979
Kumar R (2010) Microfilariae in lymph node aspirate associated with metastatic gastric carcinoma: a case report. Acta Cytol 54(3):319–320
Kuraishy A, Karin M, Grivennikov SI (2011) Tumor promotion via injury- and death-induced inflammation. Immunity 35(4):467–477. doi:10.1016/j.immuni.2011.09.006
Leach SA, Thompson M, Hill M (1987) Bacterially catalysed N-nitrosation reactions and their relative importance in the human stomach. Carcinogenesis 8(12):1907–1912
Lee JM, Kim SS, Cho YS (2012) The role of PPARgamma in *Helicobacter pylori* infection and gastric carcinogenesis. PPAR Res 2012:687570. doi:10.1155/2012/687570
Leek RD, Landers R, Fox SB, Ng F, Harris AL, Lewis CE (1998) Association of tumour necrosis factor alpha and its receptors with thymidine phosphorylase expression in invasive breast carcinoma. Br J Cancer 77(12):2246–2251
Lickert H, Kispert A, Kutsch S, Kemler R (2001) Expression patterns of Wnt genes in mouse gut development. Mech Dev 105(1–2):181–184
Locksley RM, Killeen N, Lenardo MJ (2001) The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell 104(4):487–501
Luo JL, Kamata H, Karin M (2005) IKK/NF-kappaB signaling: balancing life and death—a new approach to cancer therapy. J Clin Investig 115(10):2625–2632. doi:10.1172/JCI26322
Ma J, Sawai H, Matsuo Y, Ochi N, Yasuda A, Takahashi H, Wakasugi T, Funahashi H, Sato M, Okada Y, Takeyama H, Manabe T (2008) Interleukin-1alpha enhances angiogenesis and is associated with liver metastatic potential in human gastric cancer cell lines. J Surg Res 148(2):197–204. doi:10.1016/j.jss.2007.08.014
Ma XM, Yu H, Huai N (2009) Peroxisome proliferator-activated receptor-gamma is essential in the pathogenesis of gastric carcinoma. World J Gastroenterol 15(31):3874–3883
Macarthur M, Hold GL, El-Omar EM (2004) Inflammation and Cancer II. Role of chronic inflammation and cytokine gene polymorphisms in the pathogenesis of gastrointestinal malignancy. Am J Physiol Gastrointest Liver Physiol 286(4):G515–G520. doi:10.1152/ajpgi.00475.2003
Macri A, Versaci A, Loddo S, Scuderi G, Travagliante M, Trimarchi G, Teti D, Famulari C (2006) Serum levels of interleukin 1beta, interleukin 8 and tumour necrosis factor alpha as markers of gastric cancer. Biomarkers (Biochemical indicators of exposure, response, and susceptibility to chemicals) 11(2):184–193. doi:10.1080/13547500600565677
Maeda H, Akaike T (1998) Nitric oxide and oxygen radicals in infection, inflammation, and cancer. Biochem Biokhim 63(7):854–865

Maehata Y, Nakamura S, Fujisawa K, Esaki M, Moriyama T, Asano K, Fuyuno Y, Yamaguchi K, Egashira I, Kim H, Kanda M, Hirahashi M, Matsumoto T (2012) Long-term effect of *Helicobacter pylori* eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. Gastrointest Endosc 75(1):39–46. doi:10.1016/j.gie.2011.08.030

Magnus HA (1937) Observations on the presence of intestinal epithelium in the gastric mucosa. J Pathol Bacteriol 44(2):389–398

Majima T, Ichikura T, Chochi K, Kawabata T, Tsujimoto H, Sugasawa H, Kuranaga N, Takayama E, Kinoshita M, Hiraide H, Seki S, Mochizuki H (2006) Exploitation of interleukin-18 by gastric cancers for their growth and evasion of host immunity. Int J Cancer 118(2):388–395. doi:10.1002/ijc.21334

Marshall BJ, Warren JR (1984) Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1(8390):1311–1315

Matsushima K, Isomoto H, Inoue N, Nakayama T, Hayashi T, Nakayama M, Nakao K, Hirayama T, Kohno S (2011) MicroRNA signatures in *Helicobacter pylori*-infected gastric mucosa. Int J Cancer 128(2):361–370. doi:10.1002/ijc.25348

Mera R, Fontham ET, Bravo LE, Bravo JC, Piazuelo MB, Camargo MC, Correa P (2005) Long term follow up of patients treated for *Helicobacter pylori* infection. Gut 54(11):1536–1540. doi:10.1136/gut.2005.072009

Milne AN, Carneiro F, O'Morain C, Offerhaus GJ (2009) Nature meets nurture: molecular genetics of gastric cancer. Hum Genet 126(5):615–628. doi:10.1007/s00439-009-0722-x

Misleh JG, Santoro P, Strasser JF, Bennett JJ (2013) Multidisciplinary management of gastric cancer. Surg Oncol Clin N Am 22(2):247–264. doi:10.1016/j.soc.2012.12.013

Mochizuki Y, Nakanishi H, Kodera Y, Ito S, Yamamura Y, Kato T, Hibi K, Akiyama S, Nakao A, Tatematsu M (2004) TNF-alpha promotes progression of peritoneal metastasis as demonstrated using a green fluorescence protein (GFP)-tagged human gastric cancer cell line. Clin Exp Metastasis 21(1):39–47

Morita D, Ichikura T, Mochizuki H (2001) The expression of PPAR gamma in gastric cancer. Nihon rinsho Jpn J Clin Med 59(Suppl 4):595–597

Morson BC (1955) Intestinal metaplasia of the gastric mucosa. Br J Cancer 9(3):365–376

Muller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, McClanahan T, Murphy E, Yuan W, Wagner SN, Barrera JL, Mohar A, Verastegui E, Zlotnik A (2001) Involvement of chemokine receptors in breast cancer metastasis. Nature 410(6824):50–56. doi:10.1038/35065016

Nakayama Y, Shibao K, Sako T, Ohta R, Onitsuka K, Hirata K, Nagata N, Itoh H (2000) Serum levels of interleukin-12 in patients with gastrointestinal cancer. Anticancer Res 20(1C):635–640

Nardone G, Rocco A, Malfertheiner P (2004) Review article: *helicobacter pylori* and molecular events in precancerous gastric lesions. Aliment Pharmacol Ther 20(3):261–270. doi:10.1111/j.1365-2036.2004.02075.x

Nathan C (2002) Points of control in inflammation. Nature 420(6917):846–852. doi:10.1038/nature01320

Nowicki A, Szenajch J, Ostrowska G, Wojtowicz A, Wojtowicz K, Kruszewski AA, Maruszynski M, Aukerman SL, Wiktor-Jedrzejczak W (1996) Impaired tumor growth in colony-stimulating factor 1 (CSF-1)-deficient, macrophage-deficient op/op mouse: evidence for a role of CSF-1-dependent macrophages in formation of tumor stroma. Int J Cancer 65(1):112–119. doi:10.1002/(SICI)1097-0215(19960103)65:1<112:AID-IJC19>3.0.CO;2-I

Oguma K, Oshima H, Aoki M, Uchio R, Naka K, Nakamura S, Hirao A, Saya H, Taketo MM, Oshima M (2008) Activated macrophages promote Wnt signalling through tumour necrosis factor-alpha in gastric tumour cells. EMBO J 27(12):1671–1681. doi:10.1038/emboj.2008.105

Ooi CH, Ivanova T, Wu J, Lee M, Tan IB, Tao J, Ward L, Koo JH, Gopalakrishnan V, Zhu Y, Cheng LL, Lee J, Rha SY, Chung HC, Ganesan K, So J, Soo KC, Lim D, Chan WH, Wong WK, Bowtell D, Yeoh KG, Grabsch H, Boussioutas A, Tan P (2009) Oncogenic pathway combinations predict clinical prognosis in gastric cancer. PLoS Genet 5(10):e1000676. doi:10.1371/journal.pgen.1000676

Oshima H, Matsunaga A, Fujimura T, Tsukamoto T, Taketo MM, Oshima M (2006) Carcinogenesis in mouse stomach by simultaneous activation of the Wnt signaling and prostaglandin E2 pathway. Gastroenterology 131(4):1086–1095. doi:10.1053/j.gastro.2006.07.014

Park S, Kim YS, Kim YJ, Kyung SY, Park JW, Jeong SH, Lee SP (2012) Toxocariasis masquerading as liver and lung metastatic nodules in patents with gastrointestinal cancer: clinicopathologic study of five cases. Dig Dis Sci 57(1):155–160. doi:10.1007/s10620-011-1833-5

Pereira C, Medeiros RM, Dinis-Ribeiro MJ (2009) Cyclooxygenase polymorphisms in gastric and colorectal carcinogenesis: are conclusive results available? Eur J Gastroenterol Hepatol 21(1):76–91. doi:10.1097/MEG.0b013e32830ce7ba

Pollard JW (2004) Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer 4(1):71–78. doi:10.1038/nrc1256

Pounder RE, Ng D (1995) The prevalence of *Helicobacter pylori* infection in different countries. Aliment Pharmacol Ther 9(Suppl 2):33–39

Quintana E, Shackleton M, Sabel MS, Fullen DR, Johnson TM, Morrison SJ (2008) Efficient tumour formation by single human melanoma cells. Nature 456(7222):593–598. doi:10.1038/nature07567

Rajnakova A, Moochhala S, Goh PM, Ngoi S (2001) Expression of nitric oxide synthase, cyclooxygenase, and p53 in different stages of human gastric cancer. Cancer Lett 172(2):177–185

Ristimaki A, Honkanen N, Jankala H, Sipponen P, Harkonen M (1997) Expression of cyclooxygenase-2 in human gastric carcinoma. Cancer Res 57(7):1276–1280

Rius J, Guma M, Schachtrup C, Akassoglou K, Zinkernagel AS, Nizet V, Johnson RS, Haddad GG, Karin M (2008) NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha. Nature 453(7196):807–811. doi:10.1038/nature06905

Rocha FT, Lourenco LG, Juca MJ, Costa V, Leal AT (2009) Chemoprevention by celecoxib in reflux-induced gastric adenocarcinoma in Wistar rats that underwent gastrojejunostomy. Acta Cirurgica Bras/Sociedade Brasileira para Desenvolvimento Pesquisa em Cirurgia 24(3):189–194

Saito H, Tsujitani S, Oka S, Kondo A, Ikeguchi M, Maeta M, Kaibara N (1999) The expression of transforming growth factor-beta1 is significantly correlated with the expression of vascular endothelial growth factor and poor prognosis of patients with advanced gastric carcinoma. Cancer 86(8):1455–1462

Sato H, Ishihara S, Kawashima K, Moriyama N, Suetsugu H, Kazumori H, Okuyama T, Rumi MA, Fukuda R, Nagasue N, Kinoshita Y (2000) Expression of peroxisome proliferator-activated receptor (PPAR) gamma in gastric cancer and inhibitory effects of PPARgamma agonists. Br J Cancer 83(10):1394–1400. doi:10.1054/bjoc.2000.1457

Schutze S, Potthoff K, Machleidt T, Berkovic D, Wiegmann K, Kronke M (1992) TNF activates NF-kappa B by phosphatidylcholine-specific phospholipase C-induced "acidic" sphingomyelin breakdown. Cell 71(5):765–776

Shin SK, Li MS, Fuerst F, Hotchkiss E, Meyer R, Kim IT, Goel A, Boland CR (2006) Oncogenic T-antigen of JC virus is present frequently in human gastric cancers. Cancer 107(3):481–488. doi:10.1002/cncr.22028

Shiotani A, Uedo N, Iishi H, Murao T, Kanzaki T, Kimura Y, Kamada T, Kusunoki H, Inoue K, Haruma K (2012) *H. pylori* eradication did not improve dysregulation of specific oncogenic miRNAs in intestinal metaplastic glands. J Gastroenterol 47(9):988–998. doi:10.1007/s00535-012-0562-7

Shmelkov SV, Butler JM, Hooper AT, Hormigo A, Kushner J, Milde T, St Clair R, Baljevic M, White I, Jin DK, Chadburn A, Murphy AJ, Valenzuela DM, Gale NW, Thurston G, Yancopoulos GD, D'Angelica M, Kemeny N, Lyden D, Rafii S (2008) CD133 expression is not restricted to stem cells, and both CD133+ and CD133− metastatic colon cancer cells initiate tumors. J Clin Investig 118(6):2111–2120. doi:10.1172/JCI34401

Slack JM (1986) Epithelial metaplasia and the second anatomy. Lancet 2(8501):268–271

Soutto M, Belkhiri A, Piazuelo MB, Schneider BG, Peng D, Jiang A, Washington MK, Kokoye Y, Crowe SE, Zaika A, Correa P, Peek RM Jr, El-Rifai W (2011) Loss of TFF1 is associated with activation of NF-kappaB-mediated inflammation and gastric neoplasia in mice and humans. J Clin Investig 121(5):1753–1767. doi:10.1172/JCI43922

Sun P, Ben Q, Tu S, Dong W, Qi X, Wu Y (2011) Serum interleukin-33 levels in patients with gastric cancer. Dig Dis Sci 56(12):3596–3601. doi:10.1007/s10620-011-1760-5

Szaflarska A, Szczepanik A, Siedlar M, Czupryna A, Sierzega M, Popiela T, Zembala M (2009) Preoperative plasma level of IL-10 but not of proinflammatory cytokines is an independent prognostic factor in patients with gastric cancer. Anticancer Res 29(12):5005–5012

Tahara T, Shibata T, Nakamura M, Yamashita H, Yoshioka D, Okubo M, Yonemura J, Maeda Y, Maruyama N, Kamano T, Kamiya Y, Fujita H, Nakagawa Y, Nagasaka M, Iwata M, Hirata I, Arisawa T (2010) Association between IL-17A, -17F and MIF polymorphisms predispose to CpG island hyper-methylation in gastric cancer. Int J Mol Med 25(3):471–477

Tahara T, Shibata T, Nakamura M, Yamashita H, Yoshioka D, Okubo M, Yonemura J, Maeda Y, Maruyama N, Kamano T, Kamiya Y, Fujita H, Nakagawa Y, Nagasaka M, Iwata M, Hirata I, Arisawa T (2011) Effect of IL-1beta and TNF-alpha polymorphisms on the prognosis and survival of gastric cancer patients. Clin Exp Med 11(4):211–217. doi:10.1007/s10238-010-0129-y

Takahashi T, Nau MM, Chiba I, Birrer MJ, Rosenberg RK, Vinocour M, Levitt M, Pass H, Gazdar AF, Minna JD (1989) p53: A frequent target for genetic abnormalities in lung cancer. Science 246(4929):491–494

Takahashi N, Okumura T, Motomura W, Fujimoto Y, Kawabata I, Kohgo Y (1999) Activation of PPARgamma inhibits cell growth and induces apoptosis in human gastric cancer cells. FEBS Lett 455(1–2):135–139

Taketo MM (1998) Cyclooxygenase-2 inhibitors in tumorigenesis (Part II). J Natl Cancer Inst 90(21):1609–1620

Thiel A, Mrena J, Ristimaki A (2011) Cyclooxygenase-2 and gastric cancer. Cancer Metastasis Rev 30(3–4):387–395. doi:10.1007/s10555-011-9312-1

Tsujimoto H, Ono S, Ichikura T, Matsumoto Y, Yamamoto J, Hase K (2010) Roles of inflammatory cytokines in the progression of gastric cancer: friends or foes? Gastric Cancer (Official Journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association) 13(4):212–221. doi:10.1007/s10120-010-0568-x

Uefuji K, Ichikura T, Mochizuki H (2005) Increased expression of interleukin-1alpha and cyclooxygenase-2 in human gastric cancer: a possible role in tumor progression. Anticancer Res 25(5):3225–3230

Ushiku T, Chong JM, Uozaki H, Hino R, Chang MS, Sudo M, Rani BR, Sakuma K, Nagai H, Fukayama M (2007) p73 gene promoter methylation in Epstein-Barr virus-associated gastric carcinoma. Int J Cancer 120(1):60–66. doi:10.1002/ijc.22275

Vafa O, Wade M, Kern S, Beeche M, Pandita TK, Hampton GM, Wahl GM (2002) c-Myc can induce DNA damage, increase reactive oxygen species, and mitigate p53 function: a mechanism for oncogene-induced genetic instability. Mol Cell 9(5):1031–1044

Valko M, Morris H, Cronin MT (2005) Metals, toxicity and oxidative stress. Curr Med Chem 12(10):1161–1208

Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M (2006) Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 160(1):1–40. doi:10.1016/j.cbi.2005.12.009

Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J (2007) Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 39(1):44–84. doi:10.1016/j.biocel.2006.07.001

Velnar T, Bailey T, Smrkolj V (2009) The wound healing process: an overview of the cellular and molecular mechanisms. J Int M Res 37(5):1528–1542

Vries RG, Huch M, Clevers H (2010) Stem cells and cancer of the stomach and intestine. Mol Oncol 4(5):373–384. doi:10.1016/j.molonc.2010.05.001

Wang P, Xia HH, Zhang JY, Dai LP, Xu XQ, Wang KJ (2007) Association of interleukin-1 gene polymorphisms with gastric cancer: a meta-analysis. Int J Cancer 120(3):552–562. doi:10.1002/ijc.22353

Wiseman M (2008) The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc 67(3):253–256. doi:10.1017/S002966510800712X

Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, Lai KC, Hu WH, Yuen ST, Leung SY, Fong DY, Ho J, Ching CK, Chen JS, China Gastric Cancer Study G (2004) Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. JAMA 291(2):187–194. doi:10.1001/jama.291.2.187

Wu CW, Chi CW, Hsieh MC, Chao MF, Lui WY, P'Eng FK (1998) Serum tumor necrosis factor in patients with gastric cancer. Anticancer Res 18(3A):1597–1599

Xu W, Li Y, Wang X, Chen B, Liu S, Wang Y, Zhao W, Wu J (2010) PPARgamma polymorphisms and cancer risk: a meta-analysis involving 32,138 subjects. Oncol Rep 24(2):579–585

Yamaoka Y (2010) Mechanisms of disease: *Helicobacter pylori* virulence factors. Nat Rev Gastroenterol Hepatol 7(11):629–641. doi:10.1038/nrgastro.2010.154

Yanaoka K, Oka M, Yoshimura N, Deguchi H, Mukoubayashi C, Enomoto S, Maekita T, Inoue I, Ueda K, Utsunomiya H, Iguchi M, Tamai H, Fujishiro M, Nakamura Y, Tsukamoto T, Inada K, Takeshita T, Ichinose M (2010) Preventive effects of etodolac, a selective cyclooxygenase-2 inhibitor, on cancer development in extensive metaplastic gastritis, a *Helicobacter pylori*-negative precancerous lesion. Int J Cancer 126(6):1467–1473. doi:10.1002/ijc.24862

Yang XF (2007) Immunology of stem cells and cancer stem cells. Cell Mol Immunol 4(3):161–171

Ye ZB, Ma T, Li H, Jin XL, Xu HM (2007) Expression and significance of intratumoral interleukin-12 and interleukin-18 in human gastric carcinoma. World J Gastroenterol 13(11):1747–1751

Yermilov V, Rubio J, Becchi M, Friesen MD, Pignatelli B, Ohshima H (1995) Formation of 8-nitroguanine by the reaction of guanine with peroxynitrite in vitro. Carcinogenesis 16(9):2045–2050

Yin Y, Si X, Gao Y, Gao L, Wang J (2013) The nuclear factor-kappaB correlates with increased expression of interleukin-6 and promotes progression of gastric carcinoma. Oncol Rep 29(1):34–38. doi:10.3892/or.2012.2089

Ying L, Marino J, Hussain SP, Khan MA, You S, Hofseth AB, Trivers GE, Dixon DA, Harris CC, Hofseth LJ (2005) Chronic inflammation promotes retinoblastoma protein hyperphosphorylation and E2F1 activation. Cancer Res 65(20):9132–9136. doi:10.1158/0008-5472.CAN-05-1358

Yokozaki H, Kuniyasu H, Semba S, Yasui W, Tahara E (1997) Molecular bases of human stomach carcinogenesis. In: Tahara E (ed) Molecular pathology of gastroenterological cancer. Springer, New York/Tokyo, pp 55–70

Zhang X, Miao X, Tan W, Ning B, Liu Z, Hong Y, Song W, Guo Y, Zhang X, Shen Y, Qiang B, Kadlubar FF, Lin D (2005) Identification of functional genetic variants in cyclooxygenase-2 and their association with risk of esophageal cancer. Gastroenterology 129(2):565–576. doi:10.1016/j.gastro.2005.05.003

Zhang Z, Li Z, Gao C, Chen P, Chen J, Liu W, Xiao S, Lu H (2008) miR-21 plays a pivotal role in gastric cancer pathogenesis and progression. Lab Invest (A Journal of Technical Methods and Pathology) 88(12):1358–1366. doi:10.1038/labinvest.2008.94

Zhang LJ, Wang SY, Huo XH, Zhu ZL, Chu JK, Ma JC, Cui DS, Gu P, Zhao ZR, Wang MW, Yu J (2009) Anti-*Helicobacter pylori* therapy followed by celecoxib on progression of gastric precancerous lesions. World J Gastroenterol 15(22):2731–2738

Zhu Y, Wang J, He Q, Zhang JQ (2011) The association between interleukin-10-592 polymorphism and gastric cancer risk: a meta-analysis. Med Oncol 28(1):133–136. doi:10.1007/s12032-010-9417-3

Zhuang Y, Peng LS, Zhao YL, Shi Y, Mao XH, Chen W, Pang KC, Liu XF, Liu T, Zhang JY, Zeng H, Liu KY, Guo G, Tong WD, Shi Y, Tang B, Li N, Yu S, Luo P, Zhang WJ, Lu DS, Yu PW, Zou QM (2012) CD8(+) T cells that produce interleukin-17 regulate myeloid-derived suppressor cells and are associated with survival time of patients with gastric cancer. Gastroenterology 143(4):951–962, e958. doi:10.1053/j.gastro.2012.06.010

Zouki C, Jozsef L, Ouellet S, Paquette Y, Filep JG (2001) Peroxynitrite mediates cytokine-induced IL-8 gene expression and production by human leukocytes. J Leukoc Biol 69(5):815–824