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

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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 COX-2, one of the target molecules of NSAIDs, and its downstream product, PGE_2, play an important role in gastrointestinal tumorigenesis. Bacterial infection stimulates the TLR/MyD88 pathway in tumor tissues, which leads to induction of COX-2 in stromal cells, including macrophages. Induction of COX-2/PGE_2 pathway in tumor stroma is important for development and maintenance of an inflammatory microenvironment in the gastrointestinal tumors. In such a microenvironment, tumor-associated macrophages express proinflammatory cytokines, including TNF-α and IL-6, and these cytokines respectively activate the NF-κB and Stat3 transcription factors in epithelial cells, as well as in stromal cells. Recent mouse studies have uncovered the role of such inflammatory network for 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 contributed to elucidation of the molecular mechanisms associated with the inflammatory network in gastrointestinal tumors, and 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.

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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 promotes 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 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, TNF-α and IL-6 activate NF-κB and Stat3, respectively, and both the TNF-α/NF-κB and

IL-6/Stat3 pathways have 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 codon 716 and 850 of the mouse Apc gene, respectively, and somatic deletion of the wild-type Apc gene results in 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 β-catenin mutation, 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 (IBD), 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 severe inflammatory response, which is

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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 development of colitis-associated colon cancer (CAC) [21]. Mutations in the β-catenin 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 mimicks 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*, 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 decreases by *H. pylori* eradication [28, 29]. Two transgenic mouse strains, *K19-Wnt1* mice expressing Wnt1 in the stomach, and *K19-C2mE* mice expressing COX-2 and mPGES-1, mimic Wnt activation and *H. pylori*-induced inflammation, respectively, in the stomach [26, 29-31]. *Gan* mice are compound transgenic mice with *K19-Wnt1* and *K19-C2mE*, which express Wnt1, COX-2, and

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mPGES-1 simultaneously in the gastric mucosa, resulting in 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 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,

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 the COX-2 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 the COX-1 gene 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 the 15-PGDH gene was disrupted, suggesting

that PGE$_2$ has a role in colon tumorigenesis [36]. Moreover, the transgenic expression of

COX-2 in the mouse intestine accelerated chemical carcinogen-induced tumorigenesis [37].

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COX-2 catalyzes 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 the P2 gene caused significant suppression of intestinal polyposis in $Apc^{\Delta716}$ mice, whereas suppression of EP1 or EP3 signaling did not affect tumorigenesis [38]. EP2 signaling increases the expression of VEGF and bFGF, which enhances angiogenesis in intestinal tumors [39]. Moreover, treatment of Apc^{Min} mice with PGE$_2$ increased the development of intestinal tumors through activation of PPARδ, which promotes survival of tumor cells [40]. Furthermore, PGE$_2$ signaling through EP2 receptor has been shown to activate Wnt/β-catenin signaling directly in colon cancer cells by 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).

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 the mPGES-1 genes in $Apc^{\Delta14}$ 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 induction of COX-2/PGE_2/EP4-induced inflammation is involved in the development of gastric cancer. Signaling through EP2 and EP4 both stimulate 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 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 distinct histological characteristics from 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

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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 TLR-mediated induction of inflammatory cytokines.   It has been shown that a disruption of the TLR2/4 or MyD88 genes in mice results in impaired mucosal repair from 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 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 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, ulcerative colitis is not associated with intestinal polyposis in the *Apc* mutant mice.   It is therefore possible that COX-2 expression is induced by a different mechanism in sporadic colon cancer compared to 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, 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 demonstrated that activation of the TLR/MyD88 pathway in epithelial cells is also important for COX-2 expression in non-IBD 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 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 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, COX-2 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 COX-2 gene 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 COX-2 gene disruption causes significant

suppression of intestinal polyposis in *Apc* mutant mice [34, 35].   It is possible that in the

case of severe ulcerative colitis, 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

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that TNF-α has tumor-promoting functions [70].   TNF-α signaling activates NF-κB, which further induces 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 the IKKβ gene 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 IKKβ 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 the TNF receptor p55 (TNF-Rp55) gene resulted in attenuated tumor formation, with reduced inflammatory cell infiltration compared with wild-type mice.   Moreover, wild-type mice transplanted with TNF-Rp55-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 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

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 inhibition of

NF-κB significantly suppressed 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 in gastric tumorigenesis in *Gan* mice has not yet been

examined.   However, TNF-α -/- *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 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

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upregulated in tumor tissues and the serum of human 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 development of a variety

of cancers, including CAC [81-84].   AOM/DSS-induced CAC development was

significantly suppressed in IL-6-/- mice and also in conditional Stat3 knockout mice that

lacked Stat3 in the intestinal epithelial cells through suppression of survival and

proliferation [81, 82].   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 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

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.   TGF-β signaling promotes

epithelial differentiation, and thus, suppression of the TGF-β signaling pathway has been

thought to promote gastrointestinal tumorigenesis.   Notably, activation of Stat3 in

gp130$^{757F/F}$ cells desensitizes 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 family cytokine 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

the 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 education of

macrophages into the pro-tumorigenic M2 or M2-like types.   Importantly, depletion of

functional macrophages in $Apc^{\Delta716}$ 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

suppression of colon tumor development [74].   Accordingly, macrophages play an

important role for 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, suggesting a role for macrophages in the maintenance of

tumor cells, as well as of tumor stromal cells [49].

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 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 induction of necrosis of tumor cells [94, 95]. Moreover, such regression of intestinal polyps was not found when CD4$^+$ CD25$^+$ cells were prepared from IL-10 -/- 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 IL-10-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, ablation of IL-17A 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 Figure 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 tumor-associated macrophages, 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

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beyond a threshold, they can promote tumorigenesis without the support of the COX-2/PGE$_2$ pathway. 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 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

The authors declare that they have no conflict of interest.

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Figure Legends

Figure 1.   The interaction of the COX-2/PGE$_2$, TNF-α/NF-κB, and IL-6/gp130/Stat3 pathways in the inflammatory environment.

Figure 2.   A schematic diagram of the inflammatory microenvironment in gastrointestinal tumor tissues.   Bacterial infection or endogenous ligand activates the TLR/MyD88 pathway in epithelial cells, which further activate stromal macrophages inducing CCL2. In the activated macrophages, NF-κB induces expression of COX-2, IL-6 and TNF-α itself. COX-2/PGE$_2$ pathway is important for 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 important role in promotion of tumorigenesis through suppression of apoptosis and acceleration of cell cycle.
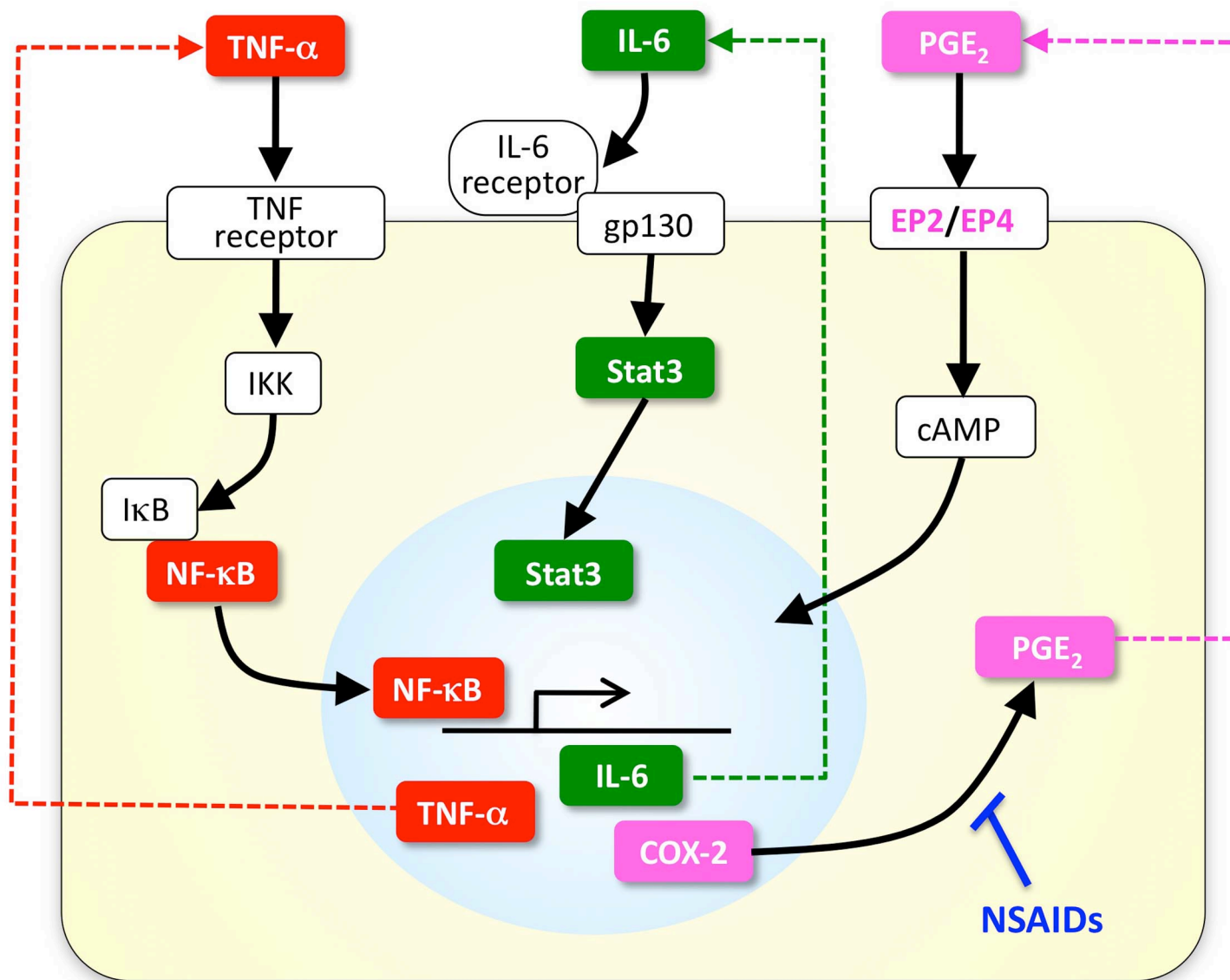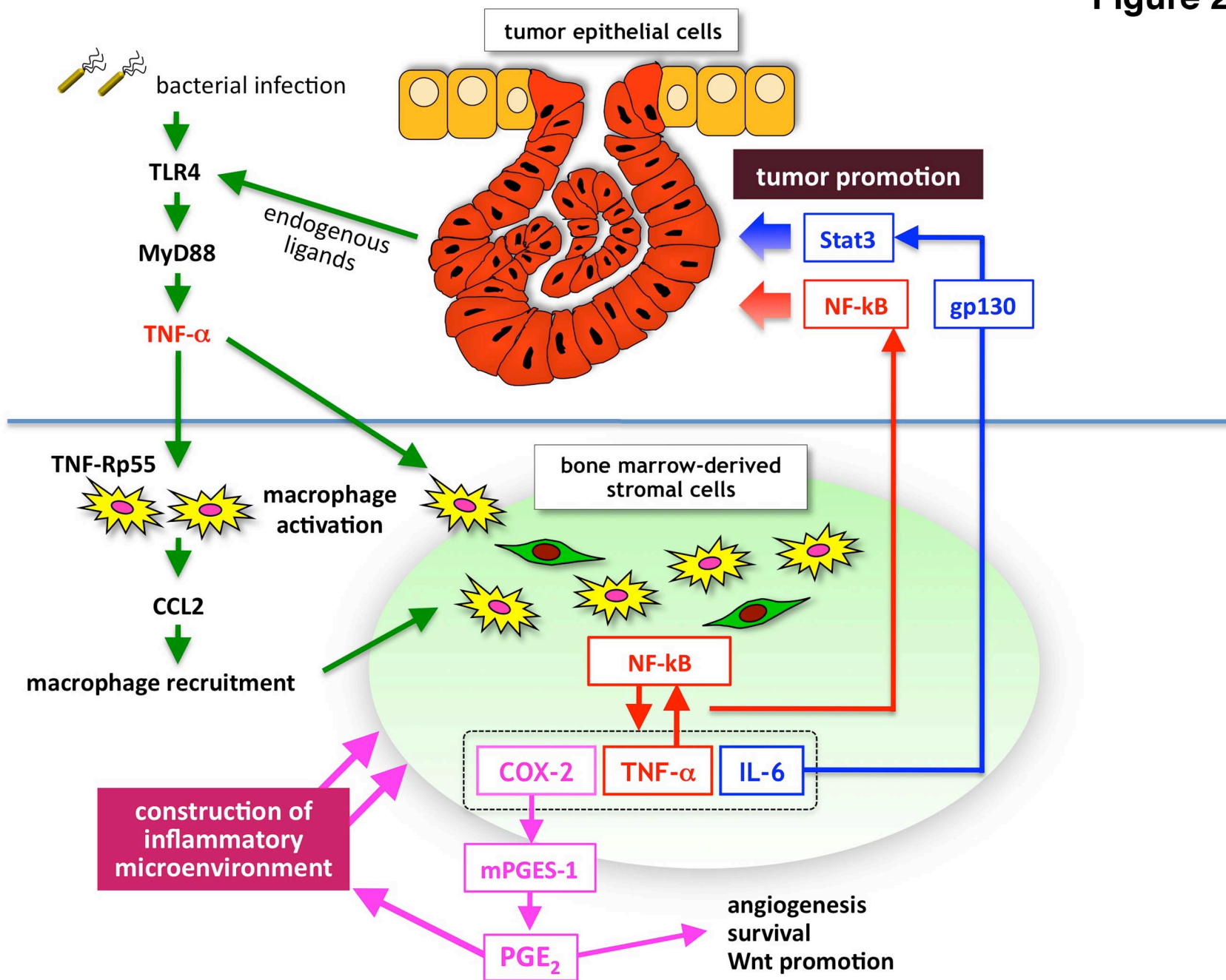
Figure 1

Figure 2

Table 1. Mouse model studies to examine inflammatory network 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
$Apc^{\Delta 468}$	$Rag2$ -/- (lymphocytes deficient)	Not affected	76
$Apc^{\Delta 468}$	anti-TNF-α antibody	suppression of intestinal polyposis	76
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	CD4$^+$ CD25$^+$ T cell transfer	suppression of CAC development	23, 24
-infected Rag2-/-		-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	78
gp130$^{757F/F}$	$Il11ra1^{n}$ knockout mice	suppression of gastric tumorigenesis	88

gene symbols uses 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.