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

**ESPS Manuscript NO: 26034**

**Manuscript Type:** **TOPIC HIGHLIGHT**

**2016 Gastric Cancer: Global view**

**Inflammatory microenvironment contributes to epithelial-mesenchymal transition in gastric cancer**

Ma HY *et al.* Inflammation and EMT in gastric cancer

Hui-Ying Ma, Xin-Zhou Liu, Chun-Min Liang

**Hui-Ying Ma, Xin-Zhou Liu, Chun-Min Liang,** Lab of Tumor Immunology, Department of Anatomy and Histology and Embryology, Shanghai Medical College of Fudan University, Shanghai 200032, China

**Author contributions:** Ma HY and Liu XZ collected data and drafted the manuscript; Liang CM supervised and revised the manuscript.

**Supported by** National Science Foundation of China, No. 31471147.

**Conflict-of-interest statement:** The authors certify that there is no actual or potential conflict of interest and publication copyright in relation to this article.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Chun-Min Liang, MD, PhD,** Lab of Tumor Immunology, Department of Anatomy and Histology and Embryology, Shanghai Medical College of Fudan University, 138 Yixueyuan Road, Shanghai 200032, China. cmliang@fudan.edu.cn

**Telephone:** +86-21-54237027

**Fax:** +86-21-54237027

**Received:** March 28, 2016

**Peer-review started:** March 28, 2016

**First decision:** May 30, 2016

**Revised:** June 12, 2016

**Accepted:** July 6, 2016

**Article in press:**

**Published online:**

**Abstract**

Gastric cancer (GC) is the fifth most common malignancy in the world. The major cause of GC is chronic infection with *Helicobacter pylori* (*H. pylori*)*.* Infection with *H. pylori* leads to an active inflammatory microenvironment that is maintained by immune cells such as T cells, macrophages, natural killer cells, among other cells. Immune cell dysfunction allows the initiation and accumulation of mutations in GC cells, inducing aberrant proliferation and protection from apoptosis. Meanwhile, immune cells can secrete certain signals, including cytokines, and chemokines, to alter intracellular signaling pathways in GC cells. Thus, GC cells obtain the ability to metastasize to lymph nodes by undergoing the epithelial-mesenchymal transition (EMT), whereby epithelial cells lose their epithelial attributes and acquire a mesenchymal cell phenotype. Metastasis is a leading cause of death for GC patients, and the involved mechanisms are still under investigation. In this review, we summarize the current research on how the inflammatory environment affects GC initiation and metastasis *via* EMT.

**Key words:** Gastric cancer; Inflammation; Epithelial-mesenchymal transition; Microenvironment; Immune cells

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The major cause of gastric cancer (GC) is *Helicobacter pylori* infection, resulting in an inflammatory microenvironment in GC. Meanwhile, the leading cause of death for GC patients is metastasis. The major pathway for metastasis is the epithelial-mesenchymal transition (EMT). Therefore, a thorough understanding of how the inflammatory microenvironment contributes to the promotion of the EMT is indispensable for developing new treatments. In this review, we summarize the mechanisms of inflammatory mediators, divided among immune cells and molecules, on the prognosis of GC patients and EMT, which suggests that a combination of immunotherapy and anti-EMT treatments may be encouraging for the treatment of GC.

Ma HY, Liu XZ, Liang CM. Inflammatory microenvironment contributes to epithelial-mesenchymal transition in gastric cancer. *World J Gastroenterol* 2016; In press

**INTRODUCTION**

Gastric cancer (GC) was the fifth most common malignancy and the third leading cause of cancer worldwide in 2012. Almost one million new cases were estimated to have occurred annually. More than 70% of these occurred in developing countries, and approximately half of all cases worldwide (405000 cases) were diagnosed in China[[1](#_ENREF_1)]. Two histologically distinct types of GC have described: diffuse-type, in which infiltrating neoplastic cells exists individually, and intestinal-type, which initiates from normal mucosa, transiting to chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, and finally to dysplasia and adenocarcinoma[[2](#_ENREF_2)]. In recent years, improvements in endoscopic detection and treatment strategies such as surgical resection and chemotherapy have contributed to 5-year survival rates of approximately 60% in Japan[[3](#_ENREF_3)]. However, despite multimodal therapy, the average overall 5-year survival worldwide still remain at 40%[[4](#_ENREF_4),[5](#_ENREF_5)], while in the United States, the 5-year survival rate is only 26%[[6](#_ENREF_6)], and more than 60% of patients will develop local relapse or metastatic disease[[4](#_ENREF_4)]. Therefore, investigating the mechanisms underlying the initiation and progression of GC will help improve early detection and treatment efficiency.

GC is the result of the accumulation of genomic damage that affects cellular functions essential for cancer development[[7](#_ENREF_7)]. The major cause of GC is chronic infection with the Gram-negative bacterium *Helicobacter pylori* (*H. pylori)*, which contributes to more than 75% of GC cases[[8](#_ENREF_8)]. Although in the past, *H. pylori* infection has been regarded as a risk factor for GC and is categorized as a Group 1 carcinogen for humans[[9-11](#_ENREF_9)], only a small number of infected individuals develop GC (approximately 2%-3% of the total infected individuals)[[12](#_ENREF_12)], which makes *H .pylori* status an unclear predictor of GC prognosis. Some studies have yielded contrasting findings, showing that GC patients with positive *H. pylori* infection have better disease-free survival and overall survival, whereas negative *H. pylori* infection indicates poor prognosis in GC patients[[13](#_ENREF_13),[14](#_ENREF_14)]. Recent meta-analyses further showed that instead of serving as a risk factor, *H. pylori* statuscould act as a protective factor in predicting GC progression[[15](#_ENREF_15)], leading to further confusion. Another key factor leading to approximately 10% of GC cases is Epstein-Barr virus (EBV) infection[[16](#_ENREF_16)]. A meta-analysis of 13 studies showed that EBV-positive patients have decreased survival, which indicates that EBV might serve as a predictive factor[[17](#_ENREF_17)]. However, studies on the role of EBV are still in their infancy. Although the relationship between *H. pylori* or EBV and the prognosis of GC patients is unclear, the fact remains that these infections can induce physiological and morphological changes within the gastric epithelium, resulting in an increased risk of neoplastic transformations such as hypochlorhydria and gastric atrophy, which are precursors of GC. The induced inflammatory microenvironment recruits more immune cells that secrete aberrant factors such TGF-β, which may further lead to tumor cell metastasis, which is a major factor in the poor survival of GC patients[[18](#_ENREF_18)].

**METASTASIS AND EPITHELIAL-MESENCHYMAL TRANSITION**

A key process in promoting tumor cells metastasis is the epithelial-mesenchymal transition (EMT), which is a process by which epithelial cells lose their epithelial attributes and acquire a mesenchymal cell phenotype[[19](#_ENREF_19),[20](#_ENREF_20)]. During this process, epithelial tumor cells are endowed with three main changes. First, cell morphology changes from a cobblestone-like monolayer of epithelial cells with apical-basal polarity to spindle-shaped mesenchymal cells with migratory pseudopodia or filopodia structures. Second, the cytoskeleton and intercellular junctions are reorganized with changes in differentiation markers such as the loss of E-cadherin and increased expression of Vimentin and Fibronectin. Third, functional changes are shown to potentiate angiogenesis and intrastation through enhanced protease expression, allowing invasion through the extracellular matrix (ECM)[[21](#_ENREF_21),[22](#_ENREF_22)]. EMT also increases resistance to apoptosis and contributes to the survival of circulating tumor cells[[23](#_ENREF_23)]. Not all of these changes are invariably observed during EMT; however, the ability to migrate and invade the ECM as a single cell is regarded as marking the functional completion of the EMT program.

The development of EMT involves many different signaling pathways. Transforming growth factor-β (TGF-β) is recognized as a potent inducer of the EMT, acting at translational, post-translational, transcriptional and post-transcriptional levels[[24](#_ENREF_24)]. After signal binds to TGF-β receptors, the EMT is initiated by either the phosphorylation of Smad2/3/4, which induces the transcription of Snail or Slug[[25](#_ENREF_25),[26](#_ENREF_26)], or through non-Smad signaling pathways, including the PI3K/Akt-mTOR pathway[[27](#_ENREF_27),[28](#_ENREF_28)], the RHO-GTPase pathway[[29](#_ENREF_29),[30](#_ENREF_30)], and the ERK, p38 and JUN N-terminal kinase (JNK) MAPK pathways[[31-33](#_ENREF_31)]. Aside from TGF-β receptors, receptor tyrosine kinases also contribute to the initiation of the EMT through the activation of the PI3K/Akt and ERK signaling pathways, which promotes cell mobility and invasive behavior[[34-36](#_ENREF_34)]. Some studies have also found that the frizzled receptor, Notch receptor, and patched (PTC) receptors as well as the IL-6 receptor can participate in EMT progression by activating the Wnt and STAT signaling, among other pathways[[37-40](#_ENREF_37)]. To activate these pathways, ligands must first bind to membrane receptors, for example, cytokines found in the GC microenvironment, such as TGF-β1 and IL-1β. These inflammatory cytokines are thought to be released from recruited immune cells, endothelial cells and fibroblasts[[41](#_ENREF_41)], indicating that members of the microenvironment regulate EMT progression.

**INFLAMMATION AND EMT IN GC**

The connection between inflammation and cancer has been studied for years, and chronic inflammation is thought to be a key contributor to tumor development[[42](#_ENREF_42)]. Chronic inflammation is a protective response to damage to tissue homeostasis, inducing a prolonged, aberrant form called a “wound”[[43](#_ENREF_43)]. The so-called “wound” continuously recruits immune cells and other protective cells and induces their secretion of inflammatory mediators. During this state, despite the excessive mediators, the damaged cells will amplify and divide frequently, leading the microenvironment to become oxidative and thus increasing the likelihood of DNA damage and mutations. Once the key damage or mutation occurs, the damaged cells start to secret pro-inflammatory cytokines to keep them active and revert themselves to tumor cells. Meanwhile, these cells manage to escape from immune surveillance and modify infiltrating immune cells into tumor-associated immune cells, which assists tumor progression rather than immune inhibition. These changes result in a “wound” that never heals and promote tumor initiation, progression and metastasis[[44-47](#_ENREF_44)]. Given that more than 85% of GC is caused by infection, which induces inflammation, inflammation is accepted as a major diver of gastric carcinogenesis[[48](#_ENREF_48),[49](#_ENREF_49)].

The tumor-associated microenvironment is characterized by tumor infiltrating lymphocytes (TILs), the secretion of inflammatory mediators and angiogenesis. TILs interact with tumor cells *via* inflammatory molecules such as cytokines (TGF-β, TNF-α, IL-6, IL-1β), chemokines (CC- and CXC- receptors) and matrix metalloproteinases (MMPs), which form an inflammatory network[[42](#_ENREF_42)]. Unfortunately, these molecules are also inducers of the EMT (Table 1), which may explain how inflammation contributes to GC cells metastasis. Upon infection by *H. pylori*, the level of soluble HB-EGF shedding is up-regulated, which further induces GC cells to undergo the EMT. This process partially relies on the expression of gastrin and MMP7[[50](#_ENREF_50),[51](#_ENREF_51)]. GC EMT could also be induced by *H. pylori* cytotoxin-associated gene A (CagA), which downregulates E-cadherin expression and increases the expression of vimentin and twist[[52](#_ENREF_52)]. Eradication of *H. pylori* reduces the expression of TGF-β1 while increasing E-cadherin expression, indicating that *H. pylori* maytrigger TGF-β1-induced EMT[[53](#_ENREF_53)]. The development and metastasis of tumor cells may occur because GC cells escape immune surveillance or because immune cells become helpers for GC cells. Therefore, the tumor-related inflammatory microenvironment has an important role in regulating GC EMT, mainly through interactions with infiltrating immune cells.

***Immune cells and EMT***

The major infiltrating functional immune cells in GC are T cells, macrophages, NK cells, DCs and MDSCs[[54](#_ENREF_54)].

T cells are mainly divided into CD8+ cytotoxic T cells and CD4+ T helper cells[[55](#_ENREF_55)]. CD8+ cytotoxic T cells (CTLs) exert active antitumor effects, and previous work has shown that GC patients with high CD8+ CTL infiltration display better prognoses[[56](#_ENREF_56)]. However, other work has shown that higher CD8+ CTLs do not indicate good outcomes with metastasis due to the occurrence of adaptive immune resistance, such as the ratio of CD8+ CTLs with programmed death-ligand 1 (PD-L1)[[57](#_ENREF_57)]. Meanwhile, CTLs can also produce IL-17 to promote inflammation and result in a poor prognosis[[58](#_ENREF_58)]. EBV-specific CD8+ CTL injection significantly reduced tumor growth and metastasis in mouse models of GC[[59](#_ENREF_59)]. Thus, treatment with autologous CD8+ CTL injection for GC patients and patients with metastatic GC seems promising[[60](#_ENREF_60)].

Naïve CD4+ T helper cells can differentiate into several subsets, including Th1, Th2, Treg, and Th17, by secreting various cytokines such as TGF-β, IL-10, and IFN-γ, which are also inducers of the EMT[[55](#_ENREF_55),[61](#_ENREF_61)]. CD4+ T cell subsets are found at significantly lower levels in metastatic tumor draining lymph nodes (TDLNs) than in metastasis-free TDLNs, which indicates that metastasis is a consequence of the loss of CD4+ T cells[[62](#_ENREF_62)]. Th1 (IFN-γ producing) and Th2 (IL-4 producing) cells play key roles in anti-tumor immunity. The balance between these two cell types can alter antitumor activity, as shown in human peripheral blood: a high Th1/Th2 ratio correlates with a better prognosis and less metastasis[[63](#_ENREF_63)]. An expansion of Th17 cells is found in GC patients’ tissues and peripheral blood, especially in patients with metastasis. High levels of IL-1β, IL-21, IL-17 and TGF-β expression are also observed, which will induce macrophages to produce more IL-6 and IL-8 to activate the NF-κB pathway and might be a reason why metastasis occurs through the induction of the EMT[[64-67](#_ENREF_64)]. Another important CD4+ T cell subset related to GC progression at CD4+ suppressor T lymphocytes, or Tregs, that express Foxp3. Higher Foxp3+ Treg infiltration is correlated with GC metastasis and poor prognosis[[68-70](#_ENREF_68)]. Similar to Th1 and Th2, the ratio of Foxp3+/CD4+ and Foxp3+/CD8+ cells is very important for the suppression of metastasis[[68](#_ENREF_68),[71](#_ENREF_71)].

Macrophages are among the most important immune cells that infiltrate the tumor microenvironment and include the following two phenotypes: M1 macrophages, which facilitate anti-tumor activity, and M2 macrophages, or tumor-associated macrophages (TAMs), which promote tumor progression[[72](#_ENREF_72)]. Although macrophages can secrete cytokines such as IL-25 to hamper tumor growth and metastasis, large amounts of infiltration by TAMs disrupt this process[[73](#_ENREF_73)]. TAM infiltration in GC can promote angiogenesis and lymphangiogenesis and predict poor overall survival[[74-76](#_ENREF_74)]; hence, TAMs are regarded as a promising therapeutic target[[77](#_ENREF_77)]. When TAMs are co-cultured with GC cells, the metastatic ability of GC cells increases, which might be the result of TGF-β1 secretion activating the TGF-β and NF-κB signaling pathways[[78](#_ENREF_78),[79](#_ENREF_79)]. IL-8, which is secreted by surrounding TAMs, could also be an inducer of GC cell metastasis, especially under hypoxic conditions[[80-82](#_ENREF_80)]. Meanwhile, chemokine factors can affect the relation between TAMs and GC cells. High CXCL12 expression on GC cells can recruit TAMs[[83](#_ENREF_83)]. Recruited TAMs then secret CCL5, which activates the STAT3 signaling pathway, leading to tumor growth and invasion[[84](#_ENREF_84)]. Activation of the NF-κB or STAT3 signaling pathway can elevate the expression of certain proteins related to mesenchymal phenotypes, such as Vimentin. In this way, GC cells start to undergo the EMT, which ultimately assists in metastasis[[85](#_ENREF_85),[86](#_ENREF_86)].

NK cells play an important role in regulating GC development and metastasis by directly clearing tumor cells. Previous studies found that in GC patients, the expression of NKG2D, an activating receptor specifically expressed on NK cells, is higher compared with healthy controls, with the same trend observed when comparing GC patients with and without lymph node metastasis[[87](#_ENREF_87),[88](#_ENREF_88)]. This NK cell dysfunction may be related to TGF-β1 levels[[89](#_ENREF_89)]. These groups of immune cells are unable to inhibit GC progression mainly due to their loss or dysfunction.

DCs are the cells that process and present antigens to T cells[[90](#_ENREF_90)]. However, their numbers still make a difference in controlling GC progression. Patients with lower DC infiltration have less lymph node metastasis and show a favorable prognosis[[91-93](#_ENREF_91)]. This effect might due to the elevated IL-1β expression and decreased IL-10 expression produced by DCs through the activation of the NF-κB signaling pathway[[94](#_ENREF_94),[95](#_ENREF_95)], which further affects the metastatic ability of GC cells. MDSCs are a relatively heterogeneous population of cells. Their expansion during cancer is associated with advanced GC stages and indicates poor prognosis[[96](#_ENREF_96),[97](#_ENREF_97)]. However, studies of MDSC function in GC are still very limited.

***Inflammatory molecules and EMT***

Inflammatory mediators are factors that act directly on tumor cells and are secreted by both GC cells and infiltrating cells in the surrounding microenvironment. These mediators can be divided into three groups: cytokines, chemokines and MMPs.

Cytokines can be secreted by all constituents of the tumor microenvironment and appears to modify the EMT of GC cells, including TNF-α, IL-8, TGFβ, TGF-α, and IL-6[[98](#_ENREF_98)]. TNF-α levels are increased by TNF-α-inducing protein (Tipα), which is released by *H. pylori.* The binding of Tipα to its membrane receptor activates the NF-κB signaling pathway, resulting in the transcription of TNF-α, which further increases the expression of N-cadherin and vimentin to enable GC cell migration and metastasis[[99-101](#_ENREF_99)]. Increased of IL-8 levels promote the EMT in GC cells at early stages of GC progression through the activation of the NF-κB pathway[[102](#_ENREF_102)]. TGFβ is the most potent and common inducer of the EMT. High TGF-β1 expression indicates poor prognosis in GC patients and is related to lymph node metastasis through the activation of the TGF-β signaling pathway[[103](#_ENREF_103),[104](#_ENREF_104)]. Inhibition of this pathway can inhibit EMT-mediated migration and invasion[[105-107](#_ENREF_105)]. TGF-α is involved in the EMT and is associated with poor OS in GC patients[[108](#_ENREF_108)]. IL-6 can rescue GC cell resistance to anti-tumor drugs and EMT by activating the STAT3 pathway[[109](#_ENREF_109),[110](#_ENREF_110)].

Chemokines are a group of secreted proteins that are produced in response to pro-inflammatory stimuli and most commonly participate in the chemotaxis of leukocyte trafficking and positioning. Current studies show that chemokines are also involved in tumor growth, angiogenesis, EMT, metastasis and immune evasion[[111-113](#_ENREF_111)]. The two most important chemokine receptors in GC are CXCR4 and CCR7. CXCR4 expression is associated with aggressive tumor behaviors such as invasion and metastasis[[114](#_ENREF_114)]. After binding its ligand CXCL12, actin polymerization is activated to induce cell motility and the EMT[[108](#_ENREF_108),[115](#_ENREF_115),[116](#_ENREF_116)]. The CXCL12-CXCR4 axis alters the migratory and invasive ability of GC cells by upregulating the expression of MMP-2 and MMP-7 to assist EMT progression[[108](#_ENREF_108),[117](#_ENREF_117)]. Meanwhile, CXCL12 can recruit myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment to promote the progression of gastric cancer[[58](#_ENREF_58)]. CCR7 is another important chemokine receptor in the progression of GC. CCR7 is associated with lymph node metastasis in GC patients[[70](#_ENREF_70),[118](#_ENREF_118)]. Through the activation of CCR7 signaling or the TGF-β1 signaling pathway, GC cells initiate the EMT by altering the expression of E-cadherin, MMP-9, and Snail, which enable them to metastasize, and led by CCR7, they metastasize toward lymph vessels, which is why GC cells metastasize to lymph nodes[[119](#_ENREF_119),[120](#_ENREF_120)].

After infection by pathogens such as *H. pylori,* the expression of matrix metalloproteinase (MMP) family is upregulated because the pathogens need to secrete proteins to assist their adherence to epithelial gastric cells[[121](#_ENREF_121),[122](#_ENREF_122)]. The MMP family is among the most important inducers of the EMT through the degradation of the extracellular matrix (ECM) and basement membrane barriers[[123](#_ENREF_123)]. Increased expression of MMP-2 and MMP-9 is reported to enhance the invasion ability of GC cells and correlates with metastatic GC[[124-126](#_ENREF_124)]. Elevated MMP-7 levels can be used as a biomarker for *H. pylori*-related GC and potentially regulate the progression of GC through the EMT[[51](#_ENREF_51),[127](#_ENREF_127),[128](#_ENREF_128)]. MMP7-/- mice infected with *H. pylori* show increased levels of M1 macrophages, which enhance the inflammatory response[[129](#_ENREF_129),[130](#_ENREF_130)]. However, the precise mechanism of how MMPs regulate the EMT of GC needs to be clarified in the future.

**CONCLUSION**

The progression of GC is mainly caused by microbial pathogens and is closely related to host inflammatory factors. The inflammatory microenvironment enables the host immune system to not only combat pathogens but also to secrete cytokines to stimulate normal gastric epithelial cells to protect themselves. During this process, the altered microenvironment may cause random mutations to occur in gastric cells. Once these mutations accumulate to a certain level, the process will continue without restoring normal homeostasis. Thus, the infection starts to become an adenoma followed by a carcinoma. Meanwhile, in the gastric cancer microenvironment, the aberrant secretion by immune cells might lead to dysfunction and also stimulate GC cells to become resistant. In this way, GC cells are likely to gain the ability to continuously proliferate, become protected from apoptosis and escape immune surveillance. Through alterations in their signaling pathways, GC cells begin to translate more mesenchymal proteins such as MMP and vimentin, allowing them to migrate and invade into the blood and lymph vessels to metastasize, otherwise known as the EMT. Current studies mainly focus on the immune cells and GC prognosis and the effects on metastasis. However, studies on the mechanisms by which immune cells alter GC cells undergoing the EMT in the inflammatory microenvironment are still very limited. As long as GC metastasis is a major cause of death, targeting the EMT combined with immunotherapy shows promising results for the treatment of GC in the future.

**ACKNOWLEDGMENTS**

The authors thank Jessie Yang for assistance in recording the audio core tip.

**REFERENCES**

1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

2 **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]

3 **Kim HS**, Lee H, Jeung HC, Noh SH, Chung HC, Roh JK, Nam CM, Rha SY. Advanced detection of recent changing trends in gastric cancer survival: up-to-date comparison by period analysis. *Jpn J Clin Oncol* 2011; **41**: 1344-1350 [PMID: 22128316 DOI: 10.1093/jjco/hyr153]

4 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

5 **Macdonald JS**, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; **345**: 725-730 [PMID: 11547741 DOI: 10.1056/NEJMoa010187]

6 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; **63**: 11-30 [PMID: 23335087 DOI: 10.3322/caac.21166]

7 **Guggenheim DE**, Shah MA. Gastric cancer epidemiology and risk factors. *J Surg Oncol* 2013; **107**: 230-236 [PMID: 23129495 DOI: 10.1002/jso.23262]

8 **Herrera V**, Parsonnet J. Helicobacter pylori and gastric adenocarcinoma. *Clin Microbiol Infect* 2009; **15**: 971-976 [PMID: 19874380 DOI: 10.1111/j.1469-0691.2009.03031.x]

9 **Forman D**, Newell DG, Fullerton F, Yarnell JW, Stacey AR, Wald N, Sitas F. Association between infection with Helicobacter pylori and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 1991; **302**: 1302-1305 [PMID: 2059685]

10 **Helicobacter**, Cancer Collaborative G. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353 [PMID: 11511555]

11 **Parsonnet J**, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, Sibley RK. Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127-1131 [PMID: 1891020 DOI: 10.1056/NEJM199110173251603]

12 **Conteduca V**, Sansonno D, Lauletta G, Russi S, Ingravallo G, Dammacco F. H. pylori infection and gastric cancer: state of the art (review). *Int J Oncol* 2013; **42**: 5-18 [PMID: 23165522 DOI: 10.3892/ijo.2012.1701]

13 **Meimarakis G**, Winter H, Assmann I, Kopp R, Lehn N, Kist M, Stolte M, Jauch KW, Hatz RA. Helicobacter pylori as a prognostic indicator after curative resection of gastric carcinoma: a prospective study. *Lancet Oncol* 2006; **7**: 211-222 [PMID: 16510330 DOI: 10.1016/S1470-2045(06)70586-1]

14 **Marrelli D**, Pedrazzani C, Berardi A, Corso G, Neri A, Garosi L, Vindigni C, Santucci A, Figura N, Roviello F. Negative Helicobacter pylori status is associated with poor prognosis in patients with gastric cancer. *Cancer* 2009; **115**: 2071-2080 [PMID: 19280589 DOI: 10.1002/cncr.24253]

15 **Wang F**, Sun G, Zou Y, Zhong F, Ma T, Li X. Protective role of Helicobacter pylori infection in prognosis of gastric cancer: evidence from 2,454 patients with gastric cancer. *PLoS One* 2013; **8**: e62440 [PMID: 23667477 DOI: 10.1371/journal.pone.0062440]

16 **Iizasa H**, Nanbo A, Nishikawa J, Jinushi M, Yoshiyama H. Epstein-Barr Virus (EBV)-associated gastric carcinoma. *Viruses* 2012; **4**: 3420-3439 [PMID: 23342366]

17 **Camargo MC**, Kim WH, Chiaravalli AM, Kim KM, Corvalan AH, Matsuo K, Yu J, Sung JJ, Herrera-Goepfert R, Meneses-Gonzalez F, Kijima Y, Natsugoe S, Liao LM, Lissowska J, Kim S, Hu N, Gonzalez CA, Yatabe Y, Koriyama C, Hewitt SM, Akiba S, Gulley ML, Taylor PR, Rabkin CS. Improved survival of gastric cancer with tumour Epstein-Barr virus positivity: an international pooled analysis. *Gut* 2014; **63**: 236-243 [PMID: 23580779 DOI: 10.1136/gutjnl-2013-304531]

18 **Li N**, Xie C, Lu NH. Transforming growth factor-β: an important mediator in Helicobacter pylori-associated pathogenesis. *Front Cell Infect Microbiol* 2015; **5**: 77 [PMID: 26583078 DOI: 10.3389/fcimb.2015.00077]

19 **Thiery JP**. Epithelial-mesenchymal transitions in tumour progression. *Nat Rev Cancer* 2002; **2**: 442-454 [PMID: 12189386 DOI: 10.1038/nrc822]

20 **Greenburg G**, Hay ED. Epithelia suspended in collagen gels can lose polarity and express characteristics of migrating mesenchymal cells. *J Cell Biol* 1982; **95**: 333-339 [PMID: 7142291]

21 **Boyer B**, Thiery JP. Epithelium-mesenchyme interconversion as example of epithelial plasticity. *APMIS* 1993; **101**: 257-268 [PMID: 8323734]

22 **Hay ED**. An overview of epithelio-mesenchymal transformation. *Acta Anat (Basel)* 1995; **154**: 8-20 [PMID: 8714286]

23 **Thiery JP**, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell* 2009; **139**: 871-890 [PMID: 19945376 DOI: 10.1016/j.cell.2009.11.007]

24 **Lamouille S**, Xu J, Derynck R. Molecular mechanisms of epithelial-mesenchymal transition. *Nat Rev Mol Cell Biol* 2014; **15**: 178-196 [PMID: 24556840 DOI: 10.1038/nrm3758]

25 **Mani SA**, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M, Campbell LL, Polyak K, Brisken C, Yang J, Weinberg RA. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell* 2008; **133**: 704-715 [PMID: 18485877 DOI: 10.1016/j.cell.2008.03.027]

26 **Feng XH**, Derynck R. Specificity and versatility in tgf-beta signaling through Smads. *Annu Rev Cell Dev Biol* 2005; **21**: 659-693 [PMID: 16212511 DOI: 10.1146/annurev.cellbio.21.022404.142018]

27 **Lamouille S**, Connolly E, Smyth JW, Akhurst RJ, Derynck R. TGF-β-induced activation of mTOR complex 2 drives epithelial-mesenchymal transition and cell invasion. *J Cell Sci* 2012; **125**: 1259-1273 [PMID: 22399812 DOI: 10.1242/jcs.095299]

28 **Lamouille S**, Derynck R. Cell size and invasion in TGF-beta-induced epithelial to mesenchymal transition is regulated by activation of the mTOR pathway. *J Cell Biol* 2007; **178**: 437-451 [PMID: 17646396 DOI: 10.1083/jcb.200611146]

29 **Bhowmick NA**, Ghiassi M, Bakin A, Aakre M, Lundquist CA, Engel ME, Arteaga CL, Moses HL. Transforming growth factor-beta1 mediates epithelial to mesenchymal transdifferentiation through a RhoA-dependent mechanism. *Mol Biol Cell* 2001; **12**: 27-36 [PMID: 11160820]

30 **Tsapara A**, Luthert P, Greenwood J, Hill CS, Matter K, Balda MS. The RhoA activator GEF-H1/Lfc is a transforming growth factor-beta target gene and effector that regulates alpha-smooth muscle actin expression and cell migration. *Mol Biol Cell* 2010; **21**: 860-870 [PMID: 20089843 DOI: 10.1091/mbc.E09-07-0567]

31 **Yamashita M**, Fatyol K, Jin C, Wang X, Liu Z, Zhang YE. TRAF6 mediates Smad-independent activation of JNK and p38 by TGF-beta. *Mol Cell* 2008; **31**: 918-924 [PMID: 18922473 DOI: 10.1016/j.molcel.2008.09.002]

32 **Xie L**, Law BK, Chytil AM, Brown KA, Aakre ME, Moses HL. Activation of the Erk pathway is required for TGF-beta1-induced EMT in vitro. *Neoplasia* 2004; **6**: 603-610 [PMID: 15548370 DOI: 10.1593/neo.04241]

33 **Marchetti A**, Colletti M, Cozzolino AM, Steindler C, Lunadei M, Mancone C, Tripodi M. ERK5/MAPK is activated by TGFbeta in hepatocytes and required for the GSK-3beta-mediated Snail protein stabilization. *Cell Signal* 2008; **20**: 2113-2118 [PMID: 18760348 DOI: 10.1016/j.cellsig.2008.08.002]

34 **Doehn U**, Hauge C, Frank SR, Jensen CJ, Duda K, Nielsen JV, Cohen MS, Johansen JV, Winther BR, Lund LR, Winther O, Taunton J, Hansen SH, Frödin M. RSK is a principal effector of the RAS-ERK pathway for eliciting a coordinate promotile/invasive gene program and phenotype in epithelial cells. *Mol Cell* 2009; **35**: 511-522 [PMID: 19716794 DOI: 10.1016/j.molcel.2009.08.002]

35 **Graham TR**, Zhau HE, Odero-Marah VA, Osunkoya AO, Kimbro KS, Tighiouart M, Liu T, Simons JW, O'Regan RM. Insulin-like growth factor-I-dependent up-regulation of ZEB1 drives epithelial-to-mesenchymal transition in human prostate cancer cells. *Cancer Res* 2008; **68**: 2479-2488 [PMID: 18381457 DOI: 10.1158/0008-5472.CAN-07-2559]

36 **Lo HW**, Hsu SC, Xia W, Cao X, Shih JY, Wei Y, Abbruzzese JL, Hortobagyi GN, Hung MC. Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression. *Cancer Res* 2007; **67**: 9066-9076 [PMID: 17909010 DOI: 10.1158/0008-5472.CAN-07-0575]

37 **Brabletz T**, Jung A, Reu S, Porzner M, Hlubek F, Kunz-Schughart LA, Knuechel R, Kirchner T. Variable beta-catenin expression in colorectal cancers indicates tumor progression driven by the tumor environment. *Proc Natl Acad Sci U S A* 2001; **98**: 10356-10361 [PMID: 11526241 DOI: 10.1073/pnas.171610498]

38 **Li X**, Deng W, Nail CD, Bailey SK, Kraus MH, Ruppert JM, Lobo-Ruppert SM. Snail induction is an early response to Gli1 that determines the efficiency of epithelial transformation. *Oncogene* 2006; **25**: 609-621 [PMID: 16158046 DOI: 10.1038/sj.onc.1209077]

39 **Xie M**, Zhang L, He CS, Xu F, Liu JL, Hu ZH, Zhao LP, Tian Y. Activation of Notch-1 enhances epithelial-mesenchymal transition in gefitinib-acquired resistant lung cancer cells. *J Cell Biochem* 2012; **113**: 1501-1513 [PMID: 22173954 DOI: 10.1002/jcb.24019]

40 **Sullivan NJ**, Sasser AK, Axel AE, Vesuna F, Raman V, Ramirez N, Oberyszyn TM, Hall BM. Interleukin-6 induces an epithelial-mesenchymal transition phenotype in human breast cancer cells. *Oncogene* 2009; **28**: 2940-2947 [PMID: 19581928 DOI: 10.1038/onc.2009.180]

41 **Hanahan D**, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell* 2012; **21**: 309-322 [PMID: 22439926 DOI: 10.1016/j.ccr.2012.02.022]

42 **Elinav E**, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer* 2013; **13**: 759-771 [PMID: 24154716 DOI: 10.1038/nrc3611]

43 **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]

44 **Medzhitov R**. Origin and physiological roles of inflammation. *Nature* 2008; **454**: 428-435 [PMID: 18650913 DOI: 10.1038/nature07201]

45 **Coussens LM**, Werb Z. Inflammation and cancer. *Nature* 2002; **420**: 860-867 [PMID: 12490959 DOI: 10.1038/nature01322]

46 **de Visser KE**, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. *Nat Rev Cancer* 2006; **6**: 24-37 [PMID: 16397525 DOI: 10.1038/nrc1782]

47 **Virchow R**. An Address on the Value of Pathological Experiments. *Br Med J* 1881; **2**: 198-203 [PMID: 20749954]

48 **Hardbower DM**, de Sablet T, Chaturvedi R, Wilson KT. Chronic inflammation and oxidative stress: the smoking gun for Helicobacter pylori-induced gastric cancer? *Gut Microbes* 2013; **4**: 475-481 [PMID: 23811829 DOI: 10.4161/gmic.25583]

49 **Wang F**, Meng W, Wang B, Qiao L. Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett* 2014; **345**: 196-202 [PMID: 23981572 DOI: 10.1016/j.canlet.2013.08.016]

50 **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]

51 **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]

52 **Yu H**, Zeng J, Liang X, Wang W, Zhou Y, Sun Y, Liu S, Li W, Chen C, Jia J. Helicobacter pylori promotes epithelial-mesenchymal transition in gastric cancer by downregulating programmed cell death protein 4 (PDCD4). *PLoS One* 2014; **9**: e105306 [PMID: 25144746 DOI: 10.1371/journal.pone.0105306]

53 **Choi YJ**, Kim N, Chang H, Lee HS, Park SM, Park JH, Shin CM, Kim JM, Kim JS, Lee DH, Jung HC. Helicobacter pylori-induced epithelial-mesenchymal transition, a potential role of gastric cancer initiation and an emergence of stem cells. *Carcinogenesis* 2015; **36**: 553-563 [PMID: 25784376 DOI: 10.1093/carcin/bgv022]

54 **Diakos CI**, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014; **15**: e493-e503 [PMID: 25281468 DOI: 10.1016/S1470-2045(14)70263-3]

55 **Subhash VV**, Yeo MS, Tan WL, Yong WP. Strategies and Advancements in Harnessing the Immune System for Gastric Cancer Immunotherapy. *J Immunol Res* 2015; **2015**: 308574 [PMID: 26579545 DOI: 10.1155/2015/308574]

56 **Lee HE**, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, Kim WH. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. *Br J Cancer* 2008; **99**: 1704-1711 [PMID: 18941457 DOI: 10.1038/sj.bjc.6604738]

57 **Thompson ED**, Zahurak M, Murphy A, Cornish T, Cuka N, Abdelfatah E, Yang S, Duncan M, Ahuja N, Taube JM, Anders RA, Kelly RJ. Patterns of PD-L1 expression and CD8 T cell infiltration in gastric adenocarcinomas and associated immune stroma. *Gut* 2016 Jan 22; Epub ahead of print [PMID: 26801886 DOI: 10.1136/gutjnl-2015-310839]

58 **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. CD8(+) T cells that produce interleukin-17 regulate myeloid-derived suppressor cells and are associated with survival time of patients with gastric cancer. *Gastroenterology* 2012; **143**: 951-62.e8 [PMID: 22710190 DOI: 10.1053/j.gastro.2012.06.010]

59 **Choi BK**, Lee SC, Lee MJ, Kim YH, Kim YW, Ryu KW, Lee JH, Shin SM, Lee SH, Suzuki S, Oh HS, Kim CH, Lee DG, Hwang SH, Yu EM, Lee IO, Kwon BS. 4-1BB-based isolation and expansion of CD8+ T cells specific for self-tumor and non-self-tumor antigens for adoptive T-cell therapy. *J Immunother* 2014; **37**: 225-236 [PMID: 24714356 DOI: 10.1097/CJI.0000000000000027]

60 **Turcotte S**, Gros A, Tran E, Lee CC, Wunderlich JR, Robbins PF, Rosenberg SA. Tumor-reactive CD8+ T cells in metastatic gastrointestinal cancer refractory to chemotherapy. *Clin Cancer Res* 2014; **20**: 331-343 [PMID: 24218514 DOI: 10.1158/1078-0432.CCR-13-1736]

61 **Lee K**, Hwang H, Nam KT. Immune response and the tumor microenvironment: how they communicate to regulate gastric cancer. *Gut Liver* 2014; **8**: 131-139 [PMID: 24672653 DOI: 10.5009/gnl.2014.8.2.131]

62 **Okita Y**, Ohira M, Tanaka H, Tokumoto M, Go Y, Sakurai K, Toyokawa T, Kubo N, Muguruma K, Sawada T, Maeda K, Hirakawa K. Alteration of CD4 T cell subsets in metastatic lymph nodes of human gastric cancer. *Oncol Rep* 2015; **34**: 639-647 [PMID: 26081040 DOI: 10.3892/or.2015.4064]

63 **Ubukata H**, Motohashi G, Tabuchi T, Nagata H, Konishi S, Tabuchi T. Evaluations of interferon-γ/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. *J Surg Oncol* 2010; **102**: 742-747 [PMID: 20872813 DOI: 10.1002/jso.21725]

64 **Liu T**, Peng L, Yu P, Zhao Y, Shi Y, Mao X, Chen W, Cheng P, Wang T, Chen N, Zhang J, Liu X, Li N, Guo G, Tong W, Zhuang Y, Zou Q. Increased circulating Th22 and Th17 cells are associated with tumor progression and patient survival in human gastric cancer. *J Clin Immunol* 2012; **32**: 1332-1339 [PMID: 22760549 DOI: 10.1007/s10875-012-9718-8]

65 **Su Z**, Sun Y, Zhu H, Liu Y, Lin X, Shen H, Chen J, Xu W, Xu H. Th17 cell expansion in gastric cancer may contribute to cancer development and metastasis. *Immunol Res* 2014; **58**: 118-124 [PMID: 24402773 DOI: 10.1007/s12026-013-8483-y]

66 **Fossiez F**, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, Pin JJ, Garrone P, Garcia E, Saeland S, Blanchard D, Gaillard C, Das Mahapatra B, Rouvier E, Golstein P, Banchereau J, Lebecque S. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J Exp Med* 1996; **183**: 2593-2603 [PMID: 8676080]

67 **Bizama C**, Benavente F, Salvatierra E, Gutiérrez-Moraga A, Espinoza JA, Fernández EA, Roa I, Mazzolini G, Sagredo EA, Gidekel M, Podhajcer OL. The low-abundance transcriptome reveals novel biomarkers, specific intracellular pathways and targetable genes associated with advanced gastric cancer. *Int J Cancer* 2014; **134**: 755-764 [PMID: 23907728 DOI: 10.1002/ijc.28405]

68 **Shen Z**, Zhou S, Wang Y, Li RL, Zhong C, Liang C, Sun Y. Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer. *J Cancer Res Clin Oncol* 2010; **136**: 1585-1595 [PMID: 20221835 DOI: 10.1007/s00432-010-0816-9]

69 **Lee HE**, Park DJ, Kim WH, Kim HH, Lee HS. High FOXP3+ regulatory T-cell density in the sentinel lymph node is associated with downstream non-sentinel lymph-node metastasis in gastric cancer. *Br J Cancer* 2011; **105**: 413-419 [PMID: 21730981 DOI: 10.1038/bjc.2011.248]

70 **Zhou S**, Shen Z, Wang Y, Ma H, Xu S, Qin J, Chen L, Tao H, Zhen Z, Chen G, Zhang Z, Li R, Xiao H, Zhong C, Yang Y, Liang C. CCR7 expression and intratumoral FOXP3+ regulatory T cells are correlated with overall survival and lymph node metastasis in gastric cancer. *PLoS One* 2013; **8**: e74430 [PMID: 24040244 DOI: 10.1371/journal.pone.0074430]

71 **Kim HI**, Kim H, Cho HW, Kim SY, Song KJ, Hyung WJ, Park CG, Kim CB. The ratio of intra-tumoral regulatory T cells (Foxp3+)/helper T cells (CD4+) is a prognostic factor and associated with recurrence pattern in gastric cardia cancer. *J Surg Oncol* 2011; **104**: 728-733 [PMID: 21792941 DOI: 10.1002/jso.22038]

72 **Rojas A**, Delgado-Lopez F, Gonzalez I. Tumor-associated macrophages in gastric cancer: more than bystanders in tumor microenvironment. *Gastric Cancer* 2016; Epub ahead of print [PMID: 26894296 DOI: 10.1007/s10120-016-0596-2]

73 **Li J**, Liao Y, Ding T, Wang B, Yu X, Chu Y, Xu J, Zheng L. Tumor-infiltrating macrophages express interleukin-25 and predict a favorable prognosis in patients with gastric cancer after radical resection. *Oncotarget* 2016; **7**: 11083-11093 [PMID: 26840565 DOI: 10.18632/oncotarget.7095]

74 **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]

75 **Wu H**, Xu JB, He YL, Peng JJ, Zhang XH, Chen CQ, Li W, Cai SR. Tumor-associated macrophages promote angiogenesis and lymphangiogenesis of gastric cancer. *J Surg Oncol* 2012; **106**: 462-468 [PMID: 22488237 DOI: 10.1002/jso.23110]

76 **Zhang H**, Wang X, Shen Z, Xu J, Qin J, Sun Y. Infiltration of diametrically polarized macrophages predicts overall survival of patients with gastric cancer after surgical resection. *Gastric Cancer* 2015; **18**: 740-750 [PMID: 25231913 DOI: 10.1007/s10120-014-0422-7]

77 **Yamaguchi T**, Fushida S, Yamamoto Y, Tsukada T, Kinoshita J, Oyama K, Miyashita T, Tajima H, Ninomiya I, Munesue S, Harashima A, Harada S, Yamamoto H, Ohta T. Tumor-associated macrophages of the M2 phenotype contribute to progression in gastric cancer with peritoneal dissemination. *Gastric Cancer* 2015; Epub ahead of print [PMID: 26621525 DOI: 10.1007/s10120-015-0579-8]

78 **Luo H**, Hao Y, Tang B, Zeng D, Shi Y, Yu P. Mouse forestomach carcinoma cells immunosuppress macrophages through TGF-β1. *Turk J Gastroenterol* 2012; **23**: 658-665 [PMID: 23794301]

79 **Shen Z**, Kauttu T, Cao J, Seppänen H, Vainionpää S, Ye Y, Wang S, Mustonen H, Puolakkainen P. Macrophage coculture enhanced invasion of gastric cancer cells via TGF-β and BMP pathways. *Scand J Gastroenterol* 2013; **48**: 466-472 [PMID: 23517295 DOI: 10.3109/00365521.2013.772226]

80 **Shen Z**, Seppänen H, Vainionpää S, Ye Y, Wang S, Mustonen H, Puolakkainen P. IL10, IL11, IL18 are differently expressed in CD14+ TAMs and play different role in regulating the invasion of gastric cancer cells under hypoxia. *Cytokine* 2012; **59**: 352-357 [PMID: 22595646 DOI: 10.1016/j.cyto.2012.04.033]

81 **Shen Z**, Ye Y, Kauttu T, Seppänen H, Vainionpää S, Wang S, Mustonen H, Puolakkainen P. The novel focal adhesion gene kindlin-2 promotes the invasion of gastric cancer cells mediated by tumor-associated macrophages. *Oncol Rep* 2013; **29**: 791-797 [PMID: 23151599 DOI: 10.3892/or.2012.2137]

82 **Shen Z**, Kauttu T, Seppänen H, Vainionpää S, Ye Y, Wang S, Mustonen H, Puolakkainen P. Both macrophages and hypoxia play critical role in regulating invasion of gastric cancer in vitro. *Acta Oncol* 2013; **52**: 852-860 [PMID: 23193956 DOI: 10.3109/0284186X.2012.718444]

83 **Park JY**, Sung JY, Lee J, Park YK, Kim YW, Kim GY, Won KY, Lim SJ. Polarized CD163+ tumor-associated macrophages are associated with increased angiogenesis and CXCL12 expression in gastric cancer. *Clin Res Hepatol Gastroenterol* 2016; **40**: 357-365 [PMID: 26508473 DOI: 10.1016/j.clinre.2015.09.005]

84 **Ding H**, Zhao L, Dai S, Li L, Wang F, Shan B. CCL5 secreted by tumor associated macrophages may be a new target in treatment of gastric cancer. *Biomed Pharmacother* 2016; **77**: 142-149 [PMID: 26796278 DOI: 10.1016/j.biopha.2015.12.004]

85 **Zhang J**, Yan Y, Yang Y, Wang L, Li M, Wang J, Liu X, Duan X, Wang J. High Infiltration of Tumor-Associated Macrophages Influences Poor Prognosis in Human Gastric Cancer Patients, Associates With the Phenomenon of EMT. *Medicine (Baltimore)* 2016; **95**: e2636 [PMID: 26871785 DOI: 10.1097/MD.0000000000002636]

86 **Yang T**, Zhang X, Wang M, Zhang J, Huang F, Cai J, Zhang Q, Mao F, Zhu W, Qian H, Xu W. Activation of mesenchymal stem cells by macrophages prompts human gastric cancer growth through NF-κB pathway. *PLoS One* 2014; **9**: e97569 [PMID: 24824968 DOI: 10.1371/journal.pone.0097569]

87 **Saito H**, Osaki T, Ikeguchi M. Decreased NKG2D expression on NK cells correlates with impaired NK cell function in patients with gastric cancer. *Gastric Cancer* 2012; **15**: 27-33 [PMID: 21626292 DOI: 10.1007/s10120-011-0059-8]

88 **Nio Y**, Shiraishi T, Imai S, Tsubono M, Morimoto H, Tseng CC, Tobe T. The clinical status and histopathological factors affecting natural killer cells of peripheral blood lymphocytes in patients with gastric cancer. *J Clin Lab Immunol* 1991; **35**: 97-108 [PMID: 1668768]

89 **Yoon SJ**, Heo DS, Kang SH, Lee KH, Kim WS, Kim GP, Lee JA, Lee KS, Bang YJ, Kim NK. Natural killer cell activity depression in peripheral blood and ascites from gastric cancer patients with high TGF-beta 1 expression. *Anticancer Res* 1998; **18**: 1591-1596 [PMID: 9673375]

90 **Rhee I**, Zhong MC, Reizis B, Cheong C, Veillette A. Control of dendritic cell migration, T cell-dependent immunity, and autoimmunity by protein tyrosine phosphatase PTPN12 expressed in dendritic cells. *Mol Cell Biol* 2014; **34**: 888-899 [PMID: 24366546 DOI: 10.1128/MCB.01369-13]

91 **Ishigami S**, Natsugoe S, Tokuda K, Nakajo A, Xiangming C, Iwashige H, Aridome K, Hokita S, Aikou T. Clinical impact of intratumoral natural killer cell and dendritic cell infiltration in gastric cancer. *Cancer Lett* 2000; **159**: 103-108 [PMID: 10974412]

92 **Ananiev J**, Gulubova MV, Manolova IM. Prognostic significance of CD83 positive tumor-infiltrating dendritic cells and expression of TGF-beta 1 in human gastric cancer. *Hepatogastroenterology* 2011; **58**: 1834-1840 [PMID: 22086706 DOI: 10.5754/hge10320]

93 **Hu M**, Li K, Maskey N, Xu Z, Peng C, Wang B, Li Y, Yang G. Decreased intratumoral Foxp3 Tregs and increased dendritic cell density by neoadjuvant chemotherapy associated with favorable prognosis in advanced gastric cancer. *Int J Clin Exp Pathol* 2014; **7**: 4685-4694 [PMID: 25197340]

94 **Kim JE**, Lee JY, Kang MJ, Jeong YJ, Choi JA, Oh SM, Lee KB, Park JH. Withaferin A Inhibits Helicobacter pylori-induced Production of IL-1β in Dendritic Cells by Regulating NF-κB and NLRP3 Inflammasome Activation. *Immune Netw* 2015; **15**: 269-277 [PMID: 26770181 DOI: 10.4110/in.2015.15.6.269]

95 **Chang LL**, Wang SW, Wu IC, Yu FJ, Su YC, Chen YP, Wu DC, Kuo CH, Hung CH. Impaired dendritic cell maturation and IL-10 production following H. pylori stimulation in gastric cancer patients. *Appl Microbiol Biotechnol* 2012; **96**: 211-220 [PMID: 22526791 DOI: 10.1007/s00253-012-4034-z]

96 **Wang L**, Chang EW, Wong SC, Ong SM, Chong DQ, Ling KL. Increased myeloid-derived suppressor cells in gastric cancer correlate with cancer stage and plasma S100A8/A9 proinflammatory proteins. *J Immunol* 2013; **190**: 794-804 [PMID: 23248262 DOI: 10.4049/jimmunol.1202088]

97 **Gabitass RF**, Annels NE, Stocken DD, Pandha HA, Middleton GW. Elevated myeloid-derived suppressor cells in pancreatic, esophageal and gastric cancer are an independent prognostic factor and are associated with significant elevation of the Th2 cytokine interleukin-13. *Cancer Immunol Immunother* 2011; **60**: 1419-1430 [PMID: 21644036 DOI: 10.1007/s00262-011-1028-0]

98 **Sansone P**, Bromberg J. Environment, inflammation, and cancer. *Curr Opin Genet Dev* 2011; **21**: 80-85 [PMID: 21144738 DOI: 10.1016/j.gde.2010.11.001]

99 **Suganuma M**, Kurusu M, Suzuki K, Nishizono A, Murakami K, Fujioka T, Fujiki H. New tumor necrosis factor-alpha-inducing protein released from Helicobacter pylori for gastric cancer progression. *J Cancer Res Clin Oncol* 2005; **131**: 305-313 [PMID: 15616827 DOI: 10.1007/s00432-004-0652-x]

100 **Watanabe T**, Takahashi A, Suzuki K, Kurusu-Kanno M, Yamaguchi K, Fujiki H, Suganuma M. Epithelial-mesenchymal transition in human gastric cancer cell lines induced by TNF-α-inducing protein of Helicobacter pylori. *Int J Cancer* 2014; **134**: 2373-2382 [PMID: 24249671 DOI: 10.1002/ijc.28582]

101 **Watanabe T**, Tsuge H, Imagawa T, Kise D, Hirano K, Beppu M, Takahashi A, Yamaguchi K, Fujiki H, Suganuma M. Nucleolin as cell surface receptor for tumor necrosis factor-alpha inducing protein: a carcinogenic factor of Helicobacter pylori. *J Cancer Res Clin Oncol* 2010; **136**: 911-921 [PMID: 20049476 DOI: 10.1007/s00432-009-0733-y]

102 **Chung HW**, Jang S, Kim H, Lim JB. Combined targeting of high-mobility group box-1 and interleukin-8 to control micrometastasis potential in gastric cancer. *Int J Cancer* 2015; **137**: 1598-1609 [PMID: 25821182 DOI: 10.1002/ijc.29539]

103 **Ma H**, Wei Y, Leng Y, Li S, Gao L, Hu H, Chen L, Wang F, Xiao H, Zhu C, Liang C. TGF-β1-induced expression of Id-1 is associated with tumor progression in gastric cancer. *Med Oncol* 2014; **31**: 19 [PMID: 24861919 DOI: 10.1007/s12032-014-0019-3]

104 **Hu WQ**, Wang LW, Yuan JP, Yan SG, Li JD, Zhao HL, Peng CW, Yang GF, Li Y. High expression of transform growth factor beta 1 in gastric cancer confers worse outcome: results of a cohort study on 184 patients. *Hepatogastroenterology* 2014; **61**: 245-250 [PMID: 24895830]

105 **Matsuoka J**, Yashiro M, Doi Y, Fuyuhiro Y, Kato Y, Shinto O, Noda S, Kashiwagi S, Aomatsu N, Hirakawa T, Hasegawa T, Shimizu K, Shimizu T, Miwa A, Yamada N, Sawada T, Hirakawa K. Hypoxia stimulates the EMT of gastric cancer cells through autocrine TGFβ signaling. *PLoS One* 2013; **8**: e62310 [PMID: 23690936 DOI: 10.1371/journal.pone.0062310]

106 **Shinto O**, Yashiro M, Kawajiri H, Shimizu K, Shimizu T, Miwa A, Hirakawa K. Inhibitory effect of a TGFbeta receptor type-I inhibitor, Ki26894, on invasiveness of scirrhous gastric cancer cells. *Br J Cancer* 2010; **102**: 844-851 [PMID: 20145621 DOI: 10.1038/sj.bjc.6605561]

107 **Chen F**, Zhuang M, Peng J, Wang X, Huang T, Li S, Lin M, Lin H, Xu Y, Li J, Chen Z, Huang Y. Baicalein inhibits migration and invasion of gastric cancer cells through suppression of the TGF-β signaling pathway. *Mol Med Rep* 2014; **10**: 1999-2003 [PMID: 25109410 DOI: 10.3892/mmr.2014.2452]

108 **Fanelli MF**, Chinen LT, Begnami MD, Costa WL, Fregnami JH, Soares FA, Montagnini AL. The influence of transforming growth factor-α, cyclooxygenase-2, matrix metalloproteinase (MMP)-7, MMP-9 and CXCR4 proteins involved in epithelial-mesenchymal transition on overall survival of patients with gastric cancer. *Histopathology* 2012; **61**: 153-161 [PMID: 22582975 DOI: 10.1111/j.1365-2559.2011.04139.x]

109 **Li P**, Shan JX, Chen XH, Zhang D, Su LP, Huang XY, Yu BQ, Zhi QM, Li CL, Wang YQ, Tomei S, Cai Q, Ji J, Li JF, Chouchane L, Yu YY, Sun FZ, Xu ZH, Liu BY, Zhu ZG. Epigenetic silencing of microRNA-149 in cancer-associated fibroblasts mediates prostaglandin E2/interleukin-6 signaling in the tumor microenvironment. *Cell Res* 2015; **25**: 588-603 [PMID: 25916550 DOI: 10.1038/cr.2015.51]

110 **Yang Z**, Guo L, Liu D, Sun L, Chen H, Deng Q, Liu Y, Yu M, Ma Y, Guo N, Shi M. Acquisition of resistance to trastuzumab in gastric cancer cells is associated with activation of IL-6/STAT3/Jagged-1/Notch positive feedback loop. *Oncotarget* 2015; **6**: 5072-5087 [PMID: 25669984 DOI: 10.18632/oncotarget.3241]

111 **Sarvaiya PJ**, Guo D, Ulasov I, Gabikian P, Lesniak MS. Chemokines in tumor progression and metastasis. *Oncotarget* 2013; **4**: 2171-2185 [PMID: 24259307 DOI: 10.18632/oncotarget.1426]

112 **Liang CM**, Chen L, Hu H, Ma HY, Gao LL, Qin J, Zhong CP. Chemokines and their receptors play important roles in the development of hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 1390-1402 [PMID: 26052384 DOI: 10.4254/wjh.v7.i10.1390]

113 **Lee HJ**, Song IC, Yun HJ, Jo DY, Kim S. CXC chemokines and chemokine receptors in gastric cancer: from basic findings towards therapeutic targeting. *World J Gastroenterol* 2014; **20**: 1681-1693 [PMID: 24587647 DOI: 10.3748/wjg.v20.i7.1681]

114 **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]

115 **Chen G**, Chen SM, Wang X, Ding XF, Ding J, Meng LH. Inhibition of chemokine (CXC motif) ligand 12/chemokine (CXC motif) receptor 4 axis (CXCL12/CXCR4)-mediated cell migration by targeting mammalian target of rapamycin (mTOR) pathway in human gastric carcinoma cells. *J Biol Chem* 2012; **287**: 12132-12141 [PMID: 22337890 DOI: 10.1074/jbc.M111.302299]

116 **Oh YS**, Kim HY, Song IC, Yun HJ, Jo DY, Kim S, Lee HJ. Hypoxia induces CXCR4 expression and biological activity in gastric cancer cells through activation of hypoxia-inducible factor-1α. *Oncol Rep* 2012; **28**: 2239-2246 [PMID: 23023480 DOI: 10.3892/or.2012.2063]

117 **Hashimoto I**, Koizumi K, Tatematsu M, Minami T, Cho S, Takeno N, Nakashima A, Sakurai H, Saito S, Tsukada K, Saiki I. Blocking on the CXCR4/mTOR signalling pathway induces the anti-metastatic properties and autophagic cell death in peritoneal disseminated gastric cancer cells. *Eur J Cancer* 2008; **44**: 1022-1029 [PMID: 18375114 DOI: 10.1016/j.ejca.2008.02.043]

118 **Mashino K**, Sadanaga N, Yamaguchi H, Tanaka F, Ohta M, Shibuta K, Inoue H, Mori M. Expression of chemokine receptor CCR7 is associated with lymph node metastasis of gastric carcinoma. *Cancer Res* 2002; **62**: 2937-2941 [PMID: 12019175]

119 **Zhang J**, Zhou Y, Yang Y. CCR7 pathway induces epithelial-mesenchymal transition through up-regulation of Snail signaling in gastric cancer. *Med Oncol* 2015; **32**: 467 [PMID: 25572817 DOI: 10.1007/s12032-014-0467-9]

120 **Ma H**, Gao L, Li S, Qin J, Chen L, Liu X, Xu P, Wang F, Xiao H, Zhou S, Gao Q, Liu B, Sun Y, Liang C. CCR7 enhances TGF-β1-induced epithelial-mesenchymal transition and is associated with lymph node metastasis and poor overall survival in gastric cancer. *Oncotarget* 2015; **6**: 24348-24360 [PMID: 26176983 DOI: 10.18632/oncotarget.4484]

121 **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]

122 **Bebb JR**, Letley DP, Thomas RJ, Aviles F, Collins HM, Watson SA, Hand NM, Zaitoun A, Atherton JC. Helicobacter pylori upregulates matrilysin (MMP-7) in epithelial cells in vivo and in vitro in a Cag dependent manner. *Gut* 2003; **52**: 1408-1413 [PMID: 12970131]

123 **Orlichenko LS**, Radisky DC. Matrix metalloproteinases stimulate epithelial-mesenchymal transition during tumor development. *Clin Exp Metastasis* 2008; **25**: 593-600 [PMID: 18286378 DOI: 10.1007/s10585-008-9143-9]

124 **Shan YQ**, Ying RC, Zhou CH, Zhu AK, Ye J, Zhu W, Ju TF, Jin HC. MMP-9 is increased in the pathogenesis of gastric cancer by the mediation of HER2. *Cancer Gene Ther* 2015; **22**: 101-107 [PMID: 25633484 DOI: 10.1038/cgt.2014.61]

125 . Claudin-4 expression in gastric cancer cells enhances the invasion and is associated with the increased level of matrix metalloproteinase-2 and -9 expression. *Oncol Lett* 2014; **8**: 1367-1371 [PMID: 25120725 DOI: 10.3892/ol.2014.2295]

126 **Al-Batran SE**, Pauligk C, Wirtz R, Werner D, Steinmetz K, Homann N, Schmalenberg H, Hofheinz RD, Hartmann JT, Atmaca A, Altmannsberger HM, Jäger E. The validation of matrix metalloproteinase-9 mRNA gene expression as a predictor of outcome in patients with metastatic gastric cancer. *Ann Oncol* 2012; **23**: 1699-1705 [PMID: 22112973 DOI: 10.1093/annonc/mdr552]

127 **Yeh YC**, Sheu BS, Cheng HC, Wang YL, Yang HB, Wu JJ. Elevated serum matrix metalloproteinase-3 and -7 in H. pylori-related gastric cancer can be biomarkers correlating with a poor survival. *Dig Dis Sci* 2010; **55**: 1649-1657 [PMID: 19690958 DOI: 10.1007/s10620-009-0926-x]

128 **Sakamoto N**, Naito Y, Oue N, Sentani K, Uraoka N, Zarni Oo H, Yanagihara K, Aoyagi K, Sasaki H, Yasui W. MicroRNA-148a is downregulated in gastric cancer, targets MMP7, and indicates tumor invasiveness and poor prognosis. *Cancer Sci* 2014; **105**: 236-243 [PMID: 24283384 DOI: 10.1111/cas.12330]

129 **Ogden SR**, Noto JM, Allen SS, Patel DA, Romero-Gallo J, Washington MK, Fingleton B, Israel DA, Lewis ND, Wilson KT, Chaturvedi R, Zhao Z, Shyr Y, Peek RM. Matrix metalloproteinase-7 and premalignant host responses in Helicobacter pylori-infected mice. *Cancer Res* 2010; **70**: 30-35 [PMID: 20048070 DOI: 10.1158/0008-5472.CAN-09-2899]

130 **Krakowiak MS**, Noto JM, Piazuelo MB, Hardbower DM, Romero-Gallo J, Delgado A, Chaturvedi R, Correa P, Wilson KT, Peek RM. Matrix metalloproteinase 7 restrains Helicobacter pylori-induced gastric inflammation and premalignant lesions in the stomach by altering macrophage polarization. *Oncogene* 2015; **34**: 1865-1871 [PMID: 24837365 DOI: 10.1038/onc.2014.135]

131 **Kuo CH**, Liu CJ, Lu CY, Hu HM, Kuo FC, Liou YS, Yang YC, Hsieh MC, Lee OK, Wu DC, Wang SS, Chen YL. 17β-estradiol inhibits mesenchymal stem cells-induced human AGS gastric cancer cell mobility via suppression of CCL5- Src/Cas/Paxillin signaling pathway. *Int J Med Sci* 2014; **11**: 7-16 [PMID: 24396281 DOI: 10.7150/ijms.6851]

132 **Hou X**, Zhang Y, Qiao H. CCL18 promotes the invasion and migration of gastric cancer cells via ERK1/2/NF-κB signaling pathway. *Tumour Biol* 2016; **37**: 641-651 [PMID: 26242263 DOI: 10.1007/s13277-015-3825-0]

133 **Leung SY**, Yuen ST, Chu KM, Mathy JA, Li R, Chan AS, Law S, Wong J, Chen X, So S. Expression profiling identifies chemokine (C-C motif) ligand 18 as an independent prognostic indicator in gastric cancer. *Gastroenterology* 2004; **127**: 457-469 [PMID: 15300578]

134 **Li R**, Zhang H, Liu H, Lin C, Cao Y, Zhang W, Shen Z, Xu J. High expression of C-C chemokine receptor 2 associates with poor overall survival in gastric cancer patients after surgical resection. *Oncotarget* 2016 Mar 14; Epub ahead of print [PMID: 26992207 DOI: 10.18632/oncotarget.8069]

135 **Du P**, Liu Y, Ren H, Zhao J, Zhang X, Patel R, Hu C, Gan J, Huang G. Expression of chemokine receptor CCR7 is a negative prognostic factor for patients with gastric cancer: a meta-analysis. *Gastric Cancer* 2016 Mar 16; Epub ahead of print [PMID: 26984468 DOI: 10.1007/s10120-016-0602-8]

136 **Han G**, Wu D, Yang Y, Li Z, Zhang J, Li C. CrkL meditates CCL20/CCR6-induced EMT in gastric cancer. *Cytokine* 2015; **76**: 163-169 [PMID: 26044596 DOI: 10.1016/j.cyto.2015.05.009]

137 **Ohtani H**, Nakayama T, Yoshie O. In situ expression of the CCL20-CCR6 axis in lymphocyte-rich gastric cancer and its potential role in the formation of lymphoid stroma. *Pathol Int* 2011; **61**: 645-651 [PMID: 22029675 DOI: 10.1111/j.1440-1827.2011.02717.x]

138 **Wang J**, Hu W, Wu X, Wang K, Yu J, Luo B, Luo G, Wang W, Wang H, Li J, Wen J. CXCR1 promotes malignant behavior of gastric cancer cells in vitro and in vivo in AKT and ERK1/2 phosphorylation. *Int J Oncol* 2016; **48**: 2184-2196 [PMID: 26983663 DOI: 10.3892/ijo.2016.3428]

139 **Li Z**, Wang Y, Dong S, Ge C, Xiao Y, Li R, Ma X, Xue Y, Zhang Q, Lv J, Tan Q, Zhu Z, Song X, Tan J. Association of CXCR1 and 2 expressions with gastric cancer metastasis in ex vivo and tumor cell invasion in vitro. *Cytokine* 2014; **69**: 6-13 [PMID: 25022956 DOI: 10.1016/j.cyto.2014.05.004]

140 **Li K**, Zhu Z, Luo J, Fang J, Zhou H, Hu M, Maskey N, Yang G. Impact of chemokine receptor CXCR3 on tumor-infiltrating lymphocyte recruitment associated with favorable prognosis in advanced gastric cancer. *Int J Clin Exp Pathol* 2015; **8**: 14725-14732 [PMID: 26823797]

141 **Haas M**, Dimmler A, Hohenberger W, Grabenbauer GG, Niedobitek G, Distel LV. Stromal regulatory T-cells are associated with a favourable prognosis in gastric cancer of the cardia. *BMC Gastroenterol* 2009; **9**: 65 [PMID: 19732435 DOI: 10.1186/1471-230X-9-65]

142 **Yoo YA**, Kang MH, Lee HJ, Kim BH, Park JK, Kim HK, Kim JS, Oh SC. Sonic hedgehog pathway promotes metastasis and lymphangiogenesis via activation of Akt, EMT, and MMP-9 pathway in gastric cancer. *Cancer Res* 2011; **71**: 7061-7070 [PMID: 21975935 DOI: 10.1158/0008-5472.CAN-11-1338]

**P-Reviewer:** Bi J, Cao XC, Wang WH **S-Editor:** Yu J **L-Editor:** **E-Editor:**

**Table 1 Important inflammatory mediators involved in the EMT in GC**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Categories | Factors | Ref | Categories | Factors | Ref |
| Immune cells | CD8+ cytotoxic T cells | [[56](#_ENREF_56),[60](#_ENREF_60)] |  | IL-6 | [[109](#_ENREF_109),[110](#_ENREF_110)] |
|  | Th1/Th2 cells ratio | [[63](#_ENREF_63)] |  | IL-8 | [[102](#_ENREF_102)] |
|  | Th17 cells | [[64](#_ENREF_64), [65](#_ENREF_65), [67](#_ENREF_67)] | Chemokines and receptors | CCL5 | [[84](#_ENREF_84),[131](#_ENREF_131)] |
|  | Foxp3+ Tregs | [[68-70](#_ENREF_68)] |  | CCL18 | [[132](#_ENREF_132),[133](#_ENREF_133)] |
|  | Foxp3+/CD4+ ratio | [[71](#_ENREF_71)] |  | CCR2 | [[134](#_ENREF_134)] |
|  | Foxp3+/CD8+ ratio | [[68](#_ENREF_68)] |  | CCR7 | [[135](#_ENREF_135)] |
|  | NK cells | [[87-89](#_ENREF_87)] |  | CCL20-CCR6 | [[136](#_ENREF_136),[137](#_ENREF_137)] |
|  | TAMs | [[78](#_ENREF_78),[79](#_ENREF_79)] |  | CXCR1 | [[138](#_ENREF_138),[139](#_ENREF_139)] |
|  | DCs | [[93-95](#_ENREF_93)] |  | CXCR3 | [[140](#_ENREF_140)] |
|  | TAM/Foxp3+ ratio | [[141](#_ENREF_141)] |  | CXCL12-CXCR4 | [[108](#_ENREF_108),[117](#_ENREF_117)] |
| Cytokines | TGF-β1 | [[103](#_ENREF_103),[104](#_ENREF_104)] | MMPs | MMP-2 | [[125](#_ENREF_125)] |
|  | TNF-α | [[99](#_ENREF_99),[100](#_ENREF_100)] |  | MMP-9 | [[124-126](#_ENREF_124),[142](#_ENREF_142)] |
|  | TGF-α | [[108](#_ENREF_108)] |  | MMP-7 | [[51](#_ENREF_51),[127](#_ENREF_127),[128](#_ENREF_128)] |