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The therapeutic value of targeting inflammation in gastrointestinal cancers

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Abstract

Inflammation has been implicated in the initiation and progression of gastrointestinal (GI) cancers. Inflammation also plays important roles in subverting immune tolerance, escape from immune surveillance, and conferring resistance to chemotherapeutic agents. Targeting key regulators and mediators of inflammation represents an attractive strategy for GI cancer prevention and treatment. However, the targeting of inflammation in GI cancer is not straight-forward and sometimes inflammation may contribute to tumor regression. We discuss the origins and effects of inflammation in GI cancer and how to target it successfully.

Keywords

Cytokines; Tumor initiation; Tumor promotion; Targeting therapy

Inflammation in GI cancer

GI malignancies, including colorectal, gastric, liver and pancreatic cancers, are the most frequently diagnosed cancers and the leading causes of cancer-related deaths worldwide [1]. The general organismal response to GI cancers is tightly associated with inflammation and wound healing. In fact, an association between inflammation and cancer was first suggested by Virchow in 1863, based on his observations that tumors usually arose at sites of chronic inflammation and that inflammatory cells were present in most tumors [2]. A large body of evidence indicates that inflammation exerts multiple effects on tumorigenesis, yet not all of the underlying mechanisms have been fully elucidated. In certain GI cancers, localized

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inflammation exists before the malignancy appears. Most notable examples for such inflammatory conditions and subsequent tumors include ulcerative colitis and colitis associated colorectal cancer (CAC), *Helicobacter pylori* infection and gastric cancer, and HBV or HCV infections or non-alcoholic steatohepatitis (NASH) and hepatocellular carcinoma (HCC). However, inflammation is also a consequence of initial neoplastic changes in most cancers, even those that are not linked to pre-existing infection or inflammatory disease. Most notable examples are sporadic and familial colorectal cancers (CRC), and pancreatic ductal adenocarcinoma (PDAC), both of which contain profound inflammatory infiltrates and activated stroma. Increasing evidence suggests critical roles for the intestinal microbiome and microbial products in colorectal tumorigenesis, tumor immunity, and response to therapy [3, 4]. Microbiome studies have identified a few candidate species that may be involved in human CRC [5]. In addition to tumor promotion, altered host-microbiome interactions (dysbiosis) may also modulate the response to anti-cancer drugs.

The presence of inflammatory cells and inflammatory mediators, including cytokines, chemokines, and prostaglandins, in tumors and the associated processes of tissue remodeling, fibrosis and angiogenesis are key aspects of cancer-related inflammation [6]. Although inflammation often contributes to tumor initiation and promotion, growth, invasion, metastasis, and immune evasion, under certain circumstances it can also lead to tumor regression. Inflammation is a key component of host defense, where it assists in the killing of pathogens, clearance of tissue damage and regeneration [7, 8]. Acute inflammation, if properly resolved, does not interfere with maintenance of homeostasis and leads to tissue repair and healing. Nevertheless, chronic inflammation caused by either infections with pathogens that avoid immune clearance or autoimmune disease can result in oncogenesis. Chronic inflammation is characterized by increased abundance of active inflammatory myeloid and lymphoid cells (macrophages, neutrophils, mast cells, myeloid-derived suppressor cells, dendritic cells, natural killer cells, natural killer T cells, activated or effector T and B lymphocytes) within tissues [7]. It has been documented that almost 20% of human cancers are related to chronic inflammation caused by either infections, exposure to irritants or autoimmune disease [9]. Clearly, persistent inflammation is an important driving force in the journey from tissue injury to cancer. Thus, understanding the signaling pathways involved in both positive and negative regulation of cancer-related inflammation could enable the development of new treatments or improve the efficacy of existing therapeutics. This review is primarily focused on the role of inflammation in the initiation and progression of GI cancer and how to target cancer-associated inflammation in a successful and productive manner.

Inflammation in GI cancer initiation and progression

Oncogenic mutations occurring either in differentiated cells undergoing de-differentiation or in tissue progenitors/adult stem cells lead to the initiation of malignant tumors (Figure 1). It is generally agreed that an inflammatory microenvironment is associated with genomic instability, high mutation rates and rapid proliferation of mutated cells [7]. Inflammation may also activate regenerative pathways that lead to de-differentiation and reprogramming of terminally differentiated cells, which otherwise cannot contribute to tumor initiation.

Activated inflammatory cells, including neutrophils, dendritic cells, macrophages, eosinophils and mast cells as well as effector T and B lymphocytes, potentiate tumor initiation by releasing reactive oxygen species (ROS), reactive nitrogen intermediates (RNI), serine and cysteine proteases, matrix metalloproteinases (MMPs), cytokines, growth factors and other inflammatory mediators that enhance the accumulation of cancer progenitors harboring oncogenic mutations [10, 11]. Chronic inflammation results in oxidative stress, oxidative damage, and lipid peroxidation (LPO), thereby generating excess ROS and RNS within the affected cell [12]. Oxidative damage is involved in all stages of the cancer process. 8-oxo-7,8-dihydro-2-deoxyguanosine (8oxodG), a specific oxidative DNA modification, can exert mutagenic effects on the host and thus contribute to oncogenesis. In addition to classical mutations, DNA damage can result in gene copy number changes, gene fusions and can even affect epigenetic modifications. A number of transcription factors, such as nuclear factor- κ B (NF- κ B), adaptor protein-1 (AP-1), signal transducer and activator of transcription 3 (STAT3), p53, hypoxia-inducible factor-1 α (HIF-1 α), peroxisome proliferator-activated receptor- γ (PPAR- γ), β -catenin, Notch and nuclear factor erythroid-2 related factor 2 (NRF2), are activated by oxidative stress and inflammatory stimuli and can contribute to elevated expression of genes encoding growth factors, inflammatory cytokines, chemokines, anti-apoptotic proteins, and cell cycle regulators that contribute to early tumor promotion [13, 14]. In addition, some of these transcription factors can trigger regenerative responses that entail the reprogramming of terminally differentiated cells to more proliferative and multi-potential progenitor cells that can contribute to tumor initiation. However, the primary mechanism responsible for tumor initiation is genomic instability and accumulation of inheritable genetic changes [15]. A key molecule that contributes to this process and whose expression is elevated in IBD is inducible NO synthase (iNOS) [16].

The relationship between IBD and CRC risk has been argued since 1925 [17]. IBD patients are at a very high risk of progression from dysplasia to CAC, which accounts for 10–15% of deaths in this disease [17]. A more comprehensive analysis of the impact of anti-cytokine drugs used in IBD treatment on CAC risk is needed to assess whether a reduction in colonic inflammation truly reduces cancer risk [18]. A recent study has shown that IBD and CRC patients harbor special *Escherichia coli* strains, containing pathogenicity islands that promote microfold cell translocation, angiogenesis and genotoxicity [19]. However, host genetic alterations also contribute to tumor development. A genome-wide association study (GWAS) suggested that three single nucleotide polymorphisms (rs4072037 at 1q22, rs13361707 at 5p13, and rs2274223 at 10q23) in genes that influence the host inflammatory response could significantly increase the risk of gastric cancer in the Chinese population independently or in combination with *Helicobacter pylori* [20]. Mutations in the tumor suppressor p53 gene are an early event in the multistep progression of gastric cancer, and are often present in dysplastic and metaplastic gastric epithelium [21]. Furthermore, p53 expression is significantly associated with *Helicobacter pylori* status and the development of inflammation-related gastric cancer [21]. Another recent study has provided evidence that vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF) could regulate tumor angiogenesis, providing an additional link between inflammation, cytokines and liver carcinogenesis [22]. IL-6 signaling also plays an important role in the development of HCC and may even account for the marked gender bias in the incidence of this male-prevalent

disease [23]. Initiated HCC progenitor cells (HcPCs) were found to exist within premalignant dysplastic lesions and are responsible for malignant progression upon acquisition of autocrine IL-6 signaling [24]. But prior to this step and during early stages of tumorigenesis, the initiated hepatocytes mainly respond to paracrine IL-6 production by liver inflammatory cells, which are more active in males [23]. In addition, DNA damage induced by hepatic carcinogens can lead to necrotic cell death and release of inflammatory mediators that drive early tumor promotion in HCC [25]. In fact, inflammation is also required for the hepatocarcinogenic activity of dioxin and related compounds [26].

In addition to stimulating cell proliferation and enhancing cell survival, inflammation promotes tumor development by activating the so-called angiogenic switch [7]. Inflammatory mediators also stimulate the migration, invasion and metastatic dissemination of malignant cells (Figure 1). Expression of genes involved in cell proliferation and survival is dependent on transcription factors, such as NF- κ B, STAT3, and AP-1, that are activated by numerous inflammatory cytokines [27, 28]. These include IL-6, IL-11, TNF, IL-23, and IL-1 β . Usually these cytokines are produced by inflammatory cells, but some, for instance IL-6, can also be expressed by the cancer cells themselves and act in an autocrine manner, as found in HcPCs that give rise to HCC [24]. Autocrine IL-6 signaling by cancer progenitor cells may be a general mechanism for other IL-6-dependent malignancies.

Chemokine receptors and their ligands are important for the recruitment of cytokine-producing cells into the tumor microenvironment, but they also control the movement of cancer cells [29]. Many transformed cells promiscuously express chemokine receptors and thereby migrate to, and survive at, distant sites upon recognition of local chemokines [11, 29, 30]. Chemokines expressed by cancer cells also affect tumor progression via leukocyte recruitment as well as by autocrine effects on cell proliferation and survival, invasion and metastasis [30]. CXCR4, which is frequently expressed by CRC and HCC cells, was noted to correlate with the extent of lymph node metastasis [31]. Moreover, many other chemokine receptors, including CX3CR1, CCR6, CCR7, CCR9, CXCR1, CXCR2, CXCR3, CXCR5 and CXCR7, are expressed by a variety of GI-derived malignant cells and are implicated in organ-specific metastasis [32]. Inflammatory cytokines like TNF, IL-1 β and IL-6 can further enhance the invasive potential of malignant cells by increasing expression of chemokines and chemokine receptors [33–35]. Accordingly, such chemokine and cytokine networks play a pivotal role in coordinating autocrine and paracrine interactions between malignant cells and infiltrating leukocytes, and elevating the migration, invasion and survival of malignant cells.

Inflammatory and immune cells are also recruited to preneoplastic lesions and influence malignant progression at a very early stage. For instance, immune cells form an inflammatory and immune-suppressive microenvironment that surrounds pancreatic intraepithelial neoplasia (PanIN) lesions, and allows them to escape immune surveillance [36]. A recent study suggests that oncogenic Kras contributes to evasion of anti-tumor immunity by inducing production of GM-CSF and subsequent suppression of T cell mediated immune surveillance [37]. Thus, inflammation also promotes immune evasion and suppresses anti-tumor immunity.

In general, inflammation can drive both tumor initiation and progression (Figure 1). Thus, antibodies or other molecules that antagonize the inflammation-related factors mentioned above may exert a valuable therapeutic effect on GI malignancies. Recent preclinical and early clinical studies suggest how such an effect may be achieved, as will be discussed in the following section of this review (Table 1).

Therapeutic targets in inflammation-related GI cancers

Since specific species, microbial consortia, and microbial metabolites seem to exert diverse effects on GI cancers, affecting tumor initiation and progression, as well as the response to anti-cancer drugs, targeting of the microbiome may offer a new approach to both prevention and therapy [5, 38]. Apart from pathogen-specific therapy, germ-free status and treatment with wide-spectrum antibiotics were found effective in mouse models, based on reduced numbers of tumors in chemical and genetic experimental models of colorectal carcinogenesis [3, 38]. However, it is doubtful that drastic elimination of the microbiome can be practiced in humans. Microbiota transplantation to restore eubiosis in chronic disease states, thereby reducing microbially-induced inflammation in tumorigenesis, appears to be a much more reasonable approach.

Although the full spectrum of inflammatory cell functions in tumor initiation, progression and metastasis remains to be elucidated, there is enough information that merits the consideration of such cells and the inflammatory mediators they produce as therapeutic targets. Inflammatory cells recruited into GI tumors include tumor-associated macrophages (TAMs), neutrophils, dendritic cells, immature myeloid cells (IMC), eosinophils, mast cells and T and B lymphocytes [6]. Among these cell types, TAMs and IMC are the dominant producers of inflammatory mediators, as well as mediators of angiogenesis, lymphangiogenesis, extracellular-matrix breakdown, immunosuppression, and metastasis [39, 40]. Angiogenic factors produced by TAMs include VEGF and PDGF. TAMs in GI cancer are thought to acquire an M2-polarized phenotype (alternatively activated macrophages). In addition to genes whose products are involved in promotion of tumor growth, tissue remodeling, and angiogenesis, M2 macrophages can also suppress anti-tumor immunity and promote tissue repair and proliferation [41, 42]. In general, one should aim to inhibit upstream inflammatory mediators, such as cytokines and chemokines, whose neutralization would not lead to severe loss of host defense, thereby resulting in rampant infections.

Tumor-secreted lactic acid is capable of inducing IL-23 production by TAMs under hypoxic conditions, thereby activating the IL-23-IL-17 cascade [43]. The IL-23-IL-17 cascade is also activated by either translocating commensal bacteria or microbial disintegration products to drive colorectal tumor growth and progression [3]. IL-23-IL-17 signaling also stimulates migration and tissue invasion by HCC cells, in which these cytokines control MMP2 and MMP9 expression [44]. These results underscore the IL-23-IL-17 cascade as a generally attractive therapeutic target in multiple GI malignancies. Although anticancer therapy followed by enhanced inflammation in response to the translocating commensals may contribute to tumor eradication through the upregulation of IL-17 or TNF in experimental mice models, the findings need to be interpreted with caution when moving from

experimental mice models to patients with cancer, as IL-17 expression has been linked to drug resistance [45]. A novel focal adhesion molecule, kindlin-2, was found to promote the invasion of gastric cancer cells through effects on TAMs that produce chemokines and cytokines, including IL-8, IL-11, IL-17b, IL-22 and IL-24 [46]. There is also ample evidence that TAMs and liver-recruited macrophages are involved in the initiation and progression of liver cancer, via a crosstalk between the NF- κ B, STAT3, and HIF-1 signaling pathways [47, 48]. TAMs with an M2-polarized phenotype correlate with poor prognosis in HCC patients [48]. Clodronate-encapsulated liposomes and aminobisphosphonates have been used for the depletion of macrophages in vivo and were demonstrated to reduce angiogenesis and tumor progression in several experimental cancer models [48]. Depletion of TAMs with clodronate-encapsulated liposomes or zoledronic acid in combination with sorafenib can significantly inhibit tumor progression, angiogenesis, and lung metastasis in HCC [49]. Moreover, the combination of CpG immunostimulatory oligonucleotide plus an anti-IL-10 receptor antibody switches the infiltrating TAMs from the M2 to the M1 phenotype, which can promote tumor rejection, represents another sophisticated strategy for cancer treatment [50]. On the other hand, administration of large amounts of the anti-inflammatory cytokine IL-10 was found to enable a potent anti-tumor T-cell response leading to tumor rejection [51]. IL-10, an M2 cytokine, may exert its anti-tumorigenic effect by downregulating VEGF, TNF, IL-23, IL-17, and IL-6 production in TAMs [52]. Taken together, the targeting of TAMs is an interesting therapeutic strategy in various GI cancers. Other inflammatory cells, such as neutrophils, lymphocytes, and dendritic cells, also play promoting or suppressive functions in tumorigenesis, malignant progression, and metastasis, depending on their differentiation status [53]. Such inflammatory and immune cells are also promising targets for GI cancer therapy whose validity needs to be examined in future studies. For instance, the depletion of regulatory or suppressive B or T lymphocytes, which may accumulate in liver and colon cancers, may strongly potentiate the activation of anti-tumor cytotoxic T cells [54, 55]. Antigen-specific immunotherapy is a promising strategy in GI cancer preclinical models [55]. Thus, whether a combination of regulatory T/B cell depletion with an antigen-specific immunotherapy is useful for GI cancer needs to be demonstrated by clinical trials in the future.

An important mechanism that links inflammation to cancer is the VEGF-controlled angiogenic switch. VEGF, which is produced by TAMs, is also indispensable for their recruitment and further production of chemokines and additional proangiogenic factors [56]. The expression of VEGF in TAMs is directly regulated by HIF-1 α , NF- κ B, STAT3, and AP-1 [56]. Anti-VEGF treatment using neutralizing monoclonal antibodies is the predominant anti-angiogenic therapy for various GI cancers [57]. However, the recruitment of Gr1⁺ myeloid cells, including TAM progenitors, into tumors curtails the effects of anti-VEGF therapy [57]. IL-17 is another pro-tumorigenic cytokine that confers resistance to anti-angiogenic therapy [58]. Thus, in addition to its own beneficial effects, anti-IL-17 (or anti-IL-23) therapy is likely to increase the efficacy of anti-VEGF therapy.

IL-6 produced by myeloid cells is a crucial tumor promoter in CAC, as it promotes the proliferation and survival of adenocarcinoma cells via STAT3 signaling [59, 60]. IL-6 and related cytokines, such as IL-11, drive many of the cancer “hallmarks” by activating the downstream gp130/JAK/STAT3 signaling pathway. Moreover, IL-6 signaling can induce

the production of other inflammatory cytokines, chemokines, proteases, and growth factors, including IL-6 itself, IL-1 β , IL-23, CCL5, CXCL8, MCP1, MMP9, MMP2, and VEGF, thereby stimulating the recruitment of additional bone marrow derived cells to the tumor microenvironment [61]. An IL-6R blocking antibody (Tocilizumab) and an IL-6 sequestering antibody (CNTO-328) have been approved for the treatment of juvenile and rheumatoid arthritis (RA), but now need to be evaluated for their ability to synergize with conventional chemotherapeutic drugs or act as neoadjuvants in GI malignancies [61, 62]. IL-11, another prominent pro-tumorigenic member of the IL-6 family, is significantly up-regulated in many cancers and considered to be an important stimulator of tumorigenesis and metastasis [60, 63]. IL-11 was recently suggested to exhibit a stronger correlation with STAT3 activation in human GI malignancies than IL-6, and an IL-11 neutralizing antibody has shown efficacy in mouse models of CRC [60, 64].

As mentioned above, IL-23 and its downstream cytokines IL-17 and IL-22 are involved in both CAC and sporadic CRC. Thus, IL-23 or IL-17a neutralizing antibodies or antibodies that block their receptors need to be evaluated in GI cancer, along with their ability to treat chronic inflammatory conditions [3, 65]. IL-22, a cytokine of the IL-10 superfamily, is induced during intestinal tissue damage. Interestingly, IL-22 exerts strong tissue protective effect during the peak phase of damage, but it promotes tumor development if left uncontrolled during the recovery phase. IL-22 can be neutralized by the soluble IL-22 receptor (IL-22R), known as the IL-22 binding protein (IL-22BP, also known as IL22RA2) [66]. Thus, the IL-22-IL-22BP axis may be promising therapeutic target against colon cancer due to its critical upregulation during intestinal tissue repair and tumorigenesis. However, too potent of an anti-IL-22 effect may result in mucositis, tissue damage and other untoward effects. Thus, like other anti-cytokine therapies, IL-22 neutralization needs to be approached with proper care. The first anti-cytokine drug to enter the clinic was a TNF antagonist [2]. Although mainly used in the treatment of RA, psoriasis and IBD, anti-TNF drugs exhibit encouraging efficacy in chemoprevention and treatment of malignant diseases [2]. Activation of IL-1R signaling leads to IL-6 induction, contributing to increased tumor invasiveness, angiogenesis, and immune suppression [67]. IL-1R antagonist (IL-1ra) can inhibit these processes, suggesting a therapeutic application in cancer [67]. However, under no circumstances should IL-1R inhibition be combined with TNF inhibition as this can result in complete loss of innate immune defenses [68]. COX2 inhibitors, aspirin, and anti-inflammatory steroids, are all well-established anti-inflammatory drugs that have proven themselves as effective prophylactics that prevent cancer development, or therapeutics that slow down malignant progression, and/or reduce mortality in early GI malignancies [69, 70]. Whether such drugs can be used against invasive and metastatic tumors remains to be found.

Emerging evidence suggests that microRNAs, a group of small non-coding RNAs, also contribute to GI cancer pathogenesis, including liver cancer and gastric cancer [71]. Unique expression profiles of microRNAs were found in various cancer types at different stages [72, 73]. Overexpression of the DLK1-DIO3 microRNA cluster on chromosome 14q32.2 positively correlates with HCC stem cell markers, including CD133, CD90, EpCAM, and Nestin, and is associated with poor survival [71]. MicroRNAs have emerged as attractive GI cancer biomarkers due to their tumor-specific and tissue-specific expression profiles. Thus,

inhibitors of microRNAs or anti-miRs represent a totally new way to treat cancer, but such approaches require further investigation and validation.

Several signaling pathways associated with inflammation and stress are critical players in GI cancer pathogenesis including NF- κ B, PI3K/Akt, STAT3, HIF-1 α and the stress-activated MAPKs p38 and JNK (Figure 2). The PI3K/Akt pathway is involved in the late-stage progression and metastasis of gastric cancer [74]. The effect of NF- κ B and STAT3 on the initiation and progression of colon, gastric and liver cancers has been extensively investigated, as they are the two major transcription factors controlling the proliferation and survival of pre-neoplastic and malignant cells [75, 76]. NF- κ B is a central coordinator in innate and adaptive immune responses. It is activated by the inflammation-responsive I κ B kinase (IKK) in response to pro-inflammatory cytokines as well as microbial products like LPS, and exerts tumor-promoting functions within malignant cells and inflammatory cells [77]. In addition, mutant p53, which is frequently present in human cancer, prolongs TNF-induced NF- κ B activation and promotes inflammation-associated CRC [78]. It was also suggested that aberrant expression of activation-induced cytidine deaminase (AID), whose normal function is in immunoglobulin gene rearrangements, can contribute to tumor initiation in the GI track, where it is induced by NF- κ B in response to various inflammatory cytokines [79]. Persistent NF- κ B activation in intestinal epithelial cells (IECs) may also accelerate tumor initiation by enhancing nitrosative DNA damage [16]. NF- κ B also modulates Wnt signaling by promoting Wnt activation. NF- κ B can induce the dedifferentiation of nonstem cells that acquire tumor-initiating capacity [80, 81]. Conversely, IEC-specific ablation of RelA/p65 retards stem cell expansion [81]. Thus, NF- κ B-dependent inflammatory signaling is crucial for dedifferentiation and generation of tumor-initiating cells, providing a rationale for targeting of NF- κ B in CRC prevention and therapy. In addition, specific inactivation of IKK β -driven NF- κ B signaling in tumor-infiltrating leukocytes was demonstrated to inhibit CAC development, and a strong inhibitory effect was also observed after IKK β ablation in intestinal epithelial cells [82]. Targeting of the NF- κ B pathway thus seems to be a valid preventive and therapeutic strategy in GI cancer.

Many different inhibitors targeting the IKK-NF- κ B signaling pathway, including non-steroidal anti-inflammatory drugs (NSAIDs) (5-ASA, aspirin), thiopurines (6-MP), and proteasome inhibitors (PS-341), were described [83, 84]. Such compounds were shown to exert beneficial effects on tumor development or increase the response to radio- and chemotherapy. Interestingly, aspirin and 5-ASA have diverse activity in the GI tract, although they share structural homology. 5-ASA has well established anti-inflammatory and chemopreventive properties in CRC [85, 86]. However, frequent use of some NSAIDs but not aspirin seems to increase the absolute incidence of CD and UC, and therefore such drugs are not useful for chemoprevention [53, 87]. It should also be noted that NSAIDs and various natural compounds, such as curcumin and polyphenols, are not specific for IKK or NF- κ B and modestly inhibit other signaling pathways involved in tumorigenesis. Furthermore, potent and systemic inhibition of IKK/NF- κ B might be of limited benefit in the prevention and treatment of cancer due to inhibition of innate and adaptive immunity [88]. Perhaps natural products, such as curcumin, guggulsterone, silymarin, and plumbagin, which are weak inhibitors of NF- κ B and/or STAT3 may be more effective in cancer prevention because of their lower toxicity, potency and specificity [89–91].

Many studies demonstrated the association of STAT3 with colon, gastric and liver cancers [59, 92]. STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation [93]. Moreover, increased STAT3 activity and elevated TLR2 expression are associated with poor survival in gastric cancer [93]. Interestingly, the suppressive role of protein tyrosine phosphatase receptor type O (PTPRO), an emerging target for liver cancer treatment, could be ascribed to STAT3 inactivation [94]. IL-6, and related cytokines, such as IL-11, that are induced upon NF- κ B activation, are potent activators of STAT3 and thereby link these two factors into a critical NF- κ B-IL-6-IL-11-STAT3 oncogenic module that is active in most GI cancers. STAT3 signaling can also regulate the IL-23 and IL-12 balance, leading to elevated IL-23 expression that, as discussed above, exerts a strong pro-tumorigenic effect [95, 96]. STAT3 inhibits the expression of IL-12, which has anti-tumorigenic properties, in tumor-associated dendritic cells, thereby attenuating anti-tumor immunity [96]. Little is known about the upstream mechanisms leading to constitutive activation of NF- κ B and STAT3 in GI cancer cells. One possibility are cytokines such as TNF, IL-1 β , IL-6 and IL-11, which are produced by infiltrating inflammatory cells. Both IL-6 and IL-11 are induced in response to NF- κ B activation in immune cells of the tumor microenvironment can lead to STAT3 activation in both malignant and immune cells [28, 60, 64]. Thus, interference with either NF- κ B, IL-6, IL-11 or STAT3 activation can interrupt this module and exert equivalent anti-tumorigenic effects. Although occasionally they exhibit antagonistic interactions, NF- κ B and STAT3 can cooperatively promote the development and progression of most GI cancers [28, 97], and therefore present interesting therapeutic targets. Compounds that specifically interfere with the transcriptional cooperation between NF- κ B and STAT3 may offer a high degree of specificity. One way to inhibit STAT3 activation is through the use of JAK kinase inhibitors, such as ruxolitinib, which was recently approved for the treatment of myelofibrosis [98]. Indeed, JAK inhibitors have shown efficacy in experimental models of GI malignancies [99].

The cancer stem cell hypothesis suggests that tumors are hierarchically organized with relatively rare “cancer stem cells” (CSCs) or tumor-initiating cells (TICs), that are responsible for generation of more differentiated transformed cells. CSCs are resistant to conventional chemotherapy [100]. STAT3 signaling may be important for CSC renewal in HCC [101]. We found that the NIK-IKK α signaling module mediates the expansion of mammary/breast cancer CSC [102]. Thus, it may be possible to target CSC by targeting the inflammatory pathways involved in their self-renewal and maintenance. Most interestingly, a unique phenomenon of somatic cell reprogramming into pluripotent cells by exposure to sublethal stress stimuli, called stimulus-triggered acquisition of pluripotency (STAP), was recently reported [103, 104]. STAP represents another promising cellular target against GI cancers.

Concluding remarks

It is clear that inflammation is closely linked to initiation, promotion, malignant progression, metastatic spread, immune evasion and drug resistance in most GI cancers. Anti-inflammatory therapy targeting inflammatory cytokines, chemokines, inflammatory cells, and inflammation-responsive transcription factors (NF- κ B, STAT3, HIF1 α , and AP-1)

represents an attractive and a promising therapeutic strategy, especially in GI cancer where inflammation plays important pathogenic functions. In addition to these more conventional therapeutic targets, microRNAs that are involved in tumor-associated inflammation should also be considered as therapeutic targets. Translating all of these basic findings and hypotheses into actual drug development and clinical trials is a considerable, but not an insurmountable, challenge that will require many participants with different types of expertise.

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Highlights

- Inflammation influences numerous gastrointestinal malignancies
- Inflammation controls tumor initiation, promotion and malignant progression
- Inflammation can be targeted both for tumor prevention and improved therapy

Figure 1. Role of inflammation in tumor initiation and progression

Inflammation can result in mutations and epigenetic changes that favor tumor initiation. ROS and RNI produced by activated inflammatory/immune cells, and DNA damaging toxins produced by carcinogenic pathogens, induce mutations and genomic alterations resulting in appearance of premalignant cells that proliferate and survive in response to cytokines produced by inflammatory immune cells.

Figure 2. Roles of NF-κB/STAT3/HIF-1α/AP-1 signaling pathways in GI cancers

Tumor promoting factors and cytokines stimulate immune/inflammatory cells to produce inflammatory mediators that activate key transcription factors, such as NF-κB, STAT3, HIF-1α, and AP-1. These transcription factor control numerous processes in pre-malignant and malignant GI epithelial cells, including survival, proliferation, angiogenesis, migration, invasion, and metastasis.

Table 1
Drugs targeting GI cancer-related inflammation

Drugs that have been successfully translated to the clinic, either as marketed drugs or in clinical trials.

Drug	Target	Stage of development	Anti-cancer effects
NSAIDs	COX inhibitors	Approved	<ul style="list-style-type: none"> Enhance cell differentiation, apoptosis, adhesion, radiosensitivity, and susceptibility to oxidative stress; Reduce cell proliferation, angiogenesis, and migration
Thiopurines	6-MP	Approved	<ul style="list-style-type: none"> Inhibit DNA synthesis and malignant cell growth
Cetuximab	EGFR	Approved	<ul style="list-style-type: none"> A mAb against EGFR that inhibits malignant cell growth
Panitumumab	EGFR	Approved	<ul style="list-style-type: none"> A mAb against EGFR that inhibits malignant cell growth
Trastuzumab	HER2	Approved	<ul style="list-style-type: none"> A humanized mAb against HER2 that inhibits malignant cell growth
Bevacizumab	VEGF	Approved	<ul style="list-style-type: none"> A mAb that inhibits angiogenesis by directly targeting the VEGF protein
Infliximab	TNF	Approved	<ul style="list-style-type: none"> An anti-TNF monoclonal antibody that increases cell apoptosis and radiosensitivity
TNFrade	TNF	Phase I/II/III	<ul style="list-style-type: none"> Agonist that enhances cell apoptosis and radiosensitivity
TNF Kinoid	TNF	Phase II	<ul style="list-style-type: none"> A recombinant TNF carrier that regulate cancer-related inflammation
Proteasome inhibitors	PS-341	Approved	<ul style="list-style-type: none"> Regulates cell cycle, tumor growth, and survival by inhibiting NF-κB activation through stabilization of the inhibitor protein IκB
Aminobisphosphonates	Zoledronic	Phase III	<ul style="list-style-type: none"> Depletes TAMs and inhibits tumor progression, angiogenesis, and metastasis
Multi-kinase inhibitor	Sorafenib	Phase I/II	<ul style="list-style-type: none"> Depletes TAMs and inhibits tumor progression, angiogenesis, and metastasis
CNTO-328	IL-6	Phase I/II	<ul style="list-style-type: none"> IL-6 sequestering antibody that modulates cancer-related inflammation
Tocilizumab	IL-6R	Phase I/II	<ul style="list-style-type: none"> IL-6R blocking antibody that modulates cancer-related inflammation