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REVIEW

The inflammatory network in the gastrointestinal tumor microenvironment: lessons from mouse models

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Abstract Accumulating evidence has indicated that inflammatory responses are important for cancer development. Epidemiological studies have shown that regular use of non-steroidal anti-inflammatory drugs (NSAIDs) reduces the risk of colon cancer development. Subsequently, mouse genetic studies have shown that cyclooxygenase (COX)-2, one of the target molecules of NSAIDs, and its downstream product, prostaglandin E_2 (PGE_2), play an important role in gastrointestinal tumorigenesis. Bacterial infection stimulates the Toll-like receptor (TLR)/MyD88 pathway in tumor tissues, which leads to the induction of COX-2 in stromal cells, including macrophages. Induction of the COX-2/PGE_2 pathway in tumor stroma is important for the development and maintenance of an inflammatory microenvironment in gastrointestinal tumors. In such a microenvironment, tumor-associated macrophages express proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6, and these cytokines, respectively, activate the nuclear factor (NF)-κB and Stat3 transcription factors in epithelial cells, as well as in stromal cells. Recent mouse studies have uncovered the role of such an inflammatory network in the promotion of gastrointestinal tumor development. Genetically engineered and chemically induced mouse tumor models which mimic sporadic or inflammation-associated tumorigenesis were used in these studies. In this review article, we focus on mouse genetic studies using these tumor models, which have contributed to the elucidation of the molecular mechanisms associated with the inflammatory network in gastrointestinal tumors, and we also discuss the role of each pathway in cancer development. The involvement of immune cells such as macrophages, mast cells, and regulatory T cells in tumor promotion is also discussed.

Keywords Gastrointestinal cancer · Inflammation · COX-2 · NF-κB · Stat3

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Introduction

About 150 years ago, Rudolf Virchow described the presence of leukocytes in tumors, and hypothesized that the origin of cancer was at the site of chronic inflammation. It has been reported that chronic infections are associated with 15–20% of malignant cancers [1, 2]. The principal infectious agents are *Helicobacter pylori*, hepatitis B and C viruses, and the human papilloma virus, which are closely associated with gastric cancer, hepatocellular carcinoma, and cervical cancer, respectively. Moreover, about 30% of all cancers have been attributed to smoking and 20% to obesity [3], and it has been shown that both tobacco smoke and obesity can trigger inflammatory responses in the lungs and liver, respectively, which promote tumorigenesis [4, 5]. These results, together with those of other recent studies (reviewed in [6–8]), indicate that inflammation plays an important role in promoting cancer development, and "tumor-promoting inflammation" is now included in the next generation of the criteria considered to be "hallmarks of cancer" [9].

Epidemiological studies have revealed that regular use of non-steroidal anti-inflammatory drugs (NSAIDs) lowers the mortality rate from cancers in the gastrointestinal tract [10, 11]. The target molecules of NSAIDs are cyclooxygenase (COX)-1 and COX-2, and accumulating evidence has indicated that COX-2 and its downstream product, prostaglandin E_2 (PGE_2), play an important role in cancer

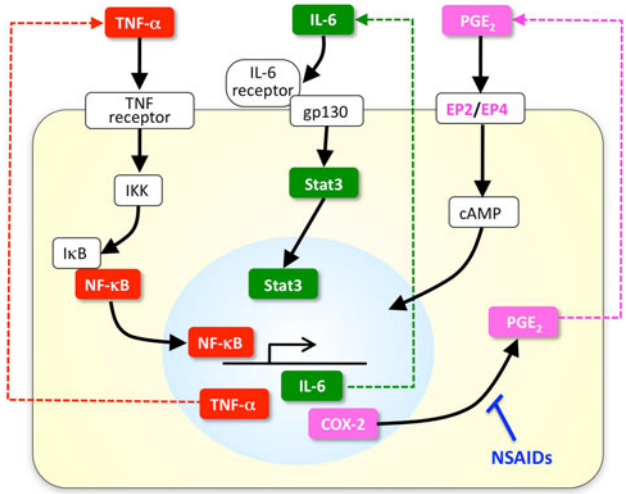

Fig. 1 The interaction of the cyclooxygenase-2 (*COX-2*)/prostaglandin E_2 (*PGE_2*), tumor necrosis factor-α (*TNF-α*)/nuclear factor-κB (*NF-κB*), and interleukin-6 (*IL-6*)/gp130/Stat3 pathways in the inflammatory environment. *cAMP* cyclic AMP, *IKK* inhibitor of κB kinase, *IκB* inhibitor of κB, *NSAIDs* non-steroidal anti-inflammatory drugs

development [12, 13]. On the other hand, proinflammatory cytokines are expressed in the tumor microenvironment, and such cytokine signaling is also important for cancer development through the activation of downstream transcription factors [6]. Among them, tumor necrosis factor (TNF)-α and interleukin (IL)-6 activate nuclear factor (NF)-κB and Stat3, respectively, and both the TNF-α/NF-κB and IL-6/Stat3 pathways have been shown to be important for the development of inflammation-associated intestinal tumorigenesis [7, 8]. Moreover, NF-κB induces the expression of COX-2, IL-6, and TNF-α. Accordingly, these signaling pathways construct an inflammatory network in the tumor microenvironment, which plays an important role in tumor promotion (Fig. 1). In this review, we discuss the roles of these inflammatory pathways in gastrointestinal tumorigenesis, which have been identified by a number of mouse model studies, as listed in Table 1.

Mouse models of gastrointestinal cancer

The roles of inflammatory responses in gastrointestinal cancers have been studied using several tumor mouse models (Table 1). $Apc^{\Delta 716}$ knockout mice and Apc^{Min} mice carry heterozygous truncation mutations at codons 716 and 850 of the mouse *Apc* gene, respectively, and somatic deletion of the wild-type *Apc* gene results in the activation of Wnt/β-catenin signaling, which causes tumor development in the entire intestinal tract [14, 15]. Approximately 80% of colorectal cancers harbor *APC* gene mutations and half of the remainder have mutations in *Ctnnb1* gene encoding β-catenin, both of which activate Wnt/β-catenin signaling [16–18]. Thus, $Apc^{\Delta 716}$ and Apc^{Min} mice recapitulate the molecular mechanism of sporadic colon cancer development. Several other types of *Apc* mutant mice also develop intestinal polyposis (as described in this review and Table 1).

On the other hand, inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are also risk factors for colorectal cancer [19, 20]. IBD-related colon cancers are associated with a severe inflammatory response, which is an important microenvironment required for inflammation-associated tumor development. The treatment of mice with a genotoxic chemical carcinogen, azoxymethane (AOM), followed by a non-genotoxic agent, dextran sodium sulfate (DSS), induces the development of colitis-associated colon cancer (CAC) [21]. Mutations in *Ctnnb1* gene induced by AOM result in the activation of the Wnt/β-catenin pathway, which is thought to trigger tumor initiation [22]. On the other hand, DSS induces colonic inflammation in rodents, which is required for tumor promotion. Accordingly, the AOM/DSS model is a well-established and widely used mouse model for CAC development, and it mimics IBD-related colon cancer (Table 1). *Rag2* gene-deficient mice lack functional lymphocytes, and are susceptible to infection-induced inflammation in the colon. When *Rag2*−/− mice are infected with the enteric bacterial pathogen, *Helicobacter hepaticus*, the mice rapidly develop CAC [23, 24]. This model system is also used for IBD-related colon cancer (Table 1).

Activation of Wnt/β-catenin signaling is found in approximately 30–50% of gastric cancers, suggesting a causal role of Wnt signaling in a subpopulation of gastric cancers [25, 26]. On the other hand, *Helicobacter pylori* infection is an important risk factor for gastric cancer [27]. In *H. pylori*-associated gastritis, COX-2 expression is induced significantly, whereas its level is decreased by *H. pylori* eradication [28, 29]. Two transgenic mouse strains, *K19-Wnt1* mice expressing *Wnt1* in the stomach, and *K19-C2mE* mice expressing *Ptgs2* and *Ptges* that encode COX-2 and microsomal PGE synthase-1 (mPGES-1), mimic Wnt activation and *H. pylori*-induced inflammation, respectively, in the stomach [26, 29–31]. *Gan* mice, which are compound transgenic mice with *K19-Wnt1* and *K19-C2mE*, express *Wnt1*, *Ptgs2*, and *Ptges* simultaneously in the gastric mucosa, resulting in the activation of both Wnt signaling and the COX-2/PGE_2 pathways, as found in human gastric cancer. *Gan* mice are thus used as a model of inflammation-associated gastric tumors [26, 30, 31] (Table 1).

The COX-2/PGE_2/EP2 pathway in gastrointestinal tumorigenesis

It has been demonstrated that treatment of familial adenomatous polyposis (FAP) patients with NSAIDs results in

Table 1 Mouse model studies performed to examine inflammatory networks in gastrointestinal tumorigenesis

Tumor model	Mouse line crossed/treatment	Tumor phenotype changes	References
Sporadic intestinal tumor model (*Apc* mutant mice)			
$Apc^{\Delta 716}$	*Ptgs2*[a] knockout mice	Suppression of intestinal polyposis	[34]
Apc^{Min}	*Ptgs1*[b], *Ptgs2* knockout mice	Suppression of intestinal polyposis	[35]
Apc^{Min}	*Hpgd*[c] knockout mice	Increase of colon polyps	[36]
AOM	*Ptgs2* transgenic mice	Increase of intestinal tumor	[37]
$Apc^{\Delta 716}$	*Ptger2*[d] knockout mice	Suppression of intestinal polyposis	[38]
		Inhibition of angiogenesis	[39]
Apc^{Min}	PGE_2 treatment	Promotion of intestinal polyposis	[40]
$Apc^{\Delta 14}$	*Ptges*[e] knockout mice	Suppression of intestinal polyposis	[44]
AOM	*Ptges* knockout mice	Suppression of intestinal polyposis	[45]
Apc^{Min}	*Myd88*[f] knockout mice	Suppression of intestinal polyposis	[63, 64]
		Epithelial expression of MyD88 is important	
$Apc^{\Delta 716}$	*op*/*op* (macrophage-deficient)	Suppression of intestinal polyposis	[93]
$Apc^{\Delta 468}$	$Kit^{W/W}$ (mast cell-deficient)	Suppression of intestinal polyposis	[76]
$Apc^{\Delta 468}$	*Rag2*−/− (lymphocyte-deficient)	Not affected	
$Apc^{\Delta 468}$	Anti-TNF-α antibody	Suppression of intestinal polyposis	
Apc^{Min}	$CD4^+$ $CD25^+$ T cell transfer	Suppression of intestinal polyposis	[94, 95]
		IL-10 expression in T cells is required	
Apc^{Min}	*Il17a*[g] knockout mice	Suppression of intestinal polyposis	[97]
Inflammation-associated colon tumor model (AOM/DSS-CAC model mice)			
AOM/DSS	*Tlr4* [h] knockout mice	Suppression of CAC development	[60, 62]
		Epithelial expression of TLR4 is important	
AOM/DSS	*Ptgs2* knockout mice	Exacerbation of CAC development	[68, 69]
AOM/DSS	*Ikbkb*[i] conditional KO	Suppression of CAC development	[72]
		Epithelial and myeloid expression is important	
AOM/DSS	*Tnfrsf1a*[j] knockout mice	Suppression of CAC development	[73]
		Myeloid expression of TNF-Rp55 is important	
AOM/DSS	*Ccr2*[k] knockout mice	Suppression of CAC development	[74]
		Less macrophage infiltration	
AOM/DSS	*Il6* [l] knockout mice	Suppression of CAC development	[82]
AOM/DSS	$gp130^{757F/F}$	Suppression of CAC development	[81]
AOM/DSS	*Stat3* conditional KO	Suppression of CAC development	[81, 82]
		Epithelial expression of Stat3 is important	
H. hepaticus infected Rag2−/−	$CD4^+$ $CD25^+$ T-cell transfer	Suppression of CAC development	[23, 24]
		IL-10 expression in T cells is required	
Gastritis and gastric tumor model			
K19-Wnt1	*K19-C2mE*	Gastric tumor development (*Gan* mice)	[26, 30, 31]
Gan	Celecoxib, EP4 inhibitor	Suppression of gastric tumorigenesis	[48, 49]
Gan	Clodronate liposome (macrophage-deficient)	Atrophic changes of tumor cells	[49]
K19-C2mE	*Tnf*[m] knockout mice	Suppression of gastritis/hyperplasia	[78]
K19-C2mE	*Rag2* knockout mice	Not affected	
$gp130^{757F/F}$	*Il11ra1*[n] knockout mice	Suppression of gastric tumorigenesis	[88]

AOM azoxymethane *DSS* dextran sodium sulfate, *CAC* colitis-associated colon cancer, *IL* interleukin, *TNF* tumor necrosis factor, *COX* cyclooxygenase, *15-PGDH* 15-hydroxyprostaglandin dehydrogenase, *TLR* Toll-like receptor, *mPGES-1* microsomal PGE synthase-1, *KO* knockout. Gene symbols used are: [a]COX-2, [b]COX-1, [c]15-PGDH, [d]PGE_2 receptor EP2, [e]mPGES-1, [f]MyD88, [g]IL-17A, [h]TLR-4, [i]IKKβ, [j]TNF-Rp55, [k]CCR2, [l]IL-6, [m]TNF-α, and [n]IL-11 receptor-α

significant regression of colon polyps [32]. Moreover, a large number of animal experiments have shown that treatment with NSAIDs suppressed chemical carcinogen-induced colon tumorigenesis [33]. As a target molecule of NSAIDs, the inducible enzyme COX-2 plays an important role in inflammation and cancer, while COX-1 is expressed constitutively and functions as a house-keeping gene. Importantly, disruption of *Ptgs2* gene in $Apc^{\Delta 716}$ mice and Apc^{Min} mice resulted in a significant suppression of intestinal tumorigenesis, thus indicating an essential role of COX-2 in intestinal polyp development [34, 35]. Interestingly, disruption of *Ptgs1* gene encoding COX-1 also suppressed intestinal tumorigenesis [35]. It is possible that COX-1-derived prostaglandins are required for tumor cell proliferation during the initial stage when COX-2 expression is not yet induced [33]. Other lines of genetic evidence also support the role of the COX-2 pathway in intestinal tumorigenesis. Prostaglandins are catalyzed and inactivated by 15-hydroxyprostaglandin dehydrogenase (15-PGDH). The number of colon polyps in Apc^{Min} mice was markedly increased when *Hpgd* gene encoding 15-PGDH was disrupted, suggesting that PGE_2 has a role in colon tumorigenesis [36]. Moreover, the transgenic expression of *Ptgs2* in the mouse intestine accelerated chemical carcinogen-induced tumorigenesis [37].

COX-2 catalyzes the synthesis of prostaglandin (PG) H_2, which is then converted to PGE_2. There are four G protein-coupled receptors for PGE_2; EP1, EP2, EP3, and EP4. Notably, disruption of *Ptger2* gene encoding EP2 caused significant suppression of intestinal polyposis in $Apc^{\Delta 716}$ mice, whereas suppression of EP1 or EP3 signaling did not affect tumorigenesis [38]. EP2 signaling increases the expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which enhances angiogenesis in intestinal tumors [39]. Moreover, treatment of Apc^{Min} mice with PGE_2 increased the development of intestinal tumors through the activation of peroxisome proliferators-activated receptor (PPAR) δ, which promotes the survival of tumor cells [40]. Furthermore, PGE_2 signaling through the EP2 receptor has been shown to activate Wnt/β-catenin signaling directly in colon cancer cells by the suppression of β-catenin phosphorylation [41]. Accordingly, it is possible that the COX-2/PGE_2 pathway contributes to intestinal tumorigenesis through a variety of PGE_2 functions [12, 13] (Fig. 2).

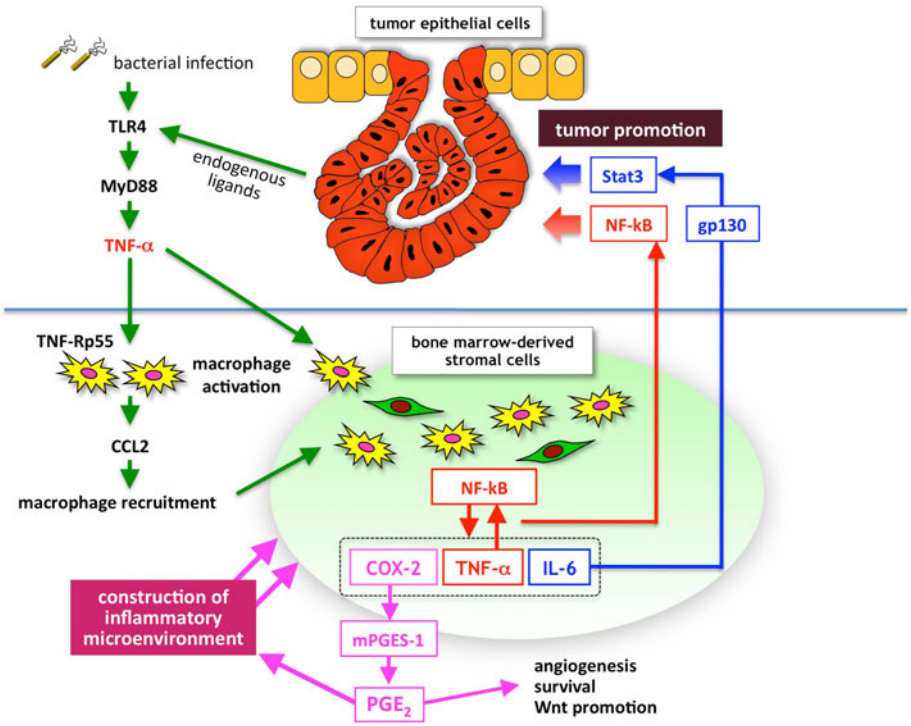

Fig. 2 A schematic diagram of the inflammatory microenvironment in gastrointestinal tumor tissues. Bacterial infection or endogenous ligand activates the Toll-like receptor (*TLR*)/MyD88 pathway in epithelial cells, which further activate stromal macrophages inducing CCL2. In the activated macrophages, NF-κB induces the expression of COX-2, IL-6, and TNF-α itself. The COX-2/PGE_2 pathway is important for the construction and maintenance of the inflammatory network, and PGE_2 accelerates angiogenesis, cell survival, and Wnt activation. TNF-α activates NF-κB in both epithelial cells and stromal macrophages, whereas IL-6 activates Stat3 in epithelial cells through gp130. NF-κB and Stat3 play an important role in the promotion of tumorigenesis through suppression of apoptosis and acceleration of the cell cycle. *mPGES-1* Microsomal PGE synthase-1

Microsomal PGE synthase-1 (mPGES-1) is an enzyme that converts PGH_2 to PGE_2, and expression of mPGES-1 is induced in gastric and colon cancers similar to COX-2 [42, 43]. Notably, disruption of *Ptges* gene encoding mPGES-1 in $Apc^{\Delta 14}$ mice or AOM-treated mice resulted in a marked decrease in the PGE_2 level in the intestinal mucosa, which led to a further significant suppression of intestinal tumorigenesis [44, 45]. Taken together, these results indicate that the simultaneous expression of COX-2 and mPGES-1 is required for intestinal tumorigenesis through the induction of PGE_2 signaling.

In gastric cancer tissues, induction of COX-2 is found in approximately 70% of cases [46, 47], and mPGES-1 expression is also induced [42], suggesting that the COX-2/PGE_2 pathway is also important for gastric tumorigenesis. In the *K19-C2mE* transgenic mice, an increased PGE_2 level causes inflammatory infiltration and metaplastic hyperplasia in the gastric mucosa [29]. Although Wnt activation alone is not sufficient for tumor development in *K19-Wnt1* mice, *Gan* mice (compound mutants of *K19-Wnt1* and *K19-C2mE* mice) develop inflammation-associated gastric tumors with 100% incidence [26], indicating that cooperation of the Wnt and PGE_2 pathways can lead to gastric tumorigenesis. Moreover, gastric inflammation and tumorigenesis were significantly suppressed in *Gan* mice when the mice were treated with a COX-2 inhibitor, celecoxib, or an EP4 receptor inhibitor [48, 49]. These results indicate that COX-2/PGE_2/EP4-induced inflammation is involved in the development of gastric cancer. Signaling through both EP2 and EP4 stimulates the intracellular cyclic AMP signaling pathway. It is therefore possible that either EP2 or EP4 receptor signaling plays an important role in gastrointestinal tumorigenesis (Fig. 1).

The Toll-like receptor (TLR)/MyD88 pathway for COX-2 induction in gastrointestinal tumors

Expression of COX-2 and mPGES-1 is detected predominantly in stromal cells, including macrophages and fibroblasts, but not in the epithelial cells of mouse intestinal polyps, and the same is true for human colon polyps [36, 50–52]. Heterozygous mutations in the *Lkb1*, *Smad4*, or *Cdx2* gene lead to the development of gastrointestinal hamartomas, which show histological characteristics distinct from those of dysplastic adenomas developed in *Apc* mutant mice [52–55]. Notably, expression of COX-2 and mPGES-1 is detected in the stromal cells, but not in tumor epithelial cells, in these models [56], thus indicating that the COX-2/PGE_2 pathway is induced in the tumor stroma by a common mechanism, regardless of the type of tumor.

Several studies have suggested the commensal flora to play a role in the homeostasis of the intestinal mucosa. Toll-like receptors (TLRs) are a family of pattern-recognition receptors that detect the molecular products of microorganisms. MyD88 is an adaptor molecule for the TLR-mediated induction of inflammatory cytokines. It has been shown that a disruption of *Tlr2/4* or *Myd88* genes encoding TLR2/4 or MyD88, respectively, in mice results in the impaired mucosal repair of DSS-induced ulcers [57], suggesting that infectious stimulation through the TLR/MyD88 pathway is important for the regeneration process of injured mucosa. Moreover, stromal macrophages are also required for the mucosal repair of DSS-induced ulcers in the colon [58]. Accordingly, it is possible that stromal macrophages are activated by the TLR/MyD88 pathway. In the case of intestinal tumorigenesis, cancer cells may use such a TLR/MyD88-induced regeneration system to increase their proliferation.

The treatment of mice with DSS induces COX-2 expression and PGE_2 production, predominantly in macrophages of the inflamed colon mucosa. However, such COX-2 induction is not found in the mice lacking the TLR4/MyD88 pathway [59], thus indicating the role of bacterial infection in inducing COX-2 expression in colitis tissues. Importantly, AOM/DSS treatment-induced colon tumor development was dramatically suppressed in *Tlr4*−/− mice [60], while exogenous administration of PGE_2 promoted CAC development in the AOM/DSS-treated *Tlr4*−/− mice [61]. Moreover, bone marrow chimera experiments have indicated that TLR4 expression in the intestinal epithelial cells, but not in myeloid cells, is required for CAC development [62]. Taken together, these results suggest that bacterial infection stimulates the TLR/MyD88 pathway in epithelial cells, which leads to activation of stromal macrophages, thus resulting in the induction of the COX-2/PGE_2 pathway in the tumor stroma (Fig. 2).

In contrast to the AOM/DSS model, intestinal polyposis in the *Apc* mutant mice is not associated with UC. It is therefore possible that COX-2 expression is induced by a different mechanism in sporadic colon cancer compared to that in IBD-related tumors. However, Apc^{Min} *Myd88*−/− mice showed significant suppression of intestinal polyposis with dramatically decreased mortality compared with control Apc^{Min} *Myd88*+/+ mice [63, 64]. Moreover, the induction of COX-2 expression was also suppressed in Apc^{Min} *Myd88*−/− mouse intestinal tumors [63]. Bone marrow chimera experiments also indicated that MyD88 expression in the epithelial cells was important for intestinal tumorigenesis [64]. These results have demonstrated that activation of the TLR/MyD88 pathway in epithelial cells is also important for COX-2 expression in non-IBD-related colon cancer (Fig. 2).

If bacterial infection is also required for COX-2 induction in the stomach, a low bacterial count due to the acidic environment in the stomach may protect against COX-2 expression in tumorous lesions. Therefore, it is possible that COX-2 induction through the TLR/MyD88 pathway is one of the important mechanisms by which *Helicobacter pylori* infection promotes gastric cancer.

It has also been shown that TLRs can be stimulated with endogenous ligands, including heat shock proteins and various products of the extracellular matrix [65]. Accordingly, it is possible that tumor cell proliferation causes tissue damage, releasing endogenous ligands for TLRs, thus resulting in their activation, which induces COX-2 expression in stromal macrophages. Such "cancer-induced inflammation" may also be one of the mechanisms responsible for the generation of an inflammatory microenvironment, especially in cancers that are not associated with infection [65].

The paradox of the COX-2 pathway in colitis-associated cancer

Although COX-2 inhibition causes suppression of gastrointestinal tumorigenesis, treatment with NSAIDs or a COX-2 inhibitor exacerbates DSS-induced colon injury in rodent models [66]. Consistently, *Ptgs2* gene knockout mice exposed to DSS showed exacerbated phenotypes, such as more severe inflammation, compared with wild-type mice [67]. One of the functions of PGE_2 is to protect the gastrointestinal mucosa. Therefore, COX-2 is important for mucosal protection and regeneration in the DSS-treated mouse colon. Notably, treatment of *Ptgs2* knockout mice with AOM/DSS resulted in a significant increase in tumors, with severe inflammatory responses [68, 69], which appears to be contradictory to the results showing that *Ptgs2* gene disruption causes significant suppression of intestinal polyposis in *Apc* mutant mice [34, 35]. It is possible that in the case of severe UC, cytokine signaling is highly activated and may be sufficient for tumor promotion if the COX-2/PGE_2 pathway is blocked (Fig. 2).

The TNF-α/NF-κB pathway in gastrointestinal tumorigenesis

TNF-α is one of key regulators of inflammatory responses. Although TNF was originally recognized as a tumor-necrotizing factor, accumulating evidence has indicated that TNF-α has tumor-promoting functions [70]. TNF-α signaling activates NF-κB, which further induces the expression of inflammatory factors including COX-2, IL-6, IL-8, and TNF-α itself (Fig. 1). Several genetic studies have demonstrated a link between the TNF-α/NF-κB pathway and cancer development [71].

Conditional disruption of *Ikbkb* gene encoding IKKβ in myeloid cells, which results in specific inhibition of NF-κB, caused significant suppression of the tumor incidence in AOM/DSS-treated mice, and was associated with decreased expression of cytokines and COX-2 [72]. Conditional deletion of *Ikbkb* in epithelial cells also suppressed AOM/DSS-induced tumorigenesis [72]. Similar results were found in TNF-α receptor gene knockout mice [73]. AOM/DSS treatment in mice lacking *Tnfrsf1a* gene encoding TNF receptor p55 (TNF-Rp55) resulted in attenuated tumor formation, with reduced inflammatory cell infiltration compared with findings in wild-type mice. Moreover, wild-type mice transplanted with *Tnfrsf1a*-deficient bone marrow developed significantly fewer tumors after AOM/DSS treatment [73], indicating that TNF-α stimulation of myeloid cells is important for tumorigenesis. Accordingly, it is possible that the TNF-α-induced NF-κB activation in myeloid cells is important for CAC development, and NF-κB activation in epithelial cells also contributes to tumor formation (Fig. 2).

It has also been shown that a disruption of *Ccr2* gene encoding a CCL2-specific receptor, CCR2, led to significantly decreased macrophage infiltration and lower tumor numbers when mice were treated with AOM/DSS [74]. CCL2 is a chemokine that is chemotactic for monocytes and macrophages [75]. Taken together, these findings indicate that the activation of NF-κB in activated macrophages by TNF-α in an autocrine or paracrine manner is important for the promotion of intestinal tumorigenesis (Fig. 2). The inhibition of TNF-α in *Apc* mutant mice by treatment with an anti-TNF-α antibody also suppressed intestinal polyposis, with the suppression of angiogenesis [76]. Accordingly, it is possible that TNF-α/NF-κB activation is important in both IBD-related and sporadic colon carcinogenesis.

An important role for the TNF-α/NF-κB pathway was also discovered in *Mdr2* knockout mice that develop inflammation-associated hepatocellular carcinoma (HCC) [77]. In this mouse model, NF-κB is activated in the liver by TNF-α signaling, and the inhibition of NF-κB significantly suppressed the development of HCC after 7 months of age [77]. On the other hand, preneoplastic dysplastic lesions in younger mice were not affected by NF-κB inhibition. It is possible that the TNF-α/NF-κB pathway is not required for the initiation step, but it does play a role in the promotion step of HCC development.

The role of the TNF-α/NF-κB pathway in gastric tumorigenesis in *Gan* mice has not yet been examined. However, *Tnf−/− K19-C2mE* mice showed significant suppression of gastritis and hyperplasia compared with control *K19-C2mE* mice, although the COX-2/PGE_2

pathway was still activated by the transgenic expression of COX-2 and mPGES-1 [78]. It is thus conceivable that the TNF-α/NF-κB pathway is activated in PGE_2-associated gastritis, and that this contributes to inflammation-associated gastric tumorigenesis.

The IL-6/gp130/Stat3 pathway in gastrointestinal tumorigenesis

One of the NF-κB-inducible cytokines is IL-6, which is important for immune responses, cell survival, apoptosis, and proliferation [79]. The expression of IL-6 is often upregulated in tumor tissues and in the sera of humans and mice with cancers, including colon cancer [80]. The IL-6 cytokine family signals through a common receptor, gp130, which activates Stat3 (Fig. 1). Stat3 plays an important role in the development of a variety of cancers, including CAC [81–84]. AOM/DSS-induced CAC development was significantly suppressed in conditional *Stat3*-knockout mice that lacked *Stat3* in the intestinal epithelial cells and also in *Il6*−/− mice [81, 82]. Survival and proliferation of tumor cells were suppressed in these mutant mice. On the other hand, the number and size of AOM/DSS-induced colon tumors increased significantly in $gp130^{757F/F}$ mice, in which gp130-dependent Stat signaling is constitutively activated [81]. These results indicate that Stat3 activated in epithelial cells plays an important role in the promotion of intestinal tumorigenesis (Fig. 2).

It has been shown that $gp130^{757F/F}$ mice develop gastric tumors with abundant infiltration of inflammatory cells [85]. Moreover, heterozygous mutations of the Stat3 gene in $gp130^{757F/F}$ mice reduced the incidence and multiplicity of gastric tumors, with the suppression of inflammatory responses [86, 87]. These results indicate that Stat3 is also an important tumor-promoting factor in gastric tumorigenesis, and that it is activated by the inflammatory network of the tumor microenvironment. Transforming growth factor (TGF)-β signaling promotes epithelial differentiation, and thus, suppression of the TGF-β signaling pathway has been thought to promote gastrointestinal tumorigenesis. Notably, the activation of Stat3 in $gp130^{757F/F}$ cells desensitizes them to TGF-β by inducing inhibitory Smad7. This may be one of the mechanisms by which Stat3 promotes tumor formation [86]. IL-11 is another member of the IL-6 cytokine family and also signals through gp130. Interestingly, disruption of the IL-11 co-receptor in $130^{757F/F}$ mice significantly ablated gastric tumorigenesis [88]. Because IL-11 is upregulated in human and mouse gastric tumors, these results suggest that the IL-11/Stat3 pathway, together with IL-6/Stat3, promotes gastric tumorigenesis.

Inflammatory cells that promote or suppress tumorigenesis

The major source of inflammatory cytokines and prostaglandins in tumor tissues is macrophages. Tumor-associated macrophages (TAMs) have been shown to promote the progression and metastasis of cancer [89]. TAMs can be classified into several distinct groups by their functions, such as inducing inflammation, invasion, angiogenesis, or metastasis. Macrophages are polarized to either the classical M1 type or the alternative M2 type, and it has been suggested that TAMs are polarized to M2 or M2-like types [90]. It has been shown that CD4+ T cells regulate the polarization of macrophages to the M2 type in mammary tumors [91]. It has recently been shown that COX-2 is important for the M2-polarization of TAMs in Apc^{Min} mouse tumors [92]. Accordingly, it is possible that the COX-2/PGE_2 pathway-induced inflammatory network is important for the education of macrophages into the protumorigenic M2 or M2-like types. Importantly, depletion of functional macrophages in $Apc^{\Delta 716}$ mice by crossing them with op/op mutant mice resulted in significant suppression of intestinal polyposis [93]. Moreover, inhibition of macrophage recruitment in AOM/DSS-treated mice by *Ccl2* gene disruption resulted in the suppression of colon tumor development [74]. Accordingly, macrophages play an important role in both sporadic and IBD-related intestinal tumorigenesis (Fig. 2). In *Gan* mouse gastric tumors, macrophage depletion caused atrophic changes of the tumor cells and apoptosis of stromal cells [49]. Accordingly, it is possible that macrophages play a role in the maintenance of both tumor epithelial cells and stromal cells.

In the $Apc^{\Delta 468}$ mouse intestinal tumors, mast cells are preferentially enriched in the polyp tissues, and these mast cells express TNF-α [76]. Notably, the depletion of mast cells in $Apc^{\Delta 468}$ mice by bone marrow transplantation from $Kit^{Wsh/Wsh}$ mice caused significant suppression of intestinal polyposis, with a decreased level of TNF-α expression. It is therefore possible that both macrophages and mast cells are important components of the inflammatory network in the tumor microenvironment.

Bone marrow transplantation from *Rag2*−/− mice did not affect the intestinal tumorigenesis in $Apc^{\Delta 468}$ mice [76]. Consistently, the gastritis phenotype was not altered in the *K19-C2mE Rag2*−/− mouse stomach [78]. These results indicate that lymphocytes are not required for the construction of the inflammatory network and the promotion of tumorigenesis in the gastrointestinal tract. Importantly, however, the adaptive transfer of $CD4^+$ $CD25^+$ regulatory T cells to Apc^{Min} mice dramatically reduced the number of intestinal polyps, with the induction of necrosis of tumor cells [94, 95]. Moreover, such regression of intestinal

polyps was not found when $CD4^+$ $CD25^+$ cells were prepared from *Il10*−/− mice.

The transfer of $CD4^+$ $CD25^+$ T cells to *Helicobacter hepaticus*-infected *Rag2*−/− mice, another IBD-related colon cancer model, resulted in suppression of colitis and tumor development, but *Il10*-disrupted $CD4^+$ $CD25^+$ T cells could not suppress the development of CAC [23, 24]. IL-10 suppresses inflammatory responses, thus indicating that regulatory T cells expressing IL-10 suppress intestinal tumorigenesis by inhibiting the formation of the inflammatory network. Although $CD25^+$ $Foxp3^+$ T cells are found in Apc^{Min} mouse polyp stroma, they no longer express IL-10, and instead switch to the production of IL-17 [95]. It is therefore possible that anti-inflammatory regulatory T cells ($Foxp3^+$ IL-10^+ IL-17^-) shift to pro-inflammatory T cells ($Foxp3^+$ IL-10^- IL-17^+) in polyp tissues [96]. Moreover, the ablation of *Il17a* gene in Apc^{Min} mice significantly suppressed the development of intestinal polyps and inflammatory cytokine expression, indicating that T-cell-derived IL-17 plays an important role in intestinal tumorigenesis [97].

Concluding remarks

The development of the inflammatory network in tumor tissues and its possible roles are summarized in Fig. 2. Chronic infection or endogenous ligands derived from tumor cells stimulate the TLRs of epithelial cells, leading to the activation of MyD88. The activation of the epithelial TLR/MyD88 pathway further induces COX-2 expression and PGE_2 production in stromal macrophages through the TNF-α/NF-κB pathway. Epidemiological studies and genetic experiments have demonstrated that COX-2 and its downstream product, PGE_2, play an important role in gastrointestinal tumorigenesis. NF-κB is activated by TNF-α in TAMs, which further induces the expression of TNF-α, IL-6, and COX-2. TNF-α in turn stimulates both tumor epithelial cells and stromal cells, activating NF-κB in these cells, which promotes tumorigenesis. On the other hand, IL-6 activates Stat3 through gp130 in epithelial cells, thus leading to an increase in cell cycling and a decrease of apoptosis. The induction of the COX-2/PGE_2 pathway is important for the development of such an inflammatory tumor microenvironment. When the TNF-α/NF-κB and/or IL-6/Stat3 pathways are activated beyond a threshold, they can promote tumorigenesis if the COX-2/PGE_2 pathway is inhibited. In the inflammatory microenvironment, not only TAMs, but also mast cells and IL-17-expressing T cells, infiltrate and contribute to tumor development. Therefore, targeting the inflammatory network in tumor tissues by the inhibition of PGE_2, NF-κB, Stat3, or downstream pathways may provide an effective preventive or therapeutic strategy against gastrointestinal cancer.

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Conflict of interest None.

References

1. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. J Intern Med. 2000;248:171–83.
2. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006;118:3030–44.
3. Aggarwal BB, Vijayalekshmi RV, Sung B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. Clin Cancer Res. 2009;15:425–30.
4. Takahashi H, Ogata H, Nishigaki R, Broide DH, Karin M. Tobacco smoke promotes lung tumorigenesis by triggering IKKβ-and JNK1-dependent inflammation. Cancer Cell. 2010;17:89–97.
5. Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, et al. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. Cell. 2010;140:197–208.
6. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860–7.
7. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436–44.
8. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140:883–99.
9. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646–74.
10. Thun MJ, Namboodiri MM, CW Jr Heath. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med. 1991;325:1593–6.
11. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, Speizer FE. Aspirin and the risk of colorectal cancer in women. N Engl J Med. 1995;333:609–14.
12. Wang D, DuBois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010;10:181–93.
13. Wang D, DuBois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 2010;29:781–8.
14. Oshima M, Oshima H, Kitagawa K, Kobayashi M, Itakura C, Taketo M. Loss of *Apc* heterozygosity and abnormal tissue building in nascent intestinal polyps in mice carrying a truncated *Apc* gene. Proc Natl Acad Sci USA. 1995;92:4482–6.
15. Moser AR, Pitot HC, Dove WF. A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse. Science. 1989;247:322–4.
16. Miyoshi Y, Nagase H, Ando H, Horii A, Ichii S, Nakatsuru S, et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. Hum Mol Genet. 1992;1:229–33.
17. Powell SM, Zilz N, Beazer-Barclay Y, Bryan TM, Hamilton SR, Thibodeau SN, et al. APC mutations occur early during colorectal tumorigenesis. Nature. 1992;359:235–7.
18. Sparks AB, Morin PJ, Vogelstein B, Kinzler KW. Mutational analysis of the APC/β-catenine/TCF pathway in colorectal cancer. Cancer Sci. 1998;58:1130–4.
19. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526–35.
20. van Hogezand RA, Eichhorn RF, Choudry A, Veenendaal RA, Lamers BHW. Malignancies in inflammatory bowel disease: fact or fiction? Scand J Gastroenterol. 2002;235:48–53.
21. Tanaka T, Kohno H, Suzuki R, Yamada Y, Sugie S, Mori H. A novel inflammation-related mouse colon carcinogenesis model

induced by azoxymethane and dextran sodium sulfate. Cancer Sci. 2003;94:965–73.
22. Okayasu I, Hatakeyama S, Yamada M, Ohkusa T, Inagaki Y, Nakaya R. Novel method in the induction of reliable experimental acute and chronic ulcerative colitis in mice. Gastroenterology. 1990;98:694–702.
23. Erdman SE, Poutahidis T, Tomczak M, Rogers AB, Cormier K, Plank B, et al. $CD4^+$ $CD25^+$ regulatory T lymphocytes inhibit microbially induced colon cancer in Rag2-deficient mice. Am J Pathol. 2003;162:691–702.
24. Erdman SE, Rao VP, Poutahidis T, Ihrig MM, Ge Z, Feng Y, et al. $CD4^+$ $CD25^+$ regulatory T lymphocytes require interleukin 10 to interrupt colon carcinogenesis in mice. Cancer Res. 2003;63:6042–50.
25. Clements WM, Wang J, Saranaik A, Kim OJ, MacDonald J, Fenoglio-Preiser C, et al. β-Catenin mutation is a frequent cause of Wnt pathway activation in gastric cancer. Cancer Res. 2002; 62:3503–6.
26. Oshima H, Matusnaga A, Fujimura T, Tsukamoto T, Taketo MM, Oshima M. Carcinogenesis in mouse stomach by simultaneous activation of the Wnt signaling and prostaglandin E_2 pathway. Gastroenterology. 2006;131:1086–95.
27. Correa P. *Helicobactor pylori* infection and gastric cancer. Cancer Epidemiol Biomark Prev. 2003;12:238s–41s.
28. Fu S, Ramanujam KS, Wong A, Fantry GT, Drachenberg CB, James SP, et al. Increased expression and cyclooxygenase 2 in *Helicobactor pylori* gastritis. Gastroenterology. 1999;116:1319–29.
29. Oshima H, Oshima M, Inaba K, Taketo MM. Hyperplastic gastric tumors induced by activated macrophages in COX-2/mPGES-1 transgenic mice. EMBO J. 2004;23:1669–78.
30. Oshima H, Oguma K, Du YC, Oshima M. Prostaglandin E_2, Wnt, and BMP in gastric tumor mouse models. Cancer Sci. 2009;100: 1779–85.
31. Oshima H, Oshima M. Mouse models of gastric tumors: Wnt activation and PG E_2 induction. Pathol Int. 2010;60:599–607.
32. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993;328:1313–6.
33. Oshima M, Taketo MM. COX selectivity and animal models for colon cancer. Curr Pharm Des. 2002;8:1021–34.
34. Oshima M, Dinchuk JE, Kargman SL, Oshima H, Hancock B, Kwong E, et al. Suppression of intestinal polyposis in $Apc^{\Delta 716}$ knockout mice by inhibition of cyclooxygenase 2 (COX-2). Cell. 1996;87:803–9.
35. Chulada PC, Thompson MB, Mahler JF, Doyle CM, Gaul BW, Lee C, et al. Genetic disruption of *Ptgs-1*, as well as of *Ptgs-2*, reduces intestinal tumorigenesis in *Min* mice. Cancer Res. 2000;60:4705–8.
36. Myung S, Rerko RM, Yan M, Platzer P, Guda K, Dotson A, et al. 15-Hydroxyprostaglandin dehydrogenase is an in vivo suppressor of colon tumorigenesis. Proc Natl Acad Sci USA. 2006;103: 12098–102.
37. Al-Salihi MA, Pearman AT, Doan T, Reichert EC, Rosenberg DW, Prescott SM, et al. Transgenic expression of cyclooxygenase-2 in mouse intestine epithelium is insufficient to initiate tumorigenesis but promotes tumor progression. Cancer Lett. 2009;273:225–32.
38. Sonoshita M, Takaku K, Sasaki N, Sugimoto Y, Ushikubi F, Natumiya S, et al. Acceleration of intestinal polyposis through prostaglandin receptor EP2 in $Apc^{\Delta 716}$ knockout mice. Nat Med. 2001;7:1048–51.
39. Seno H, Oshima M, Ishikawa TO, Oshima H, Takaku K, Chiba T, et al. Cyclooxygenase 2- and prostaglandin E_2 receptor EP_2-dependent angiogenesis in $Apc^{\Delta 716}$ mouse intestinal polyps. Cancer Res. 2002;62:506–11.
40. Wang D, Wang H, Shi Q, Katkuri S, Walhi W, Desvergne B, et al. Prostaglandin E_2 promotes colorectal adenoma growth via transactivation of the nuclear peroxisome proliferators-activated receptor δ. Cancer Cell. 2004;6:285–95.
41. Castellone MD, Teramoto H, Williams BO, Druey KM, Gutkind JS. Prostaglandin E_2 promotes colon cancer cell growth through a G_s-axin-β-catenin signaling axis. Science. 2005;310:1504–10.
42. van Rees BP, Sivula A, Thoren S, Yokozaki H, Jalobsson PJ, Offerhaus GJ, Ristimaki A. Expression of microsomal prostaglandin E synthase-1 in intestinal gastric adenocarcinoma and in gastric cancer cell lines. Int J Cancer. 2003;107:551–6.
43. Yoshimatsu K, Altorki NK, Golijanin D, Zhang F, Jakobsson PJ, Dannenberg AJ, Subbaramaiah K. Inducible prostaglandin E synthase is overexpressed in non-small cell lung cancer. Clin Cancer Res. 2001;7:2669–74.
44. Nakanishi M, Montrose DC, Clark P, Nambiar PR, Belinsky GS, Claffey KP, et al. Genetic deletion of *mPGES-1* suppresses intestinal tumorigenesis. Cancer Res. 2008;68:3251–9.
45. Nakanishi M, Menoret A, Tanaka T, Miyamoto S, Montrose DC, Vella AT, Rosenberg DW. Selective PGE_2 suppression inhibits colon carcinogenesis and modifies local mucosal immunity. Cancer Prev Res. 2011;4:1198–208.
46. Ristimaki A, Honkanen N, Jankaka H, Sipponen P, Harkonen M. Expression of cyclooxygenase-2 in human gastric carcinoma. Cancer Res. 1997;57:1276–80.
47. Saukkonen K, Rintahaka J, Sivula A, Buskens CJ, van Rees BP, Rio MC, et al. Cyclooxygenase-2 and gastric carcinogenesis. APMIS. 2003;111:915–25.
48. Oshima H, Popivanova BK, Oguma K, Kong D, Ishikawa TO, Oshima M. Activation of epidermal growth factor receptor signaling by the prostaglandin E_2 receptor EP4 pathway during gastric tumorigenesis. Cancer Sci. 2011;102:713–9.
49. Oshima H, Hioki K, Popivanova BK, Oguma K, van Rooijen N, Ishikawa TO, Oshima M. Prostaglandin E_2 signaling and bacterial infection recruit tumor-promoting macrophages to mouse gastric tumors. Gastroenterology. 2011;140:596–607.
50. Sonoshita M, Takaku K, Oshima M, Sugihara K, Taketo MM. Cyclooxygenase-2 expression in fibroblasts and endothelial cells of intestinal polyps. Cancer Res. 2002;62:6846–9.
51. Hull MA, Booth JK, Tisbury A, Scott N, Bonifer C, Markham AF, Coletta PL. Cyclooxygenase 2 is up-regulated and localized to macrophages in the intestine of Min mice. Br J Cancer. 1999;79: 1399–405.
52. Takeda H, Sonoshita M, Oshima H, Sugihara K, Chulada PC, Langenbach R, et al. Cooperation of cyclooxygenase 1 and cyclooxygenase 2 in intestinal polyposis. Cancer Res. 2003;63: 4872–7.
53. Miyoshi H, Nakau M, Ishikawa T, Seldin FM, Oshima M, Taketo MM. Gastrointestinal hamartomatous polyposis in *Lkb1* heterozygous knockout mice. Cancer Res. 2002;62:2261–6.
54. Tamai Y, Nakajima R, Ishikawa T, Takaku K, Seldin MF, Taketo MM. Colonic hamartoma development by anomalous duplication in *Cdx2* knockout mice. Cancer Res. 1999;59:2965–70.
55. Kitamura T, Kometani K, Hashida H, Matsunaga A, Miyoshi H, Hosogi H, et al. SMAD4-deficient intestinal tumors recruit $CCR1^+$ myeloid cells that promote invasion. Nat Genet. 2007;39:467–75.
56. Takeda H, Miyoshi H, Tamai Y, Oshima M, Taketo MM. Simultaneous expression of COX-2 and mPGES-1 in mouse gastrointestinal hamartomas. Br J Cancer. 2004;90:701–4.
57. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R. Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell. 2004;118:229–41.
58. Pull SL, Doherty JM, Mills JC, Gordon JI, Stappenbeck TS. Activated macrophages are an adaptive element of the colonic epithelial progenitor niche necessary for regenerative responses to injury. Proc Natl Acad Sci USA. 2005;102:99–104.

59. Fukuta M, Chen A, Klepper A, Krishnareddy S, Vamadevan AS, Thomas LS, et al. Cox-2 is regulated by toll like receptor-4 (TLR-4) signaling: role in proliferation and apoptosis in the intestine. Gastroenterology. 2006;131:862–77.
60. Fukuta M, Chen A, Vamadevan AS, Cohen J, Breglio K, Krishnareddy S, et al. Toll-like receptor-4 promotes the development of colitis-associated colorectal tumors. Gastroenterology. 2007;133:1869–81.
61. Hernandez Y, Sotolongo J, Breglio K, Conduah D, Chen A, Xu R, et al. The role of prostaglandin E_2 (PGE_2) in toll-like receptor 4 (TLR4)-mediated colitis-associated neoplasia. BMC Gastroenterol. 2010;10:82.
62. Fukata M, Hernandez Y, Conduah D, Cohen J, Chen A, Breglio K, et al. Innate immune signaling by toll-like receptor-4 (TLR-4) shapes the inflammatory microenvironment in colitis-associated tumors. Inflamm Bowel Dis. 2009;15:997–1006.
63. Rakoff-Nahoum S, Medzhitov R. Regulation of spontaneous intestinal tumorigenesis through the adaptor protein Myd88. Science. 2007;317:124–7.
64. Lee SH, Hu LL, Gonzalez-Navajas J, Seo GS, Shen C, Brick J, et al. ERK activation drives intestinal tumorigenesis in $Apc^{Min/+}$ mice. Nat Med. 2010;16:665–70.
65. Rakoff-Nahoum S, Medzhitov R. Toll-like receptors and cancer. Nat Rev Cancer. 2009;9:57–63.
66. Reuter BK, Asfaha S, Buret A, Sharkey KA, Wallace JL. Exacerbation of inflammation-associated colonic injury in rat through inhibition of cyclooxygenase-2. J Clin Invest. 1996;98:2076–85.
67. Morteau O, Morham SG, Sellon R, Dieleman LA, Langenbach R, Smithies O, et al. Impaired mucosal defense to acute colonic injury in mice lacking cyclooxygenase-1 or cyclooxygenase-2. J Clin Invest. 2000;105:469–78.
68. Ishikawa TO, Herschman HR. Tumor formation in a mouse model of colitis-associated colon cancer does not require COX-1 or COX-2 expression. Carcinogenesis. 2010;31:729–36.
69. Ishikawa TO, Oshima M, Herschman HR. Cox-2 deletion in myeloid and endothelial cells, but not in epithelial cells, exacerbates murine colitis. Carcinogenesis. 2011;32:417–26.
70. Balkwill F. Tumor necrosis factor and cancer. Nat Rev Cancer. 2009;9:361–71.
71. Karin M, Greten FR. NF-κB: Linking inflammation and immunity to cancer development and progression. Nat Rev Immunol. 2005;5:749–59.
72. Greten FR, Eckmann L, Greten TF, Park JM, Li ZW, Egan LJ, et al. IKKβ links inflammation and tumorigenesis in a mouse model of colitis-associated cancer. Cell. 2004;118:285–96.
73. Popivanova BK, Kitamura K, Wu Y, Kondo T, Kagaya T, Kaneko S, et al. Blocking TNF-α in mice reduces colorectal carcinogenesis associated with chronic colitis. 2008;118:560–70.
74. Popivanova BK, Kostadinova FI, Furuichi K, Shamekh MM, Kondo T, Wada T, et al. Blocking of a chemokine, CCL2, reduces chronic colitis-associated carcinogenesis in mice. Cancer Res. 2009;69:7884–92.
75. Matsushima K, Larsen CG, DuBois GC, Oppenheim JJ. Purification and characterization of a novel monocyte chemotactic and activating factor produced by a human myelomonocytic cell line. J Exp Med. 1989;169:1485–90.
76. Gounaris E, Erdman SE, Restaino C, Gurish MF, Friend DS, Gounairi F, et al. Mast cells are an essential hematopoietic component for polyp development. Proc Natl Acad Sci USA. 2007;104:19977–82.
77. Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, et al. NF-κB functions as a tumor promoter in inflammation-associated cancer. Nature. 2004;431:461–6.
78. Oshima M, Oshima H, Matsunaga A, Taketo MM. Hyperplastic gastric tumors with spasmolytic polypeptide-expressing metaplasia caused by tumor necrosis factor-α-dependent inflammation in cyclooxygenase-2/microsomal prostaglandin E synthase-1 transgenic mice. Cancer Res. 2005;65:9147–51.
79. Kishimoto T. Interleukin-6: from basic science to medicine—40 years in immunology. Annu Rev Immunol. 2005;23:1–21.
80. Heikkila K, Ebrahim S, Lawlor DA. Systematic review of the association between circulating interleukin-6 (IL-6) and cancer. Eur J Cancer. 2008;44:937–45.
81. Bollrath J, Phesse TJ, von Burstin VA, Putoczki T, Bennecke M, Bateman T, et al. gp130-mediated STAT3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell. 2009;15:91–102.
82. Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhapurapu S, et al. IL-6 and STAT3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell. 2009;15:103–13.
83. He G, Karin M. NF-κB and STAT3-key players in liver inflammation and cancer. Cell Res. 2011;21:159–68.
84. Li N, Grivennikov SI, Karin M. The unholy trinity: inflammation, cytokines, and STAT3 shape the cancer microenvironment. Cancer Cell. 2011;19:429–31.
85. Tebbutt NC, Giraud AS, Inglese M, Jennkins B, Waring P, Clay FJ, et al. Reciprocal regulation of gastrointestinal homeostasis by SHP2 and STAT-mediated trefoil gene activation in gp130 mutant mice. Nat Med. 2002;8:1089–97.
86. Jenkins BJ, Grail D, Nheu T, Najdovska M, Wang B, Waring P, et al. Hyperactivation of Stat3 in gp130 mutant mice promotes gastric hyperproliferation and desensitizes TGF-β signaling. Nat Med. 2005;11:845–52.
87. Judd LM, Bredin K, Kalantzis A, Jenkins BJ, Ernst M, Giraud AS. STAT3 activation regulates growth, inflammation, and vascularization in a mouse model of gastric tumorigenesis. Gastroenterology. 2006;131:1073–85.
88. Howlett M, Giraud AS, Lescesen H, Jackson CB, Kalantzis A, van Driel IR, et al. The interleukin-6 family cytokine interleukin-11 regulates homeostatic epithelial cell turnover and promotes gastric tumor development. Gastroenterology. 2009;136:976–77.
89. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010;141:39–51.
90. Biswas SK, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. Nat Immunol. 2010;11:889–85
91. DeNardo DG, Barreto JB, Andreu P, Vasquez L, Tawfik D, Kolhatkar N, et al. $CD4^+$ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. Cancer Cell. 2009;16:91–102.
92. Nakanishi Y, Nakatsuji M, Seno H, Ishizu S, Akitake-kawano R, Kanda K, et al. COX-2 inhibition alters the phenotype of tumor-associated macrophages from M2 to M1 in $Apc^{Min/+}$ mouse polyps. Carcinogenesis. 2011;32:1333–9.
93. Oguma K, Oshima H, Aoki M, Uchio R, Naka K, Nakamura S, et al. Activated macrophages promote Wnt signaling through tumour necrosis factor-a in gastric tumour cells. EMBO J. 2008; 27:1671–81.
94. Erdman SE, Sohn JJ, Rao VP, Nambiar PR, Ge Z, Fox JG, Schauer DB. $CD4^+CD25^+$ regulatory lymphocytes induce regression of intestinal tumors in $Apc^{Min/+}$ mice. Cancer Res. 2005;65:3998–4004.
95. Gounaris E, Blatner NR, Dennis K, Magnusson F, Gurish MF, Strom TB, et al. T-regulatory cells shift from a protective anti-inflammatory to a cancer-promoting proinflammatory phenotype in polyposis. Cancer Res. 2009;69:5490–6.
96. Colombo MP, Piconese S. Polyps wrap mast cells and Treg within tumorigenic tentacles. Cancer Res. 2009;69:5619–22.
97. Chae WJ, Gibson TF, Zelterman D, Hao L, Henegariu O, Bothwell ALM. Ablation of IL-17A abrogates progression of spontaneous intestinal tumorigenesis. Proc Natl Acad Sci USA. 2010;107:5540–4.