**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 6816**

**Columns:** **TOPIC HIGHLIGHTS**

WJG 20th Anniversary Special Issues (8): Gastric cancer

**Role of the tumor microenvironment in the pathogenesis of gastric carcinoma**

Chung HW *et al*. Microenvironment of gastric carcinoma

Hye Won Chung, Jong-Baeck Lim

**Hye Won Chung,** Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul 135-720, South Korea

**Jong-Baeck Lim,** Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul 135-720, South Korea

**Author contributions:** Chung HY and Lim JB designed the research; Chung HY and Lim JB performed research and analyzed the the data; and Chung HY and Lim JB wrote the paper.

**Correspondence to: Jong-Baeck Lim, MD, PhD, Associate Professor,** Department of Laboratory Medicine, Yonsei University College of Medicine, 50 Seodaemun-gu Seoul 135-720, South Korea. jlim@yuhs.ac

**Telephone**: +82-2-20193533 **Fax**: +82-2-20578926

**Received:** October 28, 2013 **Revised:** November 22, 2013

**Accepted:** December 5, 2013

**Published online:**

**Abstract**

Gastric carcinoma (GC) is the 4th most prevalent cancer and has the 2nd highest cancer-related mortality rate worldwide. Despite the incidence of GC has decreased over the past few decades, it is still a serious health problem. Chronic inflammatory status of the stomach, caused by the infection of *Helicobacter pylori (H. pylori)* infection and through the production of inflammatory mediators within the parenchyma is suspected to play an important role in the initiation and progression of GC. In this review, the correlation between chronic inflammation and *H. pylori* infection as an important factor for the development of GC will be discussed. Major components, including tumor-associated macrophages, lymphocytes, cancer-associated fibroblasts, angiogenic factors, cytokines, and chemokines of GC microenvironment, and their mechanism of action on signaling pathways will also be discussed. Increasing our understanding of how the components of the tumor microenviroment interact with GC cells and the signaling pathways involved could help identify new therapeutic and chemopreventive targets.

© 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key Word:** Tumor microenvironment; Gastric carcinoma; Inflammation; *Helicobacter pylori*; Cytokine

**Core tip:** The intensive interplay that exists between tumor cells and the tumor microenvironment can play an important role in tumor initiation, growth, and metastasis. A better understanding of the molecular pathogenesis of the tumor microenvironment of Gastric carcinoma would be crucial for the design of novel molecular targets. In this review, we have provided an overview of the currently available knowledge of the role of the TME in gastric cancer and have highlighted the potential prognostic and therapeutic implications.

Chung HW, Lim JB *et al*. Role of the tumor microenvironment in the pathogenesis of gastric carcinoma.

*World J Gastroenterol* 2013;

**Available from:**

**DOI:**

**INTRODUCTION**

Gastric carcinoma (GC) is the fourth most prevalent cancer and has the second highest cancer-related mortality rate worldwide. The risk of developing GC is 1 in 115, with a 5-year survival rate of only 20%–30%[1]. Despite that the incidence of GC has decreased over the past few decades, it is still a serious health problem[2]. The prognosis of advanced GC (AGC) with extensive node invasion and metastasis remains poor, while early GC (EGC) is associated with excellent long-term survival[3].

Ever since Rudolf Virchow, the founder of modern pathology, observed the connection between tumor cells and their surrounding tumor microenvironment (TME), TME has long been suspected to play an important role in the initiation and progression of tumors[4,5]. TME is thought to determine the behavior of cancers not only through genetic or epigenetic makeups of the tumor cells, but also through the surrounding milieu that the tumor cells interact with for survival, growth, proliferation, and metastasis. The TME is composed of many different kinds of cells such as endothelial cells, fibroblasts, lymphocytes and macrophages. It also consists of numerous soluble molecules such as growth factors, cytokines, chemokines, antibodies, proteases, various types of enzymes, and metabolites as well as a extracellular matrix. As the tumor progresses, states of hypoxia and acidosis develop in the TME[6-8], and the intensive relationship that exists between tumor cells and the TME plays a major role in tumor initiation, growth, and metastasis.

Among the numerous factors in the TME, inflammatory mediators have received attention recently, and an estimated 15%-20% of cancer deaths are associated with chronic infection and inflammation. Population-based studies have shown that individuals who are prone to chronic inflammatory disorders have an increased risk of cancer development[9]. Accordingly, treatment with non-steroidal anti-inflammatory agents decreases the incidence and mortality of several tumor types[10,11]. In the case of GC, the chronic inflammatory state of the stomach, caused by *Helicobacter pylori* (*H. pylori*) infection, as well as the production of inflammatory mediators, such as cytokines and chemokines within gastric tissues, is suspected to play an important role in the initiation and progression of GC.

Better understanding of the special interplay between GC cells and the surrounding microenvironment may be useful for recognizing the mechanism underlying development and progression as well as the discovery of novel molecular therapeutic targets[12,13]. In this review*,* we have provided an overview of the currently available knowledge of the role of the TME in GC and have highlighted the potential prognostic and therapeutic implications.

**CHRONIC INFLAMMATION AND *H. PYLORI* IN GC**

*H. pylori*, a microaerophilic, spiral gram-negative bacterium, colonizes the human stomach and, is a major cause of chronic gastritis, peptic ulcers, and gastric malignancies, including gastric non-cardia adenocarcinoma and mucosal-associated lymphoid tissue (MALT) lymphoma[14]. *H. pylori* infects over 50% of the world’s population, with 1% of those infected going on to develop gastric GC. An estimated 75% of all GC cases are associated with *H. pylori* infection[15].

The carcinogenic potential of *H. pylori* is driven by the interplay between bacterial virulence factors and the host’s immune responses resulting in chronic inflammation, which in turn leads to tumorigenesis[16]. Four major virulence factors have been identified from *H. pylori*, that is cytotoxin-associated antigen A (CagA), cag-pathogenicity island (cagPAI), vacuolating cytotoxin (VacA), and outer membrane proteins (OMPs). *H. pylori* cagPAI encodes approximately, 30 genes, including type four secretion system (TFSS) genes, which are essential for pathogenesis and are responsible for the delivery of CagA protein and peptidoglycan (PGN) into host cells[17,18]. It has recently reported that CagA binds an Src homology 2 (SH2)-containing tyrosine phosphatase (SHP-2) in a tyrosine phosphorylation- dependent manner and activates the phosphatase activity of SHP-2[19]. Deregulation of SHP-2 by CagA is an important mechanism by which CagA-positive *H. Pylori* promotes gastric carcinogenesis. *H. pylori* is a potent activator of nuclear factor-B (NF-B) in gastric epithelial cells[20,21] causing the production of tumor necrosis factor- (TNF-inducing protein (Tip), which in turn activates NF-B in gastric epithelial cells using an independent pathway involving virulence factors such as CagA[18].

Activation of NF-B by *H. pylori* infection induces the expression of a variety of genes, including those encoding the cytokines interleukin (IL)-1, IL-6. IL-8, TNF-, vascular endothelial growth factor (VEGF), cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), cell-cycle regulators, the matrix metalloproteinases (MMP)-2, MMP-7, MMP-9 and adhesion molecules[22,23]. High level of COX2 mRNA and protein expression and enzymatic activity are detected in GC cells[24], and COX-2 activity is induced by a variety of mediators including inflammatory cytokines such as TNF-, interferon-, FN-) and IL-1[25]. COX-2 facilitates tumor growth by inhibiting apoptosis, promoting cell proliferation and stimulating angiogenesis within cancer cells[26]. *H. Pylori* infection produces reactive oxygen and nitrogen species that cause DNA damage, followed by chronic gastritis and intestinal metaplasia. Nitric oxide generated by iNOS is converted to reactive nitrogen species that bring about direct DNA mutation such as those in p53, causing protein damage, inhibition of apoptosis, and promotion of angiogenesis[27,28]. CagA also activates the nuclear factor of activated T-cells (NFAT) signaling pathway, and interacts with E-cadherin to deregulate β-catenin signaling, which induces the expression of genes downstream of β-catenin, such as Caudal type homeobox gene-1 (CDX-1) and promotes the transdifferentiation of intestinal cells[29].

**SIGNALING PATHWAY OF GC-RELATED INFLAMMATION**

Multiple steps and multiple factors are involved in the development of GC. More than 90% of GCs are adenocarcinomas, which are divided into two histological types, intestinal and diffuse, based on the Lauren’s classification[30]. *H. Pylori* infection and chronic inflammation are important factors, particularly in the intestinal type of GC. The Correa’s hypothesis postulates that there is a progression from chronic gastritis to gastric atrophy, intestinal metaplasia (IM), dysplasia, and finally to cancer (“gastritis-dysplasia-carcinoma” sequence)[31]. In each step of GC progression, many cytokines and intracellular signaling pathways are involved.

GC-related inflammation activate transcription factors, mainly NF-κB, hypoxia-inducible factor (HIF)-1α, and signal transducer and activator of transcription (STAT)-3, which are the key inducers of inflammatory mediators such as cytokiness, chemokines, prostaglandins, nitric oxide (NO)[32].

The transcription factor NF-κB is a key orchestrator of innate immunity and inflammation and recent evidence suggests that it play an important role in development and maintenance of cancer-related inflammation[33]. In cancer and epithelial cells exposed to carcinogens, NF-κB promotes cell survival and proliferation through the activation of genes encoding proteins that are important for cell cycle progression such as cyclin D1, and c-Myc and the anti- apoptotic pathway (cIAPs, A1/BFL1, BCL-2, c-FLIP)[34,35]. In GC, NF- B potentiates inflammation in response to *H. Pylori* infection. Some studies reported that *H. Pylori* induces expression of the pro-inflammatory cytokine interleukin (IL)-8 through activation of NF-κB[36,20]. Moreover, NF- B amplifies the inflammatory signals of other cytokines, such as tumor necrosis factor and interferon[37]. A previous study reported that the positive rate of NF-κB/RelA is 42.6% in South Korea and NFκB/RelA expression in tumor tissues was also related to serum levels of IL-6 (*P* = 0.044) and CRP (*P* = 0.010)[38]. Interestingly, several microRNAs (miRNA) which target NF-B have been shown to be involved in development and progression of GC. miR-146a expression is up-regulated in a majority of gastric cancers where it targets CARD10 and COPS8, inhibiting GPCR-mediated activation of NF-κB, thus reducing expression of NF-B-regulated tumor-promoting cytokines and growth factors[39].

HIF-1α is centrally involved in multiple aspects of tumorigenesis including tumor angiogenesis, proliferation, metabolism, metastasis, differentiation, as well as responses to radiation and chemotherapy[40]. HIF-1α is up-regulated in inflammatory conditions and there is accumulating evidence indicating the presence of interconnections and compensatory pathways between the NF-κB and HIF-1α systems[41]. The expression of HIF-1α commonly increases in a variety of human solid tumors and elevated HIF-1α expression is associated with poor patient outcome in pancreatic cancer, glioblastoma, GC and other cancers[40,42]. Furthermore, the contribution of HIF-1α to chemoresistance has been observed in several solid tumors, including GC[43,44]. Interestingly, inhibition of HIF-1 via RNA interference (RNAi) or pharmacological compounds has improved their anti-tumor efficacy in murine cancer models[45] through modulation of the p53 and NF-κB signaling pathway. In this regards, a recent study has demonstrated that HIF-1 expression correlates with the metastatic phenotype of human GC[46].

STAT-3 is constitutively activated in several human cancer cells and tumor associated leukocytes and it represents a point of convergence for several oncogenic signalling pathways[47]. In approximately 50% of human GC, STAT3 is overactivated[48,49], and its high activation and⁄or expression status has been shown to correlate with a lower survival rate for GC patients[50]. This transcription factor supports oncogenesis through different mechanisms, ranging from the activation of genes crucial for proliferation and survival to the enhancement of angiogenesis and metastasis. In GC, IL-11 produced from tumor cells and TME activate the common signal-transducing gp130-receptor subunit to activate the JAK/STAT-3, Ras/MAPK and phosphoinositide-3-kinase (PI3K)/Akt signaling pathways[51,52,53]. Activated STAT-3 signaling pathway directly induces the transcription of the *Tlr2* gene in the gastric epithelium, which upon overexpression promotes proliferation and inhibits apoptosis of gastric epithelial cells[48]. The activation of STAT-3 in tumor cells also has been shown to increase the capacity of tumors to evade the immune system by inhibiting the maturation of dendritic cells (DCs)[54], thereby suppressing the immune response[55]. A recent study showed that STAT-3 plays a divergent role in the modulation of IL-23 and IL-12, two related cytokines, which play opposite roles in tumour development. In particular, STAT-3 inhibits anti-tumor IL-12p35 expression in DCs while promoting the expression of the pro-carcinogenic IL-23 cytokine in TAMs[56].

Epidemiological studies have highlighted that treatment with non-steroidal anti-inflammatory agents, such as COX-2 inhibitors, decrease the risk of developing certain cancers, such as colon cancer, breast cancer, and GC[10,11,57,58]. The frequency of COX-2 expression did not differ between gastric adenomas and early intestinal carcinomas, indicating that COX-2 expression might act as one of the factors related to early tumorigenesis in the stomach. Interestingly, the frequency of COX-2 expression was significantly higher in advanced carcinomas than in early carcinomas and was higher in intestinal-type carcinomas than in diffuse-type carcinomas. COX-2 expression may be more important for the progression of intestinal-type carcinomas than that of diffuse-type carcinoma[59].

Transforming growth factor (TGF)-1 mRNA and protein are highly expressed in GC cells[60-62]. TGF-1 is closely related to invasion and metastasis and the TME; it alters the biologic behavior of malignant gastric lesion[63]. TGF-1 produced by carcinoma cells stimulates collagen synthesis in both fibroblasts and cancer cells, which leads to diffuse fibrosis in the case scirrhous GC[63].

The HER family consists of four members: HER-1 [epidermal growth factor receptor (EGFR)], HER-2, HER-3, and HER-4. Activation of these receptors leads to homo- or hetero-dimerization that in turn initiates phosphorylation cascades and subsequent activation of the phosphatidylinositol-3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) and Ras–Raf–mitogenactivated mitogenactivated protein kinase/extracellular signal–related kinase (ERK) kinase (MEK)–ERK pathways, which are important in cancer cell proliferation and survival[64,65]

EGFR overexpression, observed in 27%–44% of gastric cancer cases, is generally reported to be a poor prognostic factor, despite contradictory evidence[66]. HER-2 overexpression is observed in 10%–38% of gastric cancer tumor samples[67,68], with a higher prevalence in intestinal- type and gastroesophageal junction (GEJ) tumors than that in diffuse-type and gastric tumors[68,69]. The prognostic value of HER-2 overexpression in gastric cancer remains controversial; it is generally associated with a poorer outcome[70,71], although contradictory evidence exists[72,73]. In fact, *PIK3CA* activating mutation was reported in 4%–36% of gastric cancer cases[74,75] and PTEN loss was reported in 20%–36% of cases[74,76]. For gastric cancer, the *KRAS* mutation was observed in 2%–20% of cases[77,78], and the *BRAF* mutation was observed in 0%–2.7% of cases[77,79].

The overexpression/activation of c-Met, a receptor for hepatocyte growth factor, leads to proliferation and antiapoptotic signals[80]. It was found to be activated both in vitro in human gastric cancer cell lines and in vivo in human gastric cancer tissue[81], and this may result from the infection of gastric cells by *H. pylori*[82].

The Hedgehogs (Hh) protein family includes Sonic (Shh), Indian (Ihh), and Desert (Dhh). In gastric cancer, the aberrant activation of Shh, through binding Patched 1 receptor and subsequent disinhibition of Smoothened in turn activates the transcription factor Gli-1[83].

**COMPONENT OF MICROENVIRONMENT OF GC**

***TAM***

Macrophages recruited to the tumor stroma are called TAMs. The role of TAMs in tumor progression is complicated and wide ranging. Although activated macrophages may have anti-tumor activity, tumor cells have been reported to evade the anti-tumor activity of TAMs[84,85]. Indeed, removal of macrophages by genetic mutation reduces tumor progression and metastasis[86]. TAMs are recruited from circulating monocytes into tissues in response to chemoattractants, and interact with tumor cells to make up the cancer stroma. Macrophage infiltration into tumor tissue correlates significantly with tumor vascularity in human esophageal cancer and GC[87,88]. There is a direct association between the degree of TAM infiltration and depth of tumor invasion, nodal status, and clinical stage of GC[88]. Macrophage recruitment is mediated by a variety of chemoattractants, including the following; monocyte chemoattractant protein-1 (MCP-1/CCL2), macrophage inflammatory protein-1α (MIP-1α/CCL3); and regulated upon activation, normal T cell expressed and secreted (RANTES/CCL5)[87,88].

***Lymphocytes***

Regulatory T cells (Tregs) are functionally immune-suppressive subsets of T cells that are reported to play important roles in immunological self-tolerance[89-92]. Tregs are defined more strictly as CD4+ CD25+Foxp3+ cells. The frequency of Tregs among tumor infiltrating lymphocytes (TILs), lymphocytes derived from tumor-draining regional lymph nodes (LNLs), and peripheral blood lymphocytes (PBLs) is higher in GC and esophageal cancer patients than their normal counterparts[93,94]. In addition, patients with a higher proportion of Tregs showed poorer survival rates than those with a lower proportion. Interestingly, after patients underwent curative resection for GC, the proportion of Tregs decreased and was restored to levels comparable to those for normal healthy donors[95]. These results strongly suggest that tumor-related factors induce the expansion and the accumulation of Tregs in GC. Furthermore, the frequencies of CCL17+ cells and of CCL22+ cells, both of which induce in vitro migration of Tregs, within tumors were significantly higher than those in normal gastric mucosa, Increased levels of TGF-1 in GC patients have been correlated with the frequency of Tregs, and, conversely, numerous studies have reported a correlation between an increased frequency of circulating Treg and increased levels of TGF-1 during during GC progression[96-98]. On the other hand, some reports have indicated that activated effector T cells are converted into Treg cells, capable of suppressing autologous effector T cells[99-101]. Thus, it is likely that naturally occurring Foxp3+ T regs in peripheral sites faintly perceive tumor-related signals such as CCL17 or CCL22, migrate to the tumor site, and create a favorable environment for tumor growth.

Recently, a subset of IL-17 producing T cells that are distinct from Th1 and Th2 cells have been described as key players in inflammation and autoimmune diseases as well as cancer development. Interestingly, IL-17 also has been reported to be up-regulated in *H. pylori* infected gastric mucosa. IL-17 positively regulates the synthesis of IL-8 by gastric mononuclear cells and epithelial cells, which thus emphasizes the role of IL-17 in *H. pylori*-driven inflammation[102]. When the ratio of Th17⁄Treg cells of TILs was evaluated in GC patients, it was found to be markedly higher in early disease than in advanced disease. The accumulation of Th17 cells as well as of Tregs in the TME of GC occurrs in early disease following which the infiltration of Th17 cells gradually decrease as the disease progresses, in contrast to the increased accumulation of Tregs.

***Cancer associated fibroblasts***

Cancer associated fibroblasts (CFAs) are a central elements of TME. They are the most promi­nent cell type within the tumor stroma of many cancers and play a critical role in tumor-stromal interactions[103,104]. CAFs demonstrate differential gene expression profiles compared to normal fibroblasts[105], and they acquire a modified phenotype, similar to fibroblasts associated with wound healing. Although the mechanisms that regulate activation of fibroblasts and their accumulation in tumors are not fully understood, platelet-derived growth factor (PDGF), TGF-β1, and fibroblast growth factor-2 (FGF-2) are known to be partly involved in this process[106]. There are some candidates for the origins of CAFs, such as following; fibroblasts residing in local tissues[105], periadventitial cells including pericytes and vascular smooth muscle cells[107], endothelial cells[108], and bone marrow-derived cells including various stem cells[109]. Worthley *et al*[110] recently reported that bone marrow-derived cells can differentiate into CAFs in human GC that developed in female recipients of male allogeneic stem cell transplantation. A previous study showed that direct interaction between scirrhous-type GC cells and gastric fibroblasts could promote fibrosis of the gastric wall and increasing the malignant behavior of cancer cells through vascular cell adhesion molecule-1 (VCAM-1) and induced Snail expression, and through the resultant E-cadherin suppression and vimentin induction in HSC-39 cells[111].

***Angiogenetic factors***

Angiogenesis which is necessary for tumor progression, is also influenced by the tumor microenvironment. Stromal reaction (desmoplasia) is observed in GC, but not in non-invasive neoplasms[112]. The generation of tumor stroma is triggered by tumor cells and induces the ingrowth of new blood vessels and mesenchymal cells from the adjacent normal tissue[113]. However, recent studies have shown that bone marrow-derived stem cells are integrated into the tumor stroma and differentiate into myofibroblasts and vascular endothelial cells[109,114]. A recent study reported that the density of blood vessels directly correlates with the incidence of metastasis in GC[114-117]. Angiogenesis of tumor is mediated by various molecules released by tumor cells and TME[118,119] and GC cells produce various angiogenic factors, including VEGF[120], IL-8[121], FGF-2[122], and platelet-derived endothelial cell growth factor (PD-ECGF)[123]. VEGF-A promotes the angiogenesis and progression of human GC, especially those of the intestinal type. A significant correlation between lymph node metastasis and VEGF-C expression has been reported in human GC[124,125]. However, no association was found between VEGF-D immunoreactivity and clinicopathologic features in submucosally invasive GC[126]. These results suggest that VEGF-C is a dominant regulator of lymphangiogenesis in early-stage human GC.

***Stem cells***

The stem cell niche or microenvironment is composed of different populations of cells, including not only stem cells, but also differentiated cells, soluble factors, and extracellular matrix, all of which are critical for stem cell fate and differentiation[127]. Important signaling pathways such as the Wnt, Notch, Hedgehog, phosphatidylinositide 3-kinase (PI3K), NF-κB, endothelial growth factor (EGF), TGF-β and STAT-3 pathways have been shown to regulate stem cell renewal and maintenance, and their effects overlap in both normal and cancer stem cells[128]. The Interactions of stem cells with their surroundings are currently under intensive investigation. The inflammatory mediators and oncogenic pathways also regulate stem cell differentiation either directly or indirectly and are frequently deregulated in tumors[129-131]. Given the fact that gastric stem cells are such a rare population of cells and can be affected by so many intrinsic and extrinsic factors, it is very complicated to identify the specific role of a signaling factor in regulating their differentiation and migration. It has been noted that NF-κB, IL-6, VEGF, HIF-1α, angiogenesis, reactive oxygen species and tissue factors are all involved in the maintenance of stem cell and cancer stem cells[127] and that *H. pylori* infection can alter most of their expression. This suggests that *H. pylori* might impact the local microenvironment and affect stem/progenitor cell differentiation, and also cause genetic or epigenetic damages in these cells, leading to carcinogenesis. However, further studies addressing these pathways and mediators of gastric stem cells and progenitors during infection are awaited.

**CYTOKINES/CHEMOKINES**

Infection by *H. pylori* also disrupts gastric homeostasis and induces the production of multiple inflammatory cytokine within the local mucosa. Expression of IL-1β, TNF-α, and IL-10 is associated with an increased risk for developing GC[132,133].

IL-1β is a proinflammatory cytokine involved in inflammation and immunity. IL-1β polymorphisms are associated with enhanced IL-1production and increased risk of GC[133], IL-1β also inhibits gastric acid secretion. In transgenic mice, stomach specific overexpression of IL-1β induces stepwise spontaneous gastric inflammation, metaplasia, dysplasia, and carcinoma.

Overexpression of IL-1β also mobilizes myeloid-derived suppressor cells and induces NF-κB activation as well as the expression of downstream genes such as IL-6 and TNF-α in these cells. In addition, IL-1β alone is sufficient to induce gastric preneoplasia. However, the mechanisms by which IL-1β overexpression itself finally results in oncogenic transformation is unclear. Interestingly, other inflammatory mediators can exert opposite effects. One example is IFN-, which is produced primarily by activated T cells, and natural killer cells and is a key mediator of innate and adaptive immunity. IFN- mediates responses to bacterial infection and autoimmune disease, and acts as a tumor suppressor[134]. In mice, stomach specific overexpression of IFN- alone has minimal effects on the gastric mucosa, but inhibits IL-1β- and *Helicobacter felis*–induced gastritis and neoplasia. The mechanism has been attributed to IFN-induced inhibition of gastric epithelial cell proliferation, acceleration of apoptosis of gastric T lymphocytes and decrease in the production of pro-inflammatory Th1 and Th17 cytokines. These effects may balance epithelial cell proliferation, restrain inflammation, and ultimately inhibit tumor formation[134]. Therefore, disruption of host cell inflammatory cytokine production is involved in gastric oncogenesis.

Chemokines are involved in the chemoattraction of leukocytes to inflammatory sites and can be produced by many kinds of cells in the TME including leukocytes, endothelial cells, fibroblasts and epithelial cells[135,136]. Recent reports described that chemokines not only play a role in the immune system, but also promote tumorigenesis and metastasis of cancer. CXC chemokines and their receptors (CXCR) modulate tumor behavior by three important mechanisms: regulation of angiogenesis, activation of a tumor-specific immune response and stimulation of tumor cell proliferation in an autocrine or paracrine fashion [137].

CXC chemokines containing the ELR (Glu–Leu–Arg)-motif such as interleukin-8 (IL-8)/CXCL8 have been described to promote tumor growth by stimulation of angiogenesis and chemoattraction of neutrophilic granulocytes[138-140]. Previous studies have shown that IL-1, TNF-α and infection with *H. pylori* induce or enhance the secretion of IL-8 by several gastric adenocarcinoma cell lines *in vitro*[141,142]. In addition, CXCR1 and CXCR2 expression increased in gastric carcinoma cells after infection by *H. pylori*[143,144]. In GC, expression of IL-8 in gastric adenocarcinoma is associated with increased tumor vascularization, aggressiveness, invasion, and metastasis. In addition, IL-8 may act as a diagnostic marker as it was demonstrated to be significantly elevated in serum samples of patients with gastric cancer[145,146]. IL-8 also enhances the expression of the epidermal growth factor receptor (EGFR), MMP-9, VEGF and IL-8 itself[122,147,148]. Furthermore, the polymorphism of IL-8 promoter gene is associated with higher IL-8 protein expression, more severe neutrophil infiltration, enhanced angiogenesis, especially with secretion of MMP-9 and angiopoietin-1, and increased risk of poorly differentiated gastric cancer, lymph node, and liver metastasis[149-151].

In contrast, CXC chemokines lacking the ELR-motif such as interferon-γ, inducible protein-10 (IP-10)/CXCL10, possess angiostatic activities and chemoattract anti-tumoral lymphocytes through binding to CXCR3[139,140]. It has been described that Mig, IP-10 and I-TAC were constitutively express in GC cell lines, and the production can be enhanced by IFN- in synergy with TNF-α. In contrast, in vitro infection with *H. pylori* inhibited the IFN-/TNF-α- induced Mig and IP-10 production by GC cells. Increased expression of CXCR3 ligands by endothelial cells and mononuclear cells, especially antigen-presenting cells within GC, results in the chemoattraction and activation of cytotoxic T lymphocytes that favor tumor regression.

Stromal cell-derived factor-1 (SDF-1)/CXCL12 is an exception on this rule as this chemokine lacks the ELR-motif, has angiogenic properties and mediates the dissemination of CXCR4- positive tumor cells to distant organs[140]. SDF-1 modulates the angiogenic process directly by binding to its receptors CXCR4 and/or CXCR7 expressed on endothelial cells or indirectly by the induced secretion of matrix-metalloproteases or angiogenic factors such as IL-8, VEGF, respectively[152,153]. Many studies have demonstrated that both CXCL12 and CXCR4 are differentially expressed in GC[154,155], and overexpression of CXCR4 in gastric cancer cells is associated with aggressive tumor behavior, such as tumor invasion, lymph node metastasis, liver metastasis, and poor differentiation as well as peritoneal carcinomatosis[156]. In addition, peritoneal mesothelial cells contained high concentrations of SDF-1 indicating that SDF-1 induces the migration of CXCR4-positive tumor cells to the peritoneum[157]. *H. pylori* increased CXCR4 expression in gastric cancer through increased secretion of TNF-α. CXCR4 has also been found in leukocytes and microvascular blood vessels, confirming that SDF-1 binds to endothelial cells[158]. In addition to cancer cells, stromal cells such as endothelial cells, tumor-infiltrating lymphocytes and cancer-associated fibroblasts have been demonstrated to produce elevated levels of SDF-1[158,159]

***Matrix metalloproteinases***

Matrix metalloproteinases (MMPs) lead to tissue remodeling, inflammation, tumor cell growth, migration, invasion and metastasis in many cancers. They are major modulators of the tumor microenvironment, playing key roles in tumorigenesis[160]. Different stromal and cancer cells produce various types of MMPs whose main subtypes are collagenases (MMP-1,MMp-8, MMp-13), gelatinases (MMP-2, MMP-9), matrylisins (MMP-7, MMP-26), membrane type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, MMP-25) and stromelysins (MMP-3,MMP-10, MMP-11).

Previous studies reported that MMP-1[161], MMP-7[162-164] and MMP-9[165,166] are important in development of gastritis during infection by *H. pylori* and these molecules are utilized as molecular markers. It has been suggested that overexpression of MMP-1[167] and MMP-7[162,168] is dependent upon the pathogenicity island of *H. pylori* and, interestingly, it is known that MMP-7 participates in the epithelial mesenchymal transition[169] and is also overexpressed in GC[170]. Moreover, the activity of MMP-9 is increased in macrophages resident in the gastric mucosa of subjects infected with *H. pylori*[171] and its activity is known to be reduced by the eradication of *H. pylori*[172].

MMPs are noncovalently inhibited by the tissue inhibitors known as TIMP, a family comprising four members (TIMP-1, TIMP-2, TIMP-3, TIMP-4). TIMP-3 in the only inhibitor associated with the extra cellular matrix (ECM) and the rest of the TIMP are soluble proteins[173].

The disintegrins and metalloproteinase (ADAM) family are proteases related to the MMP and comprise more than 20 proteins that are anchored to the cell membrane and present various functions which are cell adhesion, cell fusion, activation of signaling pathways and release of substrates such as cytokines and growth factors from the cell membrane or the ECM[174]. In patients with gastritis and *H. pylori* infection, levels of ADAM-10 and ADAM-17 are elevated[175], and these play key roles in cell signaling[174]. E-cadherin is a substrate of ADAM-10 and the Notch signaling pathway, in which ADAM-17 participates, and these pathways are also involved in the development of GC. ADAM-17 has been associated with the generation of transient hypochlorhydria in patients infected with *H. pylori*[176] and interestingly, high levels of hypochlorhydria are founded in GC patients.

**NEW THERAPEUTIC APPROACHES**

According to our understanding of the molecular basis of TME of GC, targeted agents have led to a modest improvement in the outcome of advanced gastric cancer (AGC) patients.

Previous studies showed that EGFR, HER-2, tyrosin kinase inhibitors (TKIs) as well as VEGF were most attractive target for molecular therapy. The ToGA trial targeted HER-2 and AVAGAST trial targeted VEGF have marked the beginning of a new era in AGC treatment. A number of other phase III clinical trials that target different target molecules are ongoing.

Notably, the ToGA trial, which is a large, phase III, randomized controlled multicenter trial[177], showed that trastuzumab in combination with chemotherapy led to a significantly higher overall response rate (ORR 47% *vs* 35%, *P* = 0.0017), significantly longer progression free survival interval (PFS; 6.7 mo *vs* 5.5 mo, *P =* 0.0002), and significantly longer overall survival duration (OS;13.8 mo *vs* 11.1 mo, *P =* 0.0046) than that of the controls. Moreover, the trastuzumab-containing regimen was generally well tolerated and did not affect quality of life. To date, trastuzumab is the first and only targeted agent for gastric cancer approved by both the United States[178] and European[179] authorities.

Although the phase III Avastin® in Gastric Cancer (AVAGAST) trial did not meet its primary endpoint of OS and was thus a negative trial for this endpoint, the ORR was significantly better in the bevacizumab arm (46% *vs* 37%, *P* = 0.0315) and the PFS interval was significantly longer (6.7 mo *vs* 5.3 mo, HR 0.8; *P* = 0.0037) than that of the controls[180].

 In first-line phase II trials, cetuximab, a recombinant human–mouse chimeric monoclonal antibody targeting EGFR, showed that the ORR was in the range of 40%–60%, the time to progression (T0P) was 5.5–8.0 mo, and the OS time was 9.5–16.0 mo[181,182]. Other study reported that cetuximab showed no clinically significant benefit in combination with docetaxel plus oxaliplatin[183]. Other EGFR targeted therapy including Erbitux®, panitumumab, matuzumab, and nimotuzumab are under evaluation in phase II/III trials in combination with chemotherapy. The EGFR TKIs such as gefitinib and erlotinib were evaluated in phase II trials but produced disappointing results as monotherapy for AGC.

Lapatinib (Tykerb), a dual TKI inhibiting both HER-2 and EGFR are under investigation in two phase III trials. One is the LoGIC trial that is the lapatinib Optimization Study in ErbB2 (HER-2)+ GC patient[184], and the other is TYTAN trial that is investigating the lapatinib with paclitaxel (Taxol) in Asian ErbB2+ (HER2+) GC patients[185].

A few signaling pathways have attracted a lot of enthusiasm. The ubiquitin–proteosome pathway that is involved in cell cycle control is one good target.

Bortezomib, a proteosome inhibitor, was shown to induce apoptosis and suppress tumor growth in GC cell lines[186]. The overexpression/activation of c-Met, a receptor for hepatocyte growth factor, leads to proliferation and antiapoptotic signals[80]. A phase II study of GSK1363089 (GSK089, formerly XL880), a c-Met TKI, showed minimal activity in a cohort of metastatic GS patients unselected for c-Met[187]. The Hedgehog (Hh) pathway further complicates the complex signaling in gastric cancer cells[83]. Clinical use of Hh inhibitors is currently only in the early phases of development[183].

Inhibition of other biological pathways in AGC is in preclinical or early clinical evaluation. Insulin like growth factor-1 receptor (IGF-1R) antibody, figitumumab, in combination with docetaxel was well tolerated in a phase I trial of patients with advanced solid tumors[198]. FGFR inhibitors, HSP90 inhibitors, histone deacetylase (HDAC) and IL-6 antibody also may play a role in AGC treatment[189-193].

**CONCLUSION**

Although recent phase III clinical trials with conventional chemotherapeutic agents have shown encouraging results in advanced GC, overall survival rates continue to be suboptimal. This highlights the need for new therapeutic strategy using targeted therapy to improve the result of GC treatment.

The association between chronic gastritis and tumors is well documented in the step-wise histopathologic (Correa) model of GC. A better understanding of the molecular pathogenesis of GC would help for improving the knowledge on this relationship and would be crucial for the design of novel molecular targets.

Previous studies reported that a synergistic interplay among the components of TME of GC, including *H. pylori* infection, immune cells and mediators, and several proteins along with matrix metalloproteinases, is essential for the initiation, progression and metastasis of GC. The understanding of how these mechanisms regulate the relationship among those components of TME of GC would contribute strongly to identifying key signaling pathways that serve as both novel biomarkers for early detection and molecular targets for new therapeutic strategies.

**REFERENCES**

1 **Torpy JM**, Lynm C, Glass RM. JAMA patient page. Stomach cancer. *JAMA* 2010; **303**: 1771 [PMID: 20442395 DOI: 10.1001/jama.303.17.1771]

2 **Terry MB**, Gaudet MM, Gammon MD. The epidemiology of gastric cancer. *Semin Radiat Oncol* 2002; **12**: 111-127 [PMID: 11979413 DOI: 10.1053/srao.30814]

3 **Hohenberger P**, Gretschel S. Gastric cancer. *Lancet* 2003; **362**: 305-315 [PMID: 12892963 DOI: 10.1016/S0140-6736(03)13975-X]

4 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 200; **357**: 539-545 [PMID: 11229684]

5 **Hussain SP**, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer* 2007; **121**: 2373-2380 [PMID: 17893866 DOI: 10.1002/ijc.23173]

6 **Witz IP**, Levy-Nissenbaum O. The tumor microenvironment in the post-PAGET era. *Cancer Lett* 2006; **242**: 1-10 [PMID: 16413116 DOI: 10.1016/j.canlet.2005.12.005]

7 **Witz IP**. Yin-yang activities and vicious cycles in the tumor microenvironment. *Cancer Res* 2008; **68**: 9-13 [PMID: 18172289 DOI: 10.1158/0008-5472.CAN-07-2917]

8 **Witz IP**. Tumor-microenvironment interactions: dangerous liaisons. Adv Cancer Res 2008; **100**: 203-229 [PMID: 18620097 DOI: 10.1016/S0065-230X(08)00007-9]

9 **Balkwill F**, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* 2005; **7**: 211-217 [PMID: 15766659 DOI: 10.1016/j.ccr.2005.02.013]

10 **Koehne CH**, Dubois RN. COX-2 inhibition and colorectal cancer. *Semin Oncol* 2004; **31**: 12-21 [PMID: 15252926 DOI: 10.1053/j.seminoncol.2004.03.041]

11 **Flossmann E**, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lancet* 2007; **369**: 1603-1613 [PMID: 17499602 DOI: 10.1016/S0140-6736(07)60747-8]

12 **De Wever O**, Demetter P, Mareel M, Bracke M. Stromal myofibroblasts are drivers of invasive cancer growth. *Int J Cancer* 2008; **123**: 2229-2238 [PMID: 18777559 DOI: 10.1002/ijc.23925]

13 **Xing F**, Saidou J, Watabe K. Cancer associated fibroblasts (CAFs) in tumor microenvironment. *Front Biosci* 2010; **15**: 166-179 [PMID: 20036813 DOI: 10.2741/3613]

14 **Peek RM**, Crabtree JE. Helicobacter infection and gastric neoplasia. *J Pathol* 2006; **208**: 233-248 [PMID: 16362989 DOI: 10.1002/path.1868]

15 **Howlader N**, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst* 2010; **102**: 1584-1598 [PMID: 20937991 DOI: 10.1093/jnci/djq366]

16 **Ding SZ**, Zheng PY. Helicobacter pylori infection induced gastric cancer; advance in gastric stem cell research and the remaining challenges. *Gut Pathog* 2012; **4**: 18 [PMID: 23217022 DOI: 10.1186/1757-4749-4-18]

17 **Segal ED**, Cha J, Lo J, Falkow S, Tompkins LS. Altered states: involvement of phosphorylated CagA in the induction of host cellular growth changes by Helicobacter pylori. *Proc Natl Acad Sci U S A* 1999; **96**: 14559-14564 [PMID: 10588744 DOI: 10.1073/pnas.96.25.14559]

18 **Suganuma M**, Yamaguchi K, Ono Y, Matsumoto H, Hayashi T, Ogawa T, Imai K, Kuzuhara T, Nishizono A, Fujiki H. TNF-alpha-inducing protein, a carcinogenic factor secreted from H. pylori, enters gastric cancer cells. *Int J Cancer* 2008; **123**: 117-122 [PMID: 18412243 DOI: 10.1002/ijc.23484]

19 **Hatakeyama M**. Linking epithelial polarity and carcinogenesis by multitasking Helicobacter pylori virulence factor CagA. *Oncogene* 2008; **27**: 7047-7054 [PMID: 19029944 DOI: 10.1038/onc.2008.353]

20 **Sharma SA**, Tummuru MK, Blaser MJ, Kerr LD. Activation of IL-8 gene expression by Helicobacter pylori is regulated by transcription factor nuclear factor-kappa B in gastric epithelial cells. *J Immunol* 1998; **160**: 2401-2407 [PMID: 9498783]

21 **Isomoto H**, Mizuta Y, Miyazaki M, Takeshima F, Omagari K, Murase K, Nishiyama T, Inoue K, Murata I, Kohno S. Implication of NF-kappaB in Helicobacter pylori-associated gastritis. *Am J Gastroenterol* 2000; **95**: 2768-2776 [PMID: 11051346]

22 **Hatz RA**, Rieder G, Stolte M, Bayerdörffer E, Meimarakis G, Schildberg FW, Enders G. Pattern of adhesion molecule expression on vascular endothelium in Helicobacter pylori-associated antral gastritis. *Gastroenterology* 1997; **112**: 1908-1919 [PMID: 9178683 DOI: 10.1053/gast.1997.v112.pm9178683]

23 **Nakanishi C**, Toi M. Nuclear factor-kappaB inhibitors as sensitizers to anticancer drugs. *Nat Rev Cancer* 2005; **5**: 297-309 [PMID: 15803156 DOI: 10.1038/nrc1588]

24 **Liu XJ**, Chen ZF, Li HL, Hu ZN, Liu M, Tian AP, Zhao D, Wu J, Zhou YN, Qiao L. Interaction between cyclooxygenase-2, Snail, and E-cadherin in gastric cancer cells. *World J Gastroenterol* 2013; **19**: 6265-6271 [PMID: 24115825]

25 **Williams CS**, Smalley W, DuBois RN. Aspirin use and potential mechanisms for colorectal cancer prevention. *J Clin Invest* 1997; **100**: 1325-1329 [PMID: 9294096 DOI: 10.1172/JCI119651]

26 **Tsujii M**, DuBois RN. Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. *Cell* 1995; **83**: 493–501 [PMID: 8521479 DOI: 10.1016/0092-8674(95)90127-2]

27 **Jaiswal M**, LaRusso NF, Gores GJ. Nitric oxide in gastrointestinal epithelial cell carcinogenesis: linking inflammation to oncogenesis. *Am J Physiol Gastrointest Liver Physiol* 2001; **281**: 626–634 [PMID: 11518674]

28 **Goto T**, Haruma K, Kitadai Y, Ito M, Yoshihara M, Sumii K, Hayakawa N, Kajiyama G. Enhanced expression of inducible nitric oxide synthase and nitrotyrosine in gastric mucosa of gastric cancer patients. *Clin Cancer Res* 1999; **5**: 1411-1415 [PMID: 10389926]

29 **Murata-Kamiya N**, Kurashima Y, Teishikata Y, Yamahashi Y, Saito Y, Higashi H, Aburatani H, Akiyama T, Peek RM Jr, Azuma T, Hatakeyama M. Helicobacter pylori CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene* 2007; **26**: 4617–4626

30 **LAUREN P**. THE TWO HISTOLOGICAL MAIN TYPES OF GASTRIC CARCINOMA: DIFFUSE AND SO-CALLED INTESTINAL-TYPE CARCINOMA. AN ATTEMPT AT A HISTO-CLINICAL CLASSIFICATION. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675]

31 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

32 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]

33 **Karin M**. Nuclear factor-kappaB in cancer development and progression. *Nature* 2006; **441**: 431-436 [PMID: 16724054 DOI: 10.1038/nature04870]

34 **Greten FR**, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, Kagnoff MF, Karin M. IKKbeta links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. *Cell* 2004; **118**: 285-296 [PMID: 15294155 DOI: 10.1016/j.cell.2004.07.013]

35 **Ditsworth D**, Zong WX. NF-kappaB: key mediator of inflammation-associated cancer. *Cancer Biol Ther* 2004; **3**: 1214-1216 [PMID: 15611628 doi: 10.4161/cbt.3.12.1391]

36 **Aihara M**, Tsuchimoto D, Takizawa H, Azuma A, Wakebe H, Ohmoto Y, Imagawa K, Kikuchi M, Mukaida N, Matsushima K. Mechanisms involved in Helicobacter pylori-induced interleukin-8 production by a gastric cancer cell line, MKN45. *Infect Immun* 1997; **65**: 3218-3224 [PMID: 9234778]

37 **Yasumoto K**, Okamoto S, Mukaida N, Murakami S, Mai M, Matsushima K. Tumor necrosis factor alpha and interferon gamma synergistically induce interleukin 8 production in a human gastric cancer cell line through acting concurrently on AP-1 and NF-kB-like binding sites of the interleukin 8 gene. *J Biol Chem* 1992; **267**: 22506-22511 [PMID: 1331059]

38 **Kwon HC**, Kim SH, Oh SY, Lee S, Lee JH, Jang JS, Kim MC, Kim KH, Kim SJ, Kim SG, Kim HJ. Clinicopathologic significance of expression of nuclear factor-κB RelA and its target gene products in gastric cancer patients. *World J Gastroenterol* 2012; **18**: 4744-4750 [PMID: 23002344 DOI: 10.3748/wjg.v18.i34.4744]

39 **Crone SG**, Jacobsen A, Federspiel B, Bardram L, Krogh A, Lund AH, Friis-Hansen L. microRNA-146a inhibits G protein-coupled receptor-mediated activation of NF-κB by targeting CARD10 and COPS8 in gastric cancer. *Mol Cancer* 2012; **11**: 71 [PMID: 22992343 DOI: 10.1186/1476-4598-11-71]

40 **Talks KL**, Turley H, Gatter KC, Maxwell PH, Pugh CW, Ratcliffe PJ, Harris AL. The expression and distribution of the hypoxia-inducible factors HIF-1α and HIF-2α in normal human tissues, cancers, and tumor-associated macrophages. *Am J Pathol* 2000; **157**: 411–421 [PMID: 10934146 DOI: 10.1016/S0002-9440(10)64554-3]

41 **Rius J**, Guma M, Schachtrup C, Akassoglou K, Zinkernagel AS, Nizet V, Johnson RS, Haddad GG, Karin M. NF-kappaB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1alpha. *Nature* 2008; **453**: 807-811 [PMID: 18432192 DOI: 10.1038/nature06905]

42 **Zhong H**, De Marzo AM, Laughner E, Lim M, Hilton DA, Zagzag D, Buechler P, Isaacs WB, Semenza GL, Simons JW. Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases. *Cancer Res* 1999; **59**: 5830-5835 [PMID: 10582706]

43 **Zhou J**, Schmid T, Schnitzer S, Brüne B. Tumor hypoxia and cancer progression. *Cancer Lett* 2006; **237**: 10-21 [PMID: 16002209 DOI: 10.1016/j.canlet.2005.05.028]

44 **Liu L**, Ning X, Sun L, Zhang H, Shi Y, Guo C, Han S, Liu J, Sun S, Han Z, Wu K, Fan D. Hypoxia-inducible factor-1 alpha contributes to hypoxia-induced chemoresistance in gastric cancer. *Cancer Sci* 2008; **99**: 121-128 [PMID: 17953712]

45 **Giaccia A**, Siim BG, Johnson RS. HIF-1 as a target for drug development. *Nat Rev Drug Discov* 2003; **2**: 803-811 [PMID: 14526383 DOI: 10.1038/nrd1199]

46 **Rohwer N**, Lobitz S, Daskalow K, Jöns T, Vieth M, Schlag PM, Kemmner W, Wiedenmann B, Cramer T, Höcker M. HIF-1alpha determines the metastatic potential of gastric cancer cells. *Br J Cancer* 2009; **100**: 772-781 [PMID: 19223895 DOI: 10.1038/sj.bjc.6604919]

47 **Yu H**, Kortylewski M, Pardoll D. Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. *Nat Rev Immunol* 2007; **7**: 41-51 [PMID: 17186030 DOI: 10.1038/nri1995]

48 **Tye H**, Kennedy CL, Najdovska M, McLeod L, McCormack W, Hughes N, Dev A, Sievert W, Ooi CH, Ishikawa TO, Oshima H, Bhathal PS, Parker AE, Oshima M, Tan P, Jenkins BJ. STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. *Cancer Cell* 2012; **22**: 466-478 [PMID: 23079657 DOI: 10.1016/j.ccr.2012.08.010]

49 **Yu H**, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer* 2009; **9**: 798-809 [PMID: 19851315 DOI: 10.1038/nrc2734]

50 **Kim DY**, Cha ST, Ahn DH, Kang HY, Kwon CI, Ko KH, Hwang SG, Park PW, Rim KS, Hong SP. STAT3 expression in gastric cancer indicates a poor prognosis. *J Gastroenterol Hepatol* 2009; **24**: 646-651 [PMID: 19175826 DOI: 10.1111/j.1440-1746.2008.05671.x]

51 **Ernst M**, Najdovska M, Grail D, Lundgren-May T, Buchert M, Tye H, Matthews VB, Armes J, Bhathal PS, Hughes NR, Marcusson EG, Karras JG, Na S, Sedgwick JD, Hertzog PJ, Jenkins BJ. STAT3 and STAT1 mediate IL-11-dependent and inflammation-associated gastric tumorigenesis in gp130 receptor mutant mice. *J Clin Invest* 2008; **118**: 1727-1738 [PMID: 18431520]

52 **Ellmark P**, Ingvarsson J, Carlsson A, Lundin BS, Wingren C, Borrebaeck CA. Identification of protein expression signatures associated with Helicobacter pylori infection and gastric adenocarcinoma using recombinant antibody microarrays. *Mol Cell Proteomics* 2006; **5**: 1638-1646 [PMID: 16844680 DOI: 10.1074/mcp.M600170-MCP200]

53 **Bollrath J**, Phesse TJ, von Burstin VA, Putoczki T, Bennecke M, Bateman T, Nebelsiek T, Lundgren-May T, Canli O, Schwitalla S, Matthews V, Schmid RM, Kirchner T, Arkan MC, Ernst M, Greten FR. gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell* 2009; **15**: 91-102 [PMID: 19185844 DOI: 10.1016/j.ccr.2009.01.002]

54 **Wang T**, Niu G, Kortylewski M, Burdelya L, Shain K, Zhang S, Bhattacharya R, Gabrilovich D, Heller R, Coppola D, Dalton W, Jove R, Pardoll D, Yu H. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. *Nat Med* 2004; **10**: 48-54 [PMID: 14702634 DOI: 10.1038/nm976]

55 **Kortylewski M**, Kujawski M, Wang T, Wei S, Zhang S, Pilon-Thomas S, Niu G, Kay H, Mulé J, Kerr WG, Jove R, Pardoll D, Yu H. Inhibiting Stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. *Nat Med* 2005; **11**: 1314-1321 [PMID: 16288283 DOI: 10.1038/nm1325]

56 **Kortylewski M**, Xin H, Kujawski M, Lee H, Liu Y, Harris T, Drake C, Pardoll D, Yu H. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. *Cancer Cell* 2009; **15**: 114-123 [PMID: 19185846 DOI: 10.1016/j.ccr.2008.12.018]

57 **Mantovani G**, Macciò A, Madeddu C, Serpe R, Antoni G, Massa E, Dessì M, Panzone F. Phase II nonrandomized study of the efficacy and safety of COX-2 inhibitor celecoxib on patients with cancer cachexia. *J Mol Med (Berl)* 2010; **88**: 85-92 [PMID: 19802504 DOI: 10.1007/s00109-009-0547-z]

58 **Chan AT**, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. *N Engl J Med* 2007; **356**: 2131-2142 [PMID: 17522398 DOI: 10.1056/NEJMoa067208]

59 **Honjo S**, Kase S, Osaki M, Ardyanto TD, Kaibara N, Ito H. Cyclooxygenase-2 Expression in Human Gastric Tubular Adenomas and Carcinomas; Correlation with Intratumoral Microvessel Density and Apoptotic Index Anticancer reserch 2004; **24**: 1439-1444

60 **Yoshida K**, Yokozaki H, Niimoto M, Ito H, Ito M, Tahara E. Expression of TGF-beta and procollagen type I and type III in human gastric carcinomas. *Int J Cancer* 1989; **44**: 394-398 [PMID: 2777404 DOI: 10.1002/ijc.2910440303]

61 **Mahara K**, Kato J, Terui T, Takimoto R, Horimoto M, Murakami T, Mogi Y, Watanabe N, Kohgo Y, Niitsu Y. Transforming growth factor beta 1 secreted from scirrhous gastric cancer cells is associated with excess collagen deposition in the tissue. *Br J Cancer* 1994; **69**: 777-783 [PMID: 8142266 DOI: 10.1038/bjc.1994.147]

62 **Horimoto M**, Kato J, Takimoto R, Terui T, Mogi Y, Niitsu Y. Identification of a transforming growth factor beta-1 activator derived from a human gastric cancer cell line. *Br J Cancer* 1995; **72**: 676-682 [PMID: 7669580 DOI: 10.1038/bjc.1995.393]

63 **Maehara Y**, Kakeji Y, Kabashima A, Emi Y, Watanabe A, Akazawa K, Baba H, Kohnoe S, Sugimachi K. Role of transforming growth factor-beta 1 in invasion and metastasis in gastric carcinoma. *J Clin Oncol* 1999; **17**: 607-614 [PMID: 10080606]

64 **Dhanasekaran DN**, Johnson GL. MAPKs: function, regulation, role in cancer and therapeutic targeting. *Oncogene* 2007; **26**: 3097-3099 [PMID: 17496908 DOI: 10.1038/sj.onc.1210395]

65 **Schlessinger J**. Common and distinct elements in cellular signaling via EGF and FGF receptors. *Science* 2004; **306**: 1506-1507 [PMID: 15567848 DOI: 10.1126/science.1105396]

66 **Matsubara J**, Nishina T, Yamada Y, Moriwaki T, Shimoda T, Kajiwara T, Nakajima TE, Kato K, Hamaguchi T, Shimada Y, Okayama Y, Oka T, Shirao K. Impacts of excision repair cross-complementing gene 1 (ERCC1), dihydropyrimidine dehydrogenase, and epidermal growth factor receptor on the outcomes of patients with advanced gastric cancer. *Br J Cancer* 2008; **98**: 832-839 [PMID: 18231104 DOI: 10.1038/sj.bjc.6604211]

67 **Yano T**, Doi T, Ohtsu A, Boku N, Hashizume K, Nakanishi M, Ochiai A. Comparison of HER2 gene amplification assessed by fluorescence in situ hybridization and HER2 protein expression assessed by immunohistochemistry in gastric cancer. *Oncol Rep* 2006; **15**: 65-71 [PMID: 16328035]

68 **Grávalos C**, Gómez-Martín C, Rivera F, Alés I, Queralt B, Márquez A, Jiménez U, Alonso V, García-Carbonero R, Sastre J, Colomer R, Cortés-Funes H, Jimeno A. Phase II study of trastuzumab and cisplatin as first-line therapy in patients with HER2-positive advanced gastric or gastroesophageal junction cancer. *Clin Transl Oncol* 2011; **13**: 179-184 [PMID: 21421462 DOI: 10.1007/s12094-011-0637-6]

69 **Zheng Y**, Wang L, Zhang JP, Yang JY, Zhao ZM, Zhang XY. Expression of p53, c-erbB-2 and Ki67 in intestinal metaplasia and gastric carcinoma. *World J Gastroenterol* 2010; **16**: 339-344 [PMID: 20082479 DOI: 10.3748/wjg.v16.i3.339]

70 **Im SA**, Lee KE, Nam E, Kim DY, Lee JH, Han HS, Seoh JY, Park HY, Cho MS, Han WS, Lee SN. Potential prognostic significance of p185(HER2) overexpression with loss of PTEN expression in gastric carcinomas. *Tumori* ; **91**: 513-521 [PMID: 16457151]

71 **Uchino S**, Tsuda H, Maruyama K, Kinoshita T, Sasako M, Saito T, Kobayashi M, Hirohashi S. Overexpression of c-erbB-2 protein in gastric cancer. Its correlation with long-term survival of patients. *Cancer* 1993; 72: 3179–3184 [PMID: 7902202 DOI: 10.1002/1097-0142(19931201)72: 11<3179: : AID-CNCR2820721108>3.0.CO; 2-#]

72 **Grabsch H**, Sivakumar S, Gray S, Gabbert HE, Müller W. HER2 expression in gastric cancer: Rare, heterogeneous and of no prognostic value - conclusions from 924 cases of two independent series. *Cell Oncol* 2010; **32**: 57-65 [PMID: 20208134]

73 **Chua TC**, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes--a systematic review. *Int J Cancer* 2012; **130**: 2845-2856 [PMID: 21780108 DOI: 10.1002/ijc.26292]

74 **Byun DS**, Cho K, Ryu BK, Lee MG, Park JI, Chae KS, Kim HJ, Chi SG. Frequent monoallelic deletion of PTEN and its reciprocal associatioin with PIK3CA amplification in gastric carcinoma. *Int J Cancer* 2003; **104**: 318-327 [PMID: 12569555 DOI: 10.1002/ijc.10962]

75 **Li VS**, Wong CW, Chan TL, Chan AS, Zhao W, Chu KM, So S, Chen X, Yuen ST, Leung SY. Mutations of PIK3CA in gastric adenocarcinoma. *BMC Cancer* 2005; **5**: 29 [PMID: 15784156 DOI: 10.1186/1471-2407-5-29]

76 **Kang YH**, Lee HS, Kim WH. Promoter methylation and silencing of PTEN in gastric carcinoma. *Lab Invest* 2002; **82**: 285-291 [PMID: 11896207 DOI: 10.1038/labinvest.3780422]

77 **Lee SH**, Lee JW, Soung YH, Kim HS, Park WS, Kim SY, Lee JH, Park JY, Cho YG, Kim CJ, Nam SW, Kim SH, Lee JY, Yoo NJ. BRAF and KRAS mutations in stomach cancer. *Oncogene* 2003; **22**: 6942-6945 [PMID: 14534542 DOI: 10.1038/sj.onc.1206749]

78 **Hiyama T**, Haruma K, Kitadai Y, Masuda H, Miyamoto M, Tanaka S, Yoshihara M, Shimamoto F, Chayama K. K-ras mutation in helicobacter pylori-associated chronic gastritis in patients with and without gastric cancer. *Int J Cancer* 2002; **97**: 562-566 [PMID: 11807778 DOI: 10.1002/ijc.1644]

79 **Kim IJ**, Park JH, Kang HC, Shin Y, Park HW, Park HR, Ku JL, Lim SB, Park JG. Mutational analysis of BRAF and K-ras in gastric cancers: absence of BRAF mutations in gastric cancers. *Hum Genet* 2003; **114**: 118-120 [PMID: 14513361 DOI: 10.1007/s00439-003-1027-0]

80 **Migliore C**, Giordano S. Molecular cancer therapy: can our expectation be MET? *Eur J Cancer* 2008; **44**: 641-651 [PMID: 18295476 DOI: 10.1016/j.ejca.2008.01.022]

81 **Inoue T**, Kataoka H, Goto K, Nagaike K, Igami K, Naka D, Kitamura N, Miyazawa K. Activation of c-Met (hepatocyte growth factor receptor) in human gastric cancer tissue. *Cancer Sci* 2004; **95**: 803-808 [PMID: 15504247 DOI: 10.1111/j.1349-7006.2004.tb02185.x]

82 **Oliveira MJ**, Costa AC, Costa AM, Henriques L, Suriano G, Atherton JC, Machado JC, Carneiro F, Seruca R, Mareel M, Leroy A, Figueiredo C. Helicobacter pylori induces gastric epithelial cell invasion in a c-Met and type IV secretion system-dependent manner. *J Biol Chem* 2006; **281**: 34888-34896 [PMID: 16990273 DOI: 10.1074/jbc.M607067200]

83 **Han ME**, Lee YS, Baek SY, Kim BS, Kim JB, Oh SO. Hedgehog signaling regulates the survival of gastric cancer cells by regulating the expression of Bcl-2. *Int J Mol Sci* 2009; **10**: 3033-3043 [PMID: 19742123 DOI: 10.3390/ijms10073033]

84 **Allavena P**, Mantovani A. Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment. *Clin Exp Immunol* 2012; **167**: 195-205 [PMID: 22235995 DOI: 10.1111/j.1365-2249.2011.04515.x]

85 **Lewis CE**, Pollard JW. Distinct role of macrophages in different tumor microenvironments. *Cancer Res* 2006; **66**: 605-612 [PMID: 16423985 DOI: 10.1158/0008-5472.CAN-05-4005]

86 **Condeelis J**, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell* 2006; **124**: 263-266 [PMID: 16439202 DOI: 10.1016/j.cell.2006.01.007]

87 **Ohta M**, Kitadai Y, Tanaka S, Yoshihara M, Yasui W, Mukaida N, Haruma K, Chayama K. Monocyte chemoattractant protein-1 expression correlates with macrophage infiltration and tumor vascularity in human esophageal squamous cell carcinomas. *Int J Cancer* 2002; **102**: 220-224 [PMID: 12397639 DOI: 10.1002/ijc.10705]

88 **Ohta M**, Kitadai Y, Tanaka S, Yoshihara M, Yasui W, Mukaida N, Haruma K, Chayama K. Monocyte chemoattractant protein-1 expression correlates with macrophage infiltration and tumor vascularity in human gastric carcinomas. *Int J Oncol* 2003; **22**: 773-778 [PMID: 12632067]

89 **Jonuleit H**, Schmitt E, Stassen M, Tuettenberg A, Knop J, Enk AH. Identification and functional characterization of human CD4(+)CD25(+) T cells with regulatory properties isolated from peripheral blood. *J Exp Med* 2001; **193**: 1285-1294 [PMID: 11390435 DOI: 10.1084/jem.193.11.1285]

90 **Ng WF**, Duggan PJ, Ponchel F, Matarese G, Lombardi G, Edwards AD, Issacs JD, Lechler RI. Human CD4 CD25 cells: a naturally occurring population of regulatory T cells. *Blood* 2001; **98**: 2736–2744 [PMID: 11675346 DOI: 10.1182/blood.V98.9.2736]

91 **Sakaguchi S**, Sakaguchi N, Asano M, Itoh M, Toda M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. *J Immunol* 1995; **155**: 1151-1164 [PMID: 7636184]

92 **Beyer M**, Schultze JL. Regulatory T cells in cancer. *Blood* 2006; **108**: 804-811 [PMID: 16861339 DOI: 10.1182/blood-2006-02-002774]

93 **Ichihara F**, Kono K, Takahashi A, Kawaida H, Sugai H, Fujii H. Increased populations of regulatory T cells in peripheral blood and tumor-infiltrating lymphocytes in patients with gastric and esophageal cancers. *Clin Cancer Res* 2003; **9**: 4404-4408 [PMID: 14555512]

94 **Mizukami Y**, Kono K, Kawaguchi Y, Akaike H, Kamimura K, Sugai H, Fujii H. CCL17 and CCL22 chemokines within tumor microenvironment are related to accumulation of Foxp3+ regulatory T cells in gastric cancer. *Int J Cancer* 2008; **122**: 2286-2293 [PMID: 18224687 DOI: 10.1002/ijc.23392]

95 **Kono K**, Kawaida H, Takahashi A, Sugai H, Mimura K, Miyagawa N, Omata H, Fujii H. CD4(+)CD25high regulatory T cells increase with tumor stage in patients with gastric and esophageal cancers. *Cancer Immunol Immunother* 2006; **55**: 1064-1071 [PMID: 16328385 DOI: 10.1007/s00262-005-0092-8]

96 **Lu X**, Liu J, Li H, Li W, Wang X, Ma J, Tong Q, Wu K, Wang G. Conversion of intratumoral regulatory T cells by human gastric cancer cells is dependent on transforming growth factor-β1. *J Surg Oncol* 2011; **104**: 571-577 [PMID: 21695703 DOI: 10.1002/jso.22005]

97 **Lin Y**, Kikuchi S, Obata Y, Yagyu K. Serum levels of transforming growth factor beta1 are significantly correlated with venous invasion in patients with gastric cancer. *J Gastroenterol Hepatol* 2006; **21**: 432-437 [PMID: 16509870 DOI: 10.1111/j.1440-1746.2005.03939.x]

98 **Vagenas K**, Spyropoulos C, Gavala V, Tsamandas AC. TGFbeta1, TGFbeta2, and TGFbeta3 protein expression in gastric carcinomas: correlation with prognostics factors and patient survival. *J Surg Res* 2007; **139**: 182-188 [PMID: 17270215 DOI: 10.1016/j.jss.2006.10.005]

99 **Allan SE**, Crome SQ, Crellin NK, Passerini L, Steiner TS, Bacchetta R, Roncarolo MG, Levings MK. Activation-induced FOXP3 in human T effector cells does not suppress proliferation or cytokine production. *Int Immunol* 2007; **19**: 345-354 [PMID: 17329235 DOI: 10.1093/intimm/dxm014]

100 **Zheng SG**, Wang JH, Gray JD, Soucier H, Horwitz DA. Natural and induced CD4+CD25+ cells educate CD4+CD25- cells to develop suppressive activity: the role of IL-2, TGF-beta, and IL-10. *J Immunol* 2004; **172**: 5213-5221 [PMID: 15100259]

101 **Shen LS**, Wang J, Shen DF, Yuan XL, Dong P, Li MX, Xue J, Zhang FM, Ge HL, Xu D. CD4(+)CD25(+)CD127(low/-) regulatory T cells express Foxp3 and suppress effector T cell proliferation and contribute to gastric cancers progression. *Clin Immunol* 2009; **131**: 109-118 [PMID: 19153062 DOI: 10.1016/j.clim.2008.11.010]

102 **Maruyama T**, Kono K, Mizukami Y, Kawaguchi Y, Mimura K, Watanabe M, Izawa S, Fujii H. Distribution of Th17 cells and FoxP3(+) regulatory T cells in tumor-infiltrating lymphocytes, tumor-draining lymph nodes and peripheral blood lymphocytes in patients with gastric cancer. *Cancer Sci* 2010; **101**: 1947-1954 [PMID: 20550524 DOI: 10.1111/j.1349-7006.2010.01624.x]

103 **Orimo A**, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, Carey VJ, Richardson AL, Weinberg RA. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell* 2005; **121**: 335-348 [PMID: 15882617 DOI: 10.1016/j.cell.2005.02.034]

104 **Pietras K**, Ostman A. Hallmarks of cancer: interactions with the tumor stroma. *Exp Cell Res* 2010; **316**: 1324-1331 [PMID: 20211171 DOI: 10.1016/j.yexcr.2010.02.045]

105 **Bhowmick NA**, Neilson EG, Moses HL. Stromal fibroblasts in cancer initiation and progression. *Nature* 2004; **432**: 332-337 [PMID: 15549095 DOI: 10.1038/nature03096]

106 **Allinen M**, Beroukhim R, Cai L, Brennan C, Lahti-Domenici J, Huang H, Porter D, Hu M, Chin L, Richardson A, Schnitt S, Sellers WR, Polyak K. Molecular characterization of the tumor microenvironment in breast cancer. *Cancer Cell* 2004; **6**: 17-32 [PMID: 15261139 DOI: 10.1016/j.ccr.2004.06.010]

107 **Kalluri R**, Zeisberg M. Fibroblasts in cancer. *Nat Rev Cancer* 2006; **6**: 392-401 [PMID: 16572188 DOI: 10.1038/nrc1877]

108 **Zeisberg EM**, Potenta S, Xie L, Zeisberg M, Kalluri R. Discovery of endothelial to mesenchymal transition as a source for carcinoma-associated fibroblasts. *Cancer Res* 2007; **67**: 10123-10128 [PMID: 17974953 DOI: 10.1158/0008-5472.CAN-07-3127]

109 **Direkze NC**, Hodivala-Dilke K, Jeffery R, Hunt T, Poulsom R, Oukrif D, Alison MR, Wright NA. Bone marrow contribution to tumor-associated myofibroblasts and fibroblasts. *Cancer Res* 2004; **64**: 8492-8495 [PMID: 15574751 DOI: 10.1158/0008-5472.CAN-04-1708]

110 **Worthley DL**, Ruszkiewicz A, Davies R, Moore S, Nivison-Smith I, Bik To L, Browett P, Western R, Durrant S, So J, Young GP, Mullighan CG, Bardy PG, Michael MZ. Human gastrointestinal neoplasia-associated myofibroblasts can develop from bone marrow-derived cells following allogeneic stem cell transplantation. *Stem Cells* 2009; **27**: 1463-1468 [PMID: 19492298 DOI: 10.1002/stem.63]

111 **Semba S**, Kodama Y, Ohnuma K, Mizuuchi E, Masuda R, Yashiro M, Hirakawa K, Yokozaki H. Direct cancer-stromal interaction increases fibroblast proliferation and enhances invasive properties of scirrhous-type gastric carcinoma cells. *Br J Cancer* 2009; **101**: 1365-1373 [PMID: 19773759 DOI: 10.1038/sj.bjc.6605309]

112 **Hewitt RE**, Powe DG, Carter GI, Turner DR. Desmoplasia and its relevance to colorectal tumour invasion. *Int J Cancer* 1993; **53**: 62-69 [PMID: 7677932 DOI: 10.1002/ijc.2910530113]

113 **Dvorak HF**. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 1986; **315**: 1650-1659 [PMID: 3537791 DOI: 10.1056/NEJM198612253152606]

114 **Matsumoto T**, Kuroda R, Mifune Y, Kawamoto A, Shoji T, Miwa M, Asahara T, Kurosaka M. Circulating endothelial/skeletal progenitor cells for bone regeneration and healing. *Bone* 2008; **43**: 434-439 [PMID: 18547890 DOI: 10.1016/j.bone.2008.05.001]

115 **Takahashi Y**, Kitadai Y, Bucana CD, Cleary KR, Ellis LM. Expression of vascular endothelial growth factor and its receptor, KDR, correlates with vascularity, metastasis, and proliferation of human colon cancer. *Cancer Res* 1995; **55**: 3964-3968 [PMID: 7664263]

116 **Tanigawa N**, Amaya H, Matsumura M, Shimomatsuya T, Horiuchi T, Muraoka R, Iki M. Extent of tumor vascularization correlates with prognosis and hematogenous metastasis in gastric carcinomas. *Cancer Res* 1996; **56**: 2671-2676 [PMID: 8653715]

117 **Takahashi Y**, Cleary KR, Mai M, Kitadai Y, Bucana CD, Ellis LM. Significance of vessel count and vascular endothelial growth factor and its receptor (KDR) in intestinal-type gastric cancer. *Clin Cancer Res* 1996; **2**: 1679-1684 [PMID: 9816116]

118 **Folkman J**. How is blood vessel growth regulated in normal and neoplastic tissue? G.H.A. Clowes memorial Award lecture. *Cancer Res* 1986; **46**: 467-473 [PMID: 2416426]

119 **Folkman J**. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 1990; **82**: 4-6 [PMID: 1688381 DOI: 10.1093/jnci/82.1.4]

120 **Maeda K**, Chung YS, Ogawa Y, Takatsuka S, Kang SM, Ogawa M, Sawada T, Sowa M. Prognostic value of vascular endothelial growth factor expression in gastric carcinoma. *Cancer* 1996; 77: 858–863 [PMID: 8608475 DOI: 10.1002/(SICI)1097-0142]

121 **Kitadai Y**, Haruma K, Sumii K, Yamamoto S, Ue T, Yokozaki H, Yasui W, Ohmoto Y, Kajiyama G, Fidler IJ, Tahara E. Expression of interleukin-8 correlates with vascularity in human gastric carcinomas. *Am J Pathol* 1998; **152**: 93-100 [PMID: 9422527]

122 **Tanimoto H**, Yoshida K, Yokozaki H, Yasui W, Nakayama H, Ito H, Ohama K, Tahara E. Expression of basic fibroblast growth factor in human gastric carcinomas. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1991; **61**: 263-267 [PMID: 1685819 DOI: 10.1007/BF02890427]

123 **Takahashi Y**, Bucana CD, Akagi Y, Liu W, Cleary KR, Mai M, Ellis LM. Significance of platelet-derived endothelial cell growth factor in the angiogenesis of human gastric cancer. *Clin Cancer Res* 1998; **4**: 429-434 [PMID: 9516932]

124 **Amioka T**, Kitadai Y, Tanaka S, Haruma K, Yoshihara M, Yasui W, Chayama K. Vascular endothelial growth factor-C expression predicts lymph node metastasis of human gastric carcinomas invading the submucosa. *Eur J Cancer* 2002; **38**: 1413–1419 [DOI: 10.1016/S0959-8049(02)00106-5]

125 **Yonemura Y**, Endo Y, Fujita H, Fushida S, Ninomiya I, Bandou E, Taniguchi K, Miwa K, Ohoyama S, Sugiyama K, Sasaki T. Role of vascular endothelial growth factor C expression in the development of lymph node metastasis in gastric cancer. *Clin Cancer Res* 1999; **5**: 1823-1829 [PMID: 10430087]

126 **Onogawa S**, Kitadai Y, Amioka T, Kodama M, Cho S, Kuroda T, Ochiumi T, Kimura S, Kuwai T, Tanaka S, Chayama K. Expression of vascular endothelial growth factor (VEGF)-C and VEGF-D in early gastric carcinoma: correlation with clinicopathological parameters. *Cancer Lett* 2005; **226**: 85-90 [PMID: 16004935 DOI: 10.1016/j.canlet.2004.12.030]

127 **Whiteside TL**. The tumor microenvironment and its role in promoting tumor growth. *Oncogene* 2008; **27**: 5904-5912 [PMID: 18836471 DOI: 10.1038/onc.2008.271]

128 **Cabarcas SM**, Mathews LA, Farrar WL. The cancer stem cell niche--there goes the neighborhood? *Int J Cancer* 2011; **129**: 2315-2327 [PMID: 21792897 DOI: 10.1002/ijc.26312]

129 **Korkaya H**, Paulson A, Charafe-Jauffret E, Ginestier C, Brown M, Dutcher J, Clouthier SG, Wicha MS. Regulation of mammary stem/progenitor cells by PTEN/Akt/beta-catenin signaling. *PLoS Biol* 2009; **7**: e1000121 [PMID: 19492080 DOI: 10.1371/journal.pbio.1000121]

130 **Liu S**, Dontu G, Mantle ID, Patel S, Ahn NS, Jackson KW, Suri P, Wicha MS. Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. *Cancer Res* 2006; **66**: 6063-6071 [PMID: 16778178 DOI: 10.1158/0008-5472.CAN-06-0054]

131 **Iliopoulos D**, Hirsch HA, Struhl K. An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. *Cell* 2009; **139**: 693-706 [PMID: 19878981 DOI: 10.1016/j.cell.2009.10.014]

132 **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, Rabkin CS. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; **404**: 398-402 [PMID: 10746728 DOI: 10.1038/35006081]

133 **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. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 2003; **124**: 1193–1201 [PMID: 12730860 DOI: 10.1016/S0016-5085(03)00157-4]

134 **Tu SP**, Quante M, Bhagat G, Takaishi S, Cui G, Yang XD, Muthuplani S, Shibata W, Fox JG, Pritchard DM, Wang TC. IFN-γ inhibits gastric carcinogenesis by inducing epithelial cell autophagy and T-cell apoptosis. *Cancer Res* 2011; **71**: 4247-4259 [PMID: 21512143 DOI: 10.1158/0008-5472.CAN-10-4009]

135 **Le Y**, Zhou Y, Iribarren P, Wang J. Chemokines and chemokine receptors: their manifold roles in homeostasis and disease. *Cell Mol Immunol* 2004; **1**: 95-104 [PMID: 16212895]

136 **Luster AD**. Chemokines–chemotactic cytokines that mediate inflammation. *N Engl J Med* 1998; **3387**: 436-445 [PMID: 9459648]

137 **Raman D**, Baugher PJ, Thu YM, Richmond A. Role of chemokines in tumor growth. *Cancer Lett* 2007; **256**: 137-165 [PMID: 17629396 DOI: 10.1016/j.canlet.2007.05.013]

138 **Strieter RM**, Polverini PJ, Kunkel SL, Arenberg DA, Burdick MD, Kasper J, Dzuiba J, Van Damme J, Walz A, Marriott D. The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem* 1995; **270**: 27348-27357 [PMID: 7592998 DOI: 10.1074/jbc.270.45.27348]

139 **Strieter RM**, Burdick MD, Gomperts BN, Belperio JA, Keane MP. CXC chemokines in angiogenesis. *Cytokine Growth Factor Rev* 2005; **16**: 593-609 [PMID: 16046180 DOI: 10.1016/j.cytogfr.2005.04.007]

140 **Vandercappellen J**, Van Damme J, Struyf S. The role of CXC chemokines and their receptors in cancer. *Cancer Lett* 2008; **267**: 226-244 [PMID: 18579287 DOI: 10.1016/j.canlet.2008.04.050]

141 **Crabtree JE**, Farmery SM, Lindley IJ, Figura N, Peichl P, Tompkins DS. CagA/cytotoxic strains of Helicobacter pylori and interleukin-8 in gastric epithelial cell lines. *J Clin Pathol* 1994; **47**: 945-950 [PMID: 7962609 DOI: 10.1136/jcp.47.10.945]

142 **Beales IL**, Calam J. Stimulation of IL-8 production in human gastric epithelial cells by Helicobacter pylori, IL-1beta and TNF-alpha requires tyrosine kinase activity, but not protein kinase C. *Cytokine* 1997; **9**: 514-520 [PMID: 9237814 DOI: 10.1006/cyto.1996.0195]

143 **Bäckhed F**, Torstensson E, Seguin D, Richter-Dahlfors A, Rokbi B. Helicobacter pylori infection induces interleukin-8 receptor expression in the human gastric epithelium. *Infect Immun* 2003; **71**: 3357-3360 [PMID: 12761119 DOI: 10.1128/IAI.71.6.3357-3360.2003]

144 **Beswick EJ**, Das S, Pinchuk IV, Adegboyega P, Suarez G, Yamaoka Y, Reyes VE. Helicobacter pylori-induced IL-8 production by gastric epithelial cells up-regulates CD74 expression. *J Immunol* 2005; **175**: 171-176 [PMID: 15972644]

145 **Konturek PC**, Nikiforuk A, Kania J, Raithel M, Hahn EG, Mühldorfer S. Activation of NFkappaB represents the central event in the neoplastic progression associated with Barrett's esophagus: a possible link to the inflammation and overexpression of COX-2, PPARgamma and growth factors. *Dig Dis Sci* 2004; **49**: 1075-1083 [PMID: 15387324 DOI: 10.1023/B: DDAS.0000037790.11724.70]

146 **Macrì A**, Versaci A, Loddo S, Scuderi G, Travagliante M, Trimarchi G, Teti D, Famulari C. Serum levels of interleukin 1beta, interleukin 8 and tumour necrosis factor alpha as markers of gastric cancer. *Biomarkers* ; **11**: 184-193 [PMID: 16766394 DOI: 10.1080/13547500600565677]

147 **Kitadai Y**, Haruma K, Mukaida N, Ohmoto Y, Matsutani N, Yasui W, Yamamoto S, Sumii K, Kajiyama G, Fidler IJ, Tahara E. Regulation of disease-progression genes in human gastric carcinoma cells by interleukin 8. *Clin Cancer Res* 2000; **6**: 2735-2740 [PMID: 10914718]

148 **Opdenakker G**, Van den Steen PE, Dubois B, Nelissen I, Van Coillie E, Masure S, Proost P, Van Damme J. Gelatinase B functions as regulator and effector in leukocyte biology. *J Leukoc Biol* 2001; **69**: 851-859 [PMID: 11404367]

149 **Taguchi A**, Ohmiya N, Shirai K, Mabuchi N, Itoh A, Hirooka Y, Niwa Y, Goto H. Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 2487-2493 [PMID: 16284368 DOI: 10.1158/1055-9965.EPI-05-0326]

150 **Ye BD**, Kim SG, Park JH, Kim JS, Jung HC, Song IS. The interleukin-8-251 A allele is associated with increased risk of noncardia gastric adenocarcinoma in Helicobacter pylori-infected Koreans. *J Clin Gastroenterol* 2009; **43**: 233-239 [PMID: 18542040 DOI: 10.1097/MCG.0b013e3181646701]

151 **Song JH**, Kim SG, Jung SA, Lee MK, Jung HC, Song IS. The interleukin-8-251 AA genotype is associated with angiogenesis in gastric carcinogenesis in Helicobacter pylori-infected Koreans. *Cytokine* 2010; **51**: 158-165 [PMID: 20621718 DOI: 10.1016/j.cyto.2010.05.001]

152 **Kucia M**, Reca R, Miekus K, Wanzeck J, Wojakowski W, Janowska-Wieczorek A, Ratajczak J, Ratajczak MZ. Trafficking of normal stem cells and metastasis of cancer stem cells involve similar mechanisms: pivotal role of the SDF-1-CXCR4 axis. *Stem Cells* 2005; **23**: 879-894 [PMID: 15888687 DOI: 10.1634/stemcells.2004-0342]

153 **Zheng K**, Li HY, Su XL, Wang XY, Tian T, Li F, Ren GS. Chemokine receptor CXCR7 regulates the invasion, angiogenesis and tumor growth of human hepatocellular carcinoma cells. *J Exp Clin Cancer Res* 2010; **29**: 31 [PMID: 20380740 DOI: 10.1186/1756-9966-29-31]

154 **Lee HJ**, Kim SW, Kim HY, Li S, Yun HJ, Song KS, Kim S, Jo DY. Chemokine receptor CXCR4 expression, function, and clinical implications in gastric cancer. *Int J Oncol* 2009; **34**: 473-480 [PMID: 19148483]

155 **Zhao BC**, Zhao B, Han JG, Ma HC, Wang ZJ. Adipose-derived stem cells promote gastric cancer cell growth, migration and invasion through SDF-1/CXCR4 axis. *Hepatogastroenterology* 2010; **57**: 1382-1389 [PMID: 21443090]

156 **Zhao BC**, Wang ZJ, Mao WZ, Ma HC, Han JG, Zhao B, Xu HM. CXCR4/SDF-1 axis is involved in lymph node metastasis of gastric carcinoma. *World J Gastroenterol* 2011; **17**: 2389-2396 [PMID: 21633638 DOI: 10.3748/wjg.v17.i19.2389]

157 **Yasumoto K**, Koizumi K, Kawashima A, Saitoh Y, Arita Y, Shinohara K, Minami T, Nakayama T, Sakurai H, Takahashi Y, Yoshie O, Saiki I. Role of the CXCL12/CXCR4 axis in peritoneal carcinomatosis of gastric cancer. *Cancer Res* 2006; **66**: 2181-2187 [PMID: 16489019 DOI: 10.1158/0008-5472.CAN-05-3393]

158 **Ingold B**, Simon E, Ungethüm U, Kuban RJ, Müller BM, Lupp A, Neumann U, Ebert MP, Denkert C, Weichert W, Schulz S, Röcken C. Vascular CXCR4 expression - a novel antiangiogenic target in gastric cancer? *PLoS One* 2010; **5**: e10087 [PMID: 20386750 DOI: 10.1371/journal.pone.0010087]

159 **Ishigami S**, Natsugoe S, Okumura H, Matsumoto M, Nakajo A, Uenosono Y, Arigami T, Uchikado Y, Setoyama T, Arima H, Hokita S, Aikou T. Clinical implication of CXCL12 expression in gastric cancer. *Ann Surg Oncol* 2007; **14**: 3154-3158 [PMID: 17653799 DOI: 10.1245/s10434-007-9521-6]

160 **Nathoo N**, Chahlavi A, Barnett GH, Toms SA. Pathobiology of brain metastases. *J Clin Pathol* 2005; **58**: 237-242 [PMID: 15735152 DOI: 10.1136/jcp.2003.013623]

161 **Krueger S**, Hundertmark T, Kalinski T, Peitz U, Wex T, Malfertheiner P, Naumann M, Roessner A. Helicobacter pylori encoding the pathogenicity island activates matrix metalloproteinase 1 in gastric epithelial cells via JNK and ERK. *J Biol Chem* 2006; **281**: 2868-2875 [PMID: 16321971 DOI: 10.1074/jbc.M511053200]

162 **Crawford HC**, Krishna US, Israel DA, Matrisian LM, Washington MK, Peek RM Jr. Helicobacter pylori strain-selective induction of matrix metalloproteinase-7 in vitro and within gastric mucosa. *Gastroenterology* 2003; **125**: 1125–1136 [PMID: 14517796 DOI: 10.1016/S0016-5085(03)01206-X]

163 **Wroblewski LE**, Noble PJ, Pagliocca A, Pritchard DM, Hart CA, Campbell F, Dodson AR, Dockray GJ, Varro A. Stimulation of MMP-7 (matrilysin) by Helicobacter pylori in human gastric epithelial cells: role in epithelial cell migration. *J Cell Sci* 2003; **116**: 3017-3026 [PMID: 12808021 DOI: 10.1242/jcs.00518]

164 **McCaig C**, Duval C, Hemers E, Steele I, Pritchard DM, Przemeck S, Dimaline R, Ahmed S, Bodger K, Kerrigan DD, Wang TC, Dockray GJ, Varro A. The role of matrix metalloproteinase-7 in redefining the gastric microenvironment in response to Helicobacter pylori. *Gastroenterology* 2006; **130**: 1754-1763 [PMID: 16697739 DOI: 10.1053/j.gastro.2006.02.031]

165 **Rautelin HI**, Oksanen AM, Veijola LI, Sipponen PI, Tervahartiala TI, Sorsa TA, Lauhio A. Enhanced systemic matrix metalloproteinase response in Helicobacter pylori gastritis. *Ann Med* 2009; **41**: 208-215 [PMID: 18979291 DOI: 10.1080/07853890802482452]

166 **Bergin PJ**, Raghavan S, Svensson H, Starckx S, Van Aelst I, Gjertsson I, Opdenakker G, Quiding-Järbrink M. Gastric gelatinase B/matrix metalloproteinase-9 is rapidly increased in Helicobacter felis-induced gastritis. *FEMS Immunol Med Microbiol* 2008; **52**: 88-98 [PMID: 17995959 DOI: 10.1111/j.1574-695X.2007.00349.x]

167 **Wu JY**, Lu H, Sun Y, Graham DY, Cheung HS, Yamaoka Y. Balance between polyoma enhancing activator 3 and activator protein 1 regulates Helicobacter pylori-stimulated matrix metalloproteinase 1 expression. *Cancer Res* 2006; **66**: 5111-5120 [PMID: 16707434 DOI: 10.1158/0008-5472.CAN-06-0383]

168 **Ogden SR**, Wroblewski LE, Weydig C, Romero-Gallo J, O'Brien DP, Israel DA, Krishna US, Fingleton B, Reynolds AB, Wessler S, Peek RM. p120 and Kaiso regulate Helicobacter pylori-induced expression of matrix metalloproteinase-7. *Mol Biol Cell* 2008; **19**: 4110-4121 [PMID: 18653469 DOI: 10.1091/mbc.E08-03-0283]

169 **Yonemura Y**, Endou Y, Fujita H, Fushida S, Bandou E, Taniguchi K, Miwa K, Sugiyama K, Sasaki T. Role of MMP-7 in the formation of peritoneal dissemination in gastric cancer. *Gastric Cancer* 2000; **3**: 63-70 [PMID: 11984713 DOI: 10.1007/PL00011698]

170 **Yin Y**, Grabowska AM, Clarke PA, Whelband E, Robinson K, Argent RH, Tobias A, Kumari R, Atherton JC, Watson SA. Helicobacter pylori potentiates epithelial: mesenchymal transition in gastric cancer: links to soluble HB-EGF, gastrin and matrix metalloproteinase-7. *Gut* 2010; **59**: 1037-1045 [PMID: 20584780 DOI: 10.1136/gut.2009.199794]

171 **Bergin PJ**, Anders E, Sicheng W, Erik J, Jennie A, Hans L, Pierre M, Qiang PH, Marianne QJ. Increased production of matrix metalloproteinases in Helicobacter pylori-associated human gastritis. *Helicobacter* 2004; **9**: 201-210 [PMID: 15165255 DOI: 10.1111/j.1083-4389.2004.00232.x]

172 **Kubben FJ**, Sier CF, Schram MT, Witte AM, Veenendaal RA, van Duijn W, Verheijen JH, Hanemaaijer R, Lamers CB, Verspaget HW. Eradication of Helicobacter pylori infection favourably affects altered gastric mucosal MMP-9 levels. *Helicobacter* 2007; **12**: 498-504 [PMID: 17760717 DOI: 10.1111/j.1523-5378.2007.00527.x]

173 **Baker AH**, Edwards DR, Murphy G. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. *J Cell Sci* 2002; **115**: 3719-3727 [PMID: 12235282 DOI: 10.1242/jcs.00063]

174 **Edwards DR**, Handsley MM, Pennington CJ. The ADAM metalloproteinases. *Mol Aspects Med* 2008; **29**: 258-289 [PMID: 18762209 DOI: 10.1016/j.mam.2008.08.001]

175 **Yoshimura T**, Tomita T, Dixon MF, Axon AT, Robinson PA, Crabtree JE. ADAMs (a disintegrin and metalloproteinase) messenger RNA expression in Helicobacter pylori-infected, normal, and neoplastic gastric mucosa. *J Infect Dis* 2002; **185**: 332-340 [PMID: 11807715 DOI: 10.1086/338191]

176 **Saha A**, Backert S, Hammond CE, Gooz M, Smolka AJ. Helicobacter pylori CagL activates ADAM17 to induce repression of the gastric H, K-ATPase alpha subunit. *Gastroenterology* 2010; **139**: 239-248 [PMID: 20303353 DOI: 10.1053/j.gastro.2010.03.036]

177 **Bang YJ**, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2- positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomized controlled trial. *Lancet* 2010; **376**: 687– 697

[DOI: 10.1016/S0140-6736(10)61121-X]

178 **U.S. Food and Drug Administration.** Herceptin (trastuzumab) [prescribing information]. Available at http: //www.accessdata.fda.gov/drugsatfda\_docs/label/2010/103792s5250lbl.pdf, accessed October 26, 2011.

179 E**uropean Medicines Agency.** Herceptin [summary of product characteristics]. Available at http: //www.ema.europa.eu/docs/enMGB/document\_library/EPAR\_-\_Product\_Information/human/000278/WC500074922.pdf, accessed October 26, 2011.

180 **Ohtsu A**, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, Lim HY, Yamada Y, Wu J, Langer B, Starnawski M, Kang YK. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2011; **29**: 3968-3976 [PMID: 21844504 DOI: 10.1200/JCO.2011.36.2236]

181 **Pinto C**, Di Fabio F, Siena S, Cascinu S, Rojas Llimpe FL, Ceccarelli C, Mutri V, Giannetta L, Giaquinta S, Funaioli C, Berardi R, Longobardi C, Piana E, Martoni AA. Phase II study of cetuximab in combination with FOLFIRI in patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma (FOLCETUX study). *Ann Oncol* 2007; **18**: 510-517 [PMID: 17164226 DOI: 10.1093/annonc/mdl459]

182 **Moehler M**, Mueller A, Trarbach T, Lordick F, Seufferlein T, Kubicka S, Geissler M, Schwarz S, Galle PR, Kanzler S. Cetuximab with irinotecan, folinic acid and 5-fluorouracil as first-line treatment in advanced gastroesophageal cancer: a prospective multi-center biomarker-oriented phase II study. *Ann Oncol* 2011; **22**: 1358-1366 [PMID: 21119032 DOI: 10.1093/annonc/mdq591]

183 **Richards D**, Kocs DM, Spira AI, David McCollum A, Diab S, Hecker LI, Cohn A, Zhan F, Asmar L. Results of docetaxel plus oxaliplatin (DOCOX) ± cetuximab in patients with metastatic gastric and/or gastroesophageal junction adenocarcinoma: results of a randomised Phase 2 study. *Eur J Cancer* 2013; **49**: 2823-2831 [PMID: 23747051 DOI: 10.1016/j.ejca.2013.04.022]

184 Optimization Study in ErbB2 (HER2) Positive Gastric Cancer: A Phase III Global, Blinded Study Designed to Evaluate Clinical Endpoints and Safety of Chemotherapy Plus Lapatinib. Available at http: //www.clinicaltrials.gov/ct/show/NCT00680901, accessed January 21, 2012.

185 **Satoh T**, Bang Y, Wang J. Interim safety analysis from TYTAN: A phase III Asian study of lapatinib in combination with paclitaxel as second line therapy in gastric cancer. *J Clin Oncol* 2010; **28** suppl15: 4057

186 **Bae SH**, Ryoo HM, Kim MK, Lee KH, Sin JI, Hyun MS. Effects of the proteasome inhibitor bortezomib alone and in combination with chemotherapeutic agents in gastric cancer cell lines. *Oncol Rep* 2008; **19**: 1027-1032 [PMID: 18357392]

187 **Shah MA**, Wainberg ZA, Catenacci DV, Hochster HS, Ford J, Kunz P, Lee FC, Kallender H, Cecchi F, Rabe DC, Keer H, Martin AM, Liu Y, Gagnon R, Bonate P, Liu L, Gilmer T, Bottaro DP. Phase II study evaluating 2 dosing schedules of oral foretinib (GSK1363089), cMET/VEGFR2 inhibitor, in patients with metastatic gastric cancer. *PLoS One* 2013; **8**: e54014 [PMID: 23516391 DOI: 10.1371/journal.pone.0054014]

188 **Molife LR**, Fong PC, Paccagnella L, Reid AH, Shaw HM, Vidal L, Arkenau HT, Karavasilis V, Yap TA, Olmos D, Spicer J, Postel-Vinay S, Yin D, Lipton A, Demers L, Leitzel K, Gualberto A, de Bono JS. The insulin-like growth factor-I receptor inhibitor figitumumab (CP-751, 871) in combination with docetaxel in patients with advanced solid tumours: Results of a phase Ib dose-escalation, open-label study. *Br J Cancer* 2010; **103**: 332–339. [PMID: 20628389 DOI: 10.1038/sj.bjc.6605767]

189 **Squires M**, Ward G, Saxty G, Berdini V, Cleasby A, King P, Angibaud P, Perera T, Fazal L, Ross D, Jones CG, Madin A, Benning RK, Vickerstaffe E, O'Brien A, Frederickson M, Reader M, Hamlett C, Batey MA, Rich S, Carr M, Miller D, Feltell R, Thiru A, Bethell S, Devine LA, Graham BL, Pike A, Cosme J, Lewis EJ, Freyne E, Lyons J, Irving J, Murray C, Newell DR, Thompson NT. Potent, selective inhibitors of fibroblast growth factor receptor define fibroblast growth factor dependence in preclinical cancer models. *Mol Cancer Ther* 2011; **10**: 1542-1552 [PMID: 21764904 DOI: 10.1158/1535-7163.MCT-11-0426]

190 **Lang SA**, Klein D, Moser C, Gaumann A, Glockzin G, Dahlke MH, Dietmaier W, Bolder U, Schlitt HJ, Geissler EK, Stoeltzing O. Inhibition of heat shock protein 90 impairs epidermal growth factor-mediated signaling in gastric cancer cells and reduces tumor growth and vascularization in vivo. *Mol Cancer Ther* 2007; **6**: 1123-1132 [PMID: 17363505 DOI: 10.1158/1535-7163.MCT-06-0628]

191 **Weichert W**, Röske A, Gekeler V, Beckers T, Ebert MP, Pross M, Dietel M, Denkert C, Röcken C. Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: A retrospective analysis. *Lancet Oncol* 2008; **9**: 139-148 [PMID: 18207460 DOI:10.1016/S1470-2045(08)70004-4]

192 **Fetterly GJ**, Brady WE, LeVea CM. A phase I pharmacokinetic (PK) study of vorinostat (V) in combination with irinotecan (I), 5-fluorouracil (5FU), and leucovorin (FOLFIRI) in advanced upper gastrointestinal cancers (AGC). *J Clin Oncol* 2009; **27** suppl15: el5540

193 **Chiba T**, Marusawa H, Seno H, Watanabe N. Mechanism for gastric cancer development by Helicobacter pylori infection. *J Gastroenterol Hepatol* 2008; **23**: 1175-1181 [PMID: 18637055 DOI: 10.1111/j.1440-1746.2008.05472.x]

**P-Reviewers:** De Lusong MAA, Hasanein P, Lambrecht NW

**S-Editor:** Qi Y **L-Editor: E-Editor:**