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Cytokines, IBD and colitis-associated cancer

Ralph Francescone, PhD, Vivianty Hou, BS, and Sergei I. Grivennikov, PhD

Cancer Prevention and Control Program, Fox Chase Cancer Center, Philadelphia, PA 19111

Abstract

Inflammatory bowel diseases (IBDs) are debilitating conditions that result in intestinal damage due to chronic inflammation. In addition, the perpetual state of inflammation predisposes individuals to the development of colitis associated cancer (CAC). Because of the immense immune cell infiltration into colon, cytokines produced by immune cells are major players in the initiation and progression of IBD and CAC. In this review, we will explore the functions of many key cytokines and their roles in IBD and CAC, as well as their influences on the immune system and stromal cells. Finally, we will briefly discuss current therapies and current clinical trials targeting cytokines in IBD.

Introduction

Inflammatory bowel diseases (IBDs) are chronic relapsing conditions characterized by intestinal damage (barrier disruption, microbiota influx) and high amounts of inflammation¹⁻³. The two major forms of IBD are Crohn's Disease (CD) and ulcerative colitis (UC). Despite similar pathophysiological manifestations on the surface, CD and UC are indeed distinct diseases that may require different therapeutic approaches. For example, inflammation occurs generally in the all layers of the bowel in CD, while it occurs in the mucosal areas in UC. Additionally, IBDs pre-dispose patients to the development of a form of colon cancer known as colitis associated cancer (CAC), increasing cancer incidence up to 20%, depending on the duration of the disease⁴. CD is known to increase the risk of developing CAC by roughly 1.8 times and UC up to 8 times compared to the risk of developing colon cancer in the general population. (need solid ref)

CAC represents roughly 2% of all colorectal cancer (CRC) cases⁵, but traditionally received much attention due to clear cut mechanistic insights of connection between inflammation and cancer⁶. The underlying inflammation generated from pre-existing IBDs can initiate tumorigenesis and promote cancer development. The immune cell infiltrates in the colon create an environment rich in reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can cause DNA damage in addition to exogenous mutagens, facilitating the initiation of cancer⁷. Moreover, inflammatory cells can produce large amounts of pro-tumorigenic cytokines (growth factors) that drive tumor progression. Interestingly, while inflammation clearly plays a role in CAC, it is becoming increasingly evident that inflammation plays a major role in spontaneous colon cancer development, which is often

considered “non-inflammatory”. Therefore, extensive research is ongoing to uncover how to properly quell inflammation of the colon (Figure 1) to benefit IBD or CAC and CRC treatments. Lessons from targeting cytokines in other autoimmune diseases demonstrate that they are attractive targets to combat the over active immune system and limit damage to the intestine. This review will focus on the induction of cytokines in IBDs and colon cancer, the molecular mechanisms involved in cytokine signaling, their effect on the local microenvironment, and finally a brief summary of promising therapeutics that target cytokines.

Intestinal inflammation and tumor microenvironment: differences and similarities of IBD and CAC

Tumors are not simply comprised of cancer cells; they are a complex collection of many cell types, including immune cells, endothelial cells, mural cells, fibroblasts, and stem cells. The interactions of all of these cells make up what is known as the tumor microenvironment and they contain cytokines and chemokines that can act to promote or inhibit tumorigenesis. Quite similarly, during IBD development, largely intact epithelial layer and lamina propria are infiltrated by various types of immune cells, creating unique inflammatory microenvironment. Multiple lines of evidence suggest that inflammatory mediators may utilize similar if not identical mechanisms to promote IBD and to induce CAC^{3, 4}. On the other hand, there are distinct mechanisms that separate IBD pathogenesis from that of CAC^{3, 4}. In the following section, we will explore how the different cells of the tumor microenvironment are affected by cytokines and how they alter IBD, predispose to CAC and regulate CAC development and progression.

Cytokines in IBD and colitis associated cancer (CAC)

The development, growth, activation, and function of innate and adaptive immune cells are controlled largely by cytokines, and their effect on tumor associated immune cells is extremely influential. Mouse studies on colitis-associated cancer have yielded the greatest insights thus far into the mechanisms immune cells driven by cytokines in the tumor microenvironment.

TNF—Tumor necrosis factor (TNF) is a well-known pro-inflammatory cytokine which plays an important role in various cellular events, including cell proliferation, differentiation and cell death⁸. It has also been reported to be involved in inflammation and carcinogenesis⁹. The main sources of TNF production are from monocyte/macrophage lineages in inflammatory disorders. Yet, other cell types have also been accounted for TNF production, including mast cells, T and B lymphocytes, natural killer cells, neutrophils, endothelial cells, smooth and cardiac muscle cells, fibroblasts and osteoclasts¹⁰. Of note, the pro-inflammatory transcription factor NF- κ B is the one of the central activators of the inflammatory program, in which it upregulates other gene expressions linked to tumor cell survival, proliferation, invasion, angiogenesis and metastasis¹¹. Due to its pleiotropic functions, TNF in IBD is a potent cytokine that promotes inflammation¹². In agreement with its role promoting chronic inflammation, in CAC, it promotes tumorigenesis¹³. Neutralization of TNF protects IBD in mouse models and in patients. Furthermore, anti-TNF

monoclonal antibodies have been shown to be effective in treating Crohn's disease and ulcerative colitis¹⁴. However, soluble TNFR2 is not very effective in the treatment of IBD.

IL-6—IL-6 is mostly produced by stimulated monocytes, macrophages, T and B lymphocytes¹⁵. In particular, lamina propria macrophages and CD4⁺ T cells produce high amounts of IL-6 in experimental colitis and in IBD patients^{16, 17}. It has been shown that elevated IL-6 expression is linked to increased risk of development of colorectal adenomas¹⁸. IL-6 binds to soluble IL-6 receptor (sIL-6R) and forms IL-6-sIL-6R complex which activates intestinal target cells via gp130 surface molecule binding³. Of note, binding of IL-6 to sIL-6 receptor (IL-6-sIL-6R complex) prevents apoptosis¹⁶ and activates STAT3¹⁹, a major oncogenic transcription factor. Thus, IL-6 affects the pro-inflammatory functions by triggering multiple target cells such as antigen-presenting cells (APC) and T cells. Intriguingly, blockade of IL-6 signaling with monoclonal antibodies proved to be effective in suppressing chronic intestinal inflammation in mouse models^{16, 20}. Suppression of colitis activity was associated with the inhibition of STAT3 activation, induction of T cell apoptosis and decreased level of pro-inflammatory cytokines (e.g. IFN γ , TNF and IL-1 β)^{16, 20}. In AOM/DSS model of CAC, IL6^{-/-} mice have reduced number of tumors compared to the WT mice^{21, 22}. In addition, they also showed increased apoptosis and decreased proliferation on intestinal epithelial cells (IECs). In the rescue experiment where AOM/DSS treated IL6^{-/-} mice were given recombinant IL-6, increased tumor multiplicity and tumor sizes were observed²¹. In summary, IL-6 arises as a potential target in colon cancer.

IL-1—In inflamed mucosa of IBD, lamina propria dendritic cells (DC) and macrophages secrete huge amounts of other pro-inflammatory cytokines, such as IL-1 and IL-18²³ after being activated in response to the presence of commensal microbiota or TLR signaling³. Synthesis and release of IL-1 cytokines is a tightly regulated process with initial mRNA and pre-protein synthesis regulated by TLR and NF- κ B pathways and processing/release of mature cytokine regulated by inflammasomes. IL-1 is represented by IL-1 α and IL-1 β , which signals through IL-1R. Intestinal epithelial cells produce IL-1Ra (IL-1 receptor antagonist) which functions to inhibit IL-1 pro-inflammatory actions by binding to target cells IL-1 receptor and competitively counteracting the effects of IL-1²⁴. A decrease in IL-1Ra/IL-1 ratio was observed with increasing IBD activity and the imbalance between these two ratios suggests that IL-1Ra deficit may contribute to the pathogenesis of chronic gut inflammation²⁴. Subsequent studies in mouse colitis models have suggested that IL-1 family members possess pleiotropic functions that are dependent on the phase of the disease³. Increasing levels of IL-1 system in IBD may be a result of colonic macrophages stimulation that activates IL-1 converting enzyme/caspase 1 (ICE) and thus release the mature IL-1b into the colonic mucosa²⁵. Recently, IL-1 β activity blockage was shown to reduce tumorigenesis in mice by impairing macrophage-dependent IL-6 secretion²⁶. These findings imply that IL-1 has prominent role in the initiation of colonic inflammation³. SIGIRR/TLR8 is a negative regulator of IL-1R signaling and its knockout increases intestinal inflammation and CAC²⁷.

IL-23/IL-17 Axis (IL-17A, IL-17F, IL-22, IL-23)—Interleukin-17 (IL-17) is a cytokine which bridges the adaptive and innate immune systems²⁸. IL-17 is produced by CD4+ T helper cells named Th17 cells and is controlled by transcription factor retinoic-acid receptor related orphan receptor (ROR) γ t²⁹. IL-17 contains 6 members, IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F³⁰. Th17 cells play an important role in host defense against extracellular microorganisms, but are also involved in chronic pathologies such as inflammatory and immune-mediated diseases³¹. Development of Th17 cells can be categorized into 3 stages: differentiation (TGF β and IL-6), amplification (by IL-21) and stabilization (IL-23). In mice, naïve T cells differentiate into Th17 cells producing IL-17A cytokine in the presence of TGF β and IL-6, which promote ROR γ t and ROR α expression³², transcription factors important for Th17 differentiation. By contrast, IL-6 alone can be sufficient to drive Th17 cells to secrete IL-22 cytokine. In addition, IL-23 and STAT3 are required for expansion and maintenance of Th17 cell response³³. Of note, IL-23 is absolutely required for providing Th17 cells a pathogenic phenotype. Moreover, environmental toxins (dioxin) and chemical compounds have been shown to impact Th17 differentiation through aryl hydrocarbon receptor (AHR) transcription factor^{34, 35}.

IL-23

IL-23 is one of the members of the heterodimeric cytokines IL-12 family and it is produced by APCs during intestinal inflammation³. APCs produce high amounts of IL-23, which prolongs local T helper 17 (Th17) cell activity³³ and possibly suppresses Tregs function^{36, 37}. It was first thought to be the cytokine driving Th17 differentiation³⁸. Conversely, it is not needed for differentiation, instead for maintaining Th17 cells. Naïve T cells are not responsive to IL-23³⁹. IL-23 and IL-23R are absolutely essential for T cells driven and innate immune driven colitis^{37, 40, 41} for DSS colitis controversial phenotypes^{40, 42}. In the absence of IL-23, pro-inflammatory cytokines in colon such as TNF α , IL6 and IFN γ were reduced⁴³. Overexpression of IL-23 in the intestine induces inflammation and colon cancer by itself⁴⁴.

IL-17A and IL-17F

IL-17A and IL-17F have been shown to be elevated in tissue biopsies of IBD patients^{45, 46}. In transfer colitis model, Leppkes et al found that IL-17A and IL-17F have functional redundancy and both contribute to the pathogenesis of colitis⁴⁷. Deficiency of both IL-17A and T cell derived IL-17F by neutralizing IL-17A after IL-17F^{-/-} T-cell transfer significantly reduced colitis severity⁴⁷. Rescue experiments with administration of recombinant IL-17A alone was sufficient to induce colitis in Rag^{-/-} mice upon transfer of ROR γ t-deficient T cells⁴⁷. ROR γ t is essential for Th17 and innate lymphoid cells (ILC) 3 differentiation and controls mucosal IL-17A and IL-17F production, and they have redundant but pathogenic role in chronic intestinal inflammation. On the other hand, in DSS-colitis model, another group has found that IL-17F inhibits colon tumorigenesis and suggested it possibly does it by inhibiting angiogenesis⁴⁸.

IL-22

IL-22 is a member of IL-10 family and another effector cytokine that is produced by Th17 cells, preferentially⁴⁹, dependent on AHR transcription factor³⁹. IL-22R complex is highly expressed by epithelial cells in intestine, skin, lung as well as resident tissue cells in liver and kidney^{49, 50}. There are evidence about largely protective role of IL22 in experimental models of IBD, including T-cell transfer, DSS-colitis and in spontaneous model of intestinal inflammation in TCR $\alpha^{-/-}$ mice^{51, 52}. In TCR $\alpha^{-/-}$ mice, IL-22 overexpression reduces the disease score⁵¹; in DSS-colitis, blocking of IL-22 pathway resulted in delayed recovery and increased damage^{51, 52} and the adoptive T-cell transfer from *Il22* $^{-/-}$ mice into *Rag1* $^{-/-}$ *Il22* $^{-/-}$ mice causes more severe weight loss and mortality than the transfer of wildtype T cells into the same recipient mice⁵². Additionally, IL-22 keeps pathogenic microbiota at bay and its deficiency increases colitis⁵³. Moreover, it has been shown that IL-22 can induce chemokines and various anti-bacterial peptides^{51, 52, 54, 55}. In summary, IL-22 functions in maintaining the integrity of the epithelial barrier⁵¹, on the other hand, IL-22 is required for colitis development driven by *Helicobacter* in *Rag* $^{-/-}$ mice⁵⁵.

Cytokines and Colon Epithelial Cells—Epithelial cells of the colon are both producers and responders to cytokines and chemokines, and those signals can modulate epithelial cell activity by affecting proliferation, migration, and survival programs. This, in turn, can translate into much broader consequences at the tissue level, as the milieu of cytokines and chemokines can push the colon towards a pro-regenerative state (epithelial stemness and proliferation), suppress or induce inflammation (immune tolerance vs. IBD initiation), or create a local environment conducive to epithelial transformation and ultimately tumor development. Recent studies have begun to yield great insight into the progression of IBD and CAC and the complexities involved with the balance of cytokines.

IL-6 has been demonstrated to be greatly up-regulated in IBD and colon cancer and its effect on epithelial cells is multifaceted^{56, 57}. In CAC mouse models, IL-6 exacerbated tumorigenesis through STAT3 signaling in colon epithelial cells, which enhanced epithelial cell survival and proliferation^{21, 58}. Similarly, STAT3 signaling in colon epithelial cells was shown to promote wound healing in a colitis induced mouse model, by controlling IL-22 and its related signaling, which induced epithelial cell survival and proliferation⁵⁹. IL-6 was also demonstrated to simultaneously down-regulate the tumor suppressor p53, and up-regulate the oncogene c-myc in colon epithelial cells, promoting ribosome production, EMT, and resistance to cytotoxic stresses⁶⁰. These properties were also seen in the epithelial cells of patients with UC, and anti-inflammatory corticosteroid therapy reversed the IL-6 induced profile. Thus, IL-6 directly supports the growth of colon epithelial cells and repair of intestinal wounds, but can also promote the development of colon cancer.

IL-17 family members, such as IL-17A, IL-17C, and IL-17F, regulate the functions of colon epithelial cells in IBD and CAC. IL-17A is the most widely studied member of this family in the context of IBD and intestinal tumorigenesis. IL-17A appears to be protective against colitis, while it enhances colon cancer development. For example, blockade of IL-17A was ineffective and even exacerbated IBD in some patients, due to the critical role IL-17A plays in the maintenance of epithelial barrier homeostasis^{61, 62}. Conversely, CAC and spontaneous

CRC, IL-17A expression is elevated, and worsens disease progression^{63, 64}. IL-17C production, driven by microbiota, supported intestinal epithelial cell survival and enhanced colon cancer tumorigenesis⁶⁵. Loss of IL-17F was shown to be critical in the development of intestinal tumors in the APC^{Min+} model, but repressed IBD and CAC in AOM/DSS model⁶⁶. They also suggested that IL-17F and IL-17A work synergistically to stimulate tumorigenesis. In sum, IL-17 family members are associated with a pro-inflammatory profile, but have differential effects on the progression of IBD and colon cancer.

Because intestinal barrier function and control of microbiota is crucial to limiting damaging inflammation, toll like receptors (TLRs) are other important players in the IBD and CAC arena. TLRs are pattern recognition receptors that essentially “sense” microbes and alert the immune system to any perturbations in microbial homeostasis, through activation of transcription factors (i.e. NF- κ B) and the secretion of cytokines and danger signals⁶⁷. Epithelial over-expression of TLR-4 driven by the villin promoter, to target intestinal cells, was found to increase severity of both DSS induced colitis and colitis associated cancer in mice, by increasing inflammatory mediators, TNF- α , COX-2, and IL-12⁶⁸. However, TLRs and the adaptor protein MyD88 are also necessary for proper intestinal homeostasis. In several models, TLR-4 deficient mice were found to have impaired wound healing of the intestine, and mice with MyD88 specifically deleted from intestinal epithelial cells were shown to have disrupted barrier function and microbiota distribution⁶⁹⁻⁷¹. In all of these cases, colitis induced by DSS was exacerbated, as intestinal homeostasis was severely dysregulated. Again, the common theme here is that wound healing programs and intestinal barrier integrity generally protect against injury and colitis, but they exacerbate colitis-associated cancer. These studies on the contribution of cytokines and epithelial cells on intestinal inflammation illustrate the complexity of maintaining intestinal homeostasis versus the development of IBD and CAC.

Cytokines and Stromal Cells—While cytokines can have a direct effect on epithelial and, therefore tumor cells, their influences on the tumor microenvironment and stroma may be equally important for their role in IBD and CAC. Fibroblasts and myofibroblasts are major stromal cells particularly responsible for creating and maintain the extracellular lattice that other cell types rely on for support, structure, and growth^{72, 73}. They can shape this lattice by either depositing large amounts of extracellular matrix (ECM) proteins, such as collagens, fibronectins, and laminins, or by breaking them down with proteases, such as matrix metalloproteinases (MMPs). Thus, they play a major role in wound healing and also, perhaps not unexpectedly, in tumor growth. They are recruited to the tumor by various signals, such as chemokines, and can originate from various locations (tissue resident, bone marrow) and cell types (epithelial, mesenchymal stem cell, endothelial cells). Recent studies have demonstrated the contribution of fibroblasts on the exacerbation of colon cancer with IL-6 derived from CAFs resulting in an up-regulation of Vascular Endothelial Growth Factor (VEGF), driving angiogenesis in these tumors and activated JAK2/STAT3 pathway in CRC cells, inducing stemness and promoting cancer progression in xenograft models^{74, 75}. CAFs also have a clear inflammatory signature, characterized by expression of MCP-1 (CCL2), CCL11, CCL8, CCL20, CXCL5, and IL-9, which promoted cancer cell invasion, growth, and survival⁷⁶. CAFs were also implicated in the induction of S100A8/A9

secretion from immature monocytes, through IL-6 and IL-8 (CXCL8) production from CAFs, which facilitated monocytic differentiation into pro-tumorigenic macrophages or MDSCs⁷⁷. Crosstalk between colon cancer cells and fibroblasts was also demonstrated in a study where CAFs cultured in colon cancer cell media over-produced TGF- β , resulting in chronic activation of fibroblasts, evident by alpha smooth muscle actin expression (α -SMA), which exacerbated tumorigenesis⁷⁸. Another growth factor, epiregulin, is preferentially over-expressed in fibroblasts of colitis-associated, but not sporadic, colon cancer, which lead to tumor progression through hyper-activation of ERK⁷⁹. Thus, cytokines from stromal sources, such as CAFs, facilitate the recruitment and activation of immune cells to support an inflammatory microenvironment in IBD and CAC.

Endothelial cells are another prominent cell type in the tumor microenvironment and they serve as the foundation for blood vessels and angiogenesis, supplying the tumor with vital nutrients and oxygen. They are often affected by cytokine signaling in tumors, which can control endothelial cell proliferation, permeability, migration, and survival. One major cytokine-like factor that activates endothelial cells is VEGF. VEGF induces angiogenesis by binding to its major receptor, VEGFR2 causing downstream activation of kinases, such as ERK and PI3K, stimulating endothelial cell proliferation and migration⁸⁰. Although angiogenesis is an important part of the wound healing process, over-amplification of re-vascularization can promote both IBD and CAC. Angiogenesis is important aspect of the pathogenesis of IBD and CAC, as it serves as a gateway for immune and inflammatory cells.

A comprehensive study on intestinal epithelial expression of VEGF and its receptors determined their importance in CAC development in mice, in part by promoting angiogenesis and also by inducing inflammation⁸¹. In colon cancer patients, anti-VEGF therapies, such as Bevacizumab/Avastin (anti-VEGF monoclonal antibody), have improved survival, but their effects as a single agent are limited⁸². Targeting cytokines may further help alleviate the trepidations concerning anti-VEGF treatments. IL-17A and M-CSF were shown to mediate anti-VEGF therapy in a number of tumors, including colon cancer, and blockade of IL-17 signaling sensitized the tumors to anti-VEGF therapy⁸³. Whether the same can be done in IBD and CAC remains to be tested. Another group showed that GM-CSF was produced in high amounts by intestinal epithelial cells during CAC, which in turn facilitated epithelial release of VEGF, promoting inflammation and driving carcinogenesis⁸⁴. Blockade of GM-CSF greatly reduced VEGF levels and inflammation, stunting tumor growth. Overall, the body of work on VEGF promoting angiogenesis is extensive in tumorigenesis, but the mechanisms that regulate its expression and function by cytokines in CAC is only recently becoming elucidated. Further work must be done to overcome anti-VEGF resistance, and cytokines appear to play a major role in this process.

While much of the work on tumor angiogenesis has centered upon VEGF, cytokines and their downstream mediators can have a dramatic effect on colon cancer neo-vascularization. IL-8 stands out as a potent angiogenic factor in colon wound healing, colitis, and cancer. IL-8 is over-expressed in patients with IBDs, and is generally localized to areas of active inflammation and tissue damage^{85, 86}. In addition, in an IL-8 transgenic mouse model (expressing human IL-8, as mice do not produce this cytokine), IL-8 supported tumor progression and angiogenesis in patient and mouse colon cancer xenografts⁸⁷. IL-8 was

demonstrated to promote colon cancer development and signal through CXCR2 on intestinal endothelial cells, inducing proliferation and angiogenesis *in vitro* and *in vivo*^{88, 89}.

Moreover, IL-8 can allow tumors to overcome HIF-1 (major inducer of hypoxic response genes, such as VEGF) deficiency and maintain their angiogenic capacity⁹⁰. Thus, in addition to promoting inflammation by recruiting neutrophils and immature myeloid cells (also referred to as MDSCs), IL-8 in the tumor microenvironment intensifies colon cancer growth through the enhancement of angiogenesis, signaling directly on endothelial cells through CXCR2.

IL-1 β , a key cytokine regulated by inflammasomes, is a secreted glycoprotein that also plays a role in tumor angiogenesis⁹¹. IL-1 β seems to act indirectly on endothelial cells in order to enable angiogenesis, by instituting a pro-inflammatory program in target cells^{91, 92}. In relation to colon cancer angiogenesis, long term inhibition of COX-2 in the APC^{min/+} intestinal model of tumorigenesis resulted in increased microvascular density and IL-1 β expression in colon tumors (despite a down-regulation of NF- κ B), suggesting that IL-1 β correlates with angiogenesis⁹³. IL-1 β can also support the survival of endothelial cells by stimulating vascular smooth muscle cells (supporting vessel cells) to secrete VEGF⁹⁴. In sum, the evidence suggests IL-1 β to be an indirect activator of endothelial cells and angiogenesis, through the up-regulation of pro-inflammatory and pro-angiogenic molecules.

In addition to the accumulation of immune cells, fibroblasts, and endothelial cells, mesenchymal stem cells (MSCs) also find their way into the colon microenvironment during IBD or CAC. MSCs can originate from the bone marrow or from adipose tissue adjacent to the tumor⁹⁴. Cytokine and chemokine gradients attract MSCs to tumors or sites of inflammation, where they can promote the development of these diseases by a number of methods, including induction of vascularization, extracellular matrix remodeling, immune suppression, and differentiation into CAFs. Essentially, the evidence seems to support the notion that MSCs are protective in colitis, but contribute to CRC. However, pertaining to colon cancer, the role of MSCs is lacking and somewhat conflicting⁹⁵. Nevertheless, there has been some progress over the past few years to tease out the ability of MSCs to home to colon cancer tumors and to modulate tumor progression. So how do MSCs get recruited to tumors? TNF- α , and its related signaling through NF- κ B, strongly induce MSC migration to CRC tumors⁹⁶. Additionally, another study has suggested the importance of high mobility group box-1 (HMGB-1), a so called “danger signal” that is linked to innate immune cell infiltration, in the homing of MSCs to colon cancer tumors⁹⁷. Once they have colonized the tumor, most colon cancer studies have revealed MSCs to be pro-tumorigenic, although a majority of the evidence is in transplantable cell models/xenografts, which is outside of the scope of this review, but has been discussed in these reviews^{94, 95}. Thus, the MSCs appear to have a negative impact in spontaneous CRC development. Although MSCs can clearly promote CRC development through a number of mechanisms, MSCs can also play a protective role in the colon, especially in the case of colitis. Several studies have demonstrated that MSCs contribute to colon epithelial repair by differentiating into intestinal epithelial cells, fibroblasts, or by supporting the growth of new blood vessels in various rodent models of colitis⁹⁸⁻¹⁰⁰. Similar findings were corroborated in humans, as it was shown that in patients with intestinal inflammation that received bone marrow transplants

had MSC migration to the colon and better regeneration of damaged epithelium¹⁰¹. In a comprehensive study on the contribution of MSCs in immune regulation in mice, MSCs were shown to promote T-cell apoptosis through Fas/FasL signaling in DSS induced colitis, causing an increase in the number of Tregs and healing of the colon¹⁰². The proposed mechanism was that MCP-1 secreted by MSCs recruited T-cells to MSCs and they underwent apoptosis. Additionally, T-cell debris caused induction of TGF- β in macrophages, ultimately leading to increased Tregs numbers. Interestingly, MSCs can also suppress tumor initiation of CAC¹⁰³. A recent study found that co-injection of AOM and MSCs reduced the number of colon tumors in mice by half, significantly increasing p- β -catenin levels (inactive form), and subsequently a decrease in WNT signaling pathway. Additionally, TGF- β levels were increased, which was considered a suppressor of tumor initiation and cell proliferation in their model, and promoted G1 arrest in epithelial cells and prevented DNA damage. They concluded that MSCs can effectively prevent tumor initiation in CAC (and likely suppressed colitis), but minimally affect developed tumors. Another group discovered that MSCs isolated from allogeneic mice and then co-injected with AOM/DSS reduced CAC development and severity and decreased expression of the cytokines TNF- α , IL-1 β , and IL-6, and subsequently activation of p-STAT3. All in all, because of their potential ability of to induce repair and healing in the colon, as well as mitigate pro-inflammatory cytokines, MSCs have been suggested to be a promising therapeutic intervention in colitis and CAC, however further work must be done to validate this premise and optimize MSC sources and routes of delivery. Undoubtedly, MSCs can be pro-tumorigenic in relation to spontaneous CRC (promotes established tumors) and beneficial in CAC (prevents tumor initiation by inflammation), but this field is only in its infancy and will require further research into the precise mechanisms of MSC homing specific to CRC tumors and investigation of differential mechanisms of immunomodulation in spontaneous vs. CAC.

Overall, the tumor microenvironment is constantly evolving entity that has a diverse cellular makeup, with various pro-inflammatory, anti-inflammatory, and pro-wound healing mediators. It is the complex combination of factors that ultimately determines how tumors grow and respond to therapies. It is anticipated that targeted inhibition of many cell types will ultimately stunt more aggressive tumors by normalizing the dysregulated cellular functions altered by cytokines and related signaling. The basic interactions of cells in the tumor microenvironment are summarized in Figure 2. Also, inhibition of inflammation in IBD will widen preventive and detection window for CAC, as it will delay its development and progression.

Targeting Cytokines in IBD - bench to bedside

Clearly, cytokines and their related signaling provide an opportunity for targeted therapies to subdue IBD promoting inflammation. TNF- α has emerged as the most successful clinical cytokine based intervention in the treatment of IBD. Other anti-cytokine therapies are also under consideration, and there are a number of clinic trials ongoing targeting proteins such as IL-6, IL17A, IL-12/IL-23, and IL-13 (Table 2). As we uncover more mechanisms of action, we can expect more clinical trials targeting cytokines and their receptors, as well as more useful combination treatments as well (IL-17A and IL-17F, for example). Hopefully,

in the near future, this will lead to improved patient quality of life and prevent the associated cancers that arise due to chronic inflammation.

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Figure 1. Inflammation drives IBD and CAC pathogenesis

Cytokines induce extensive inflammation in the colon, which has a negative impact on epithelial cells, resident and recruited immune cells, and stromal cells. Inflammation can cause damage to epithelial cells and activate and recruit immune and stromal cells. This leads to a non-resolving chronic inflammatory situation, and leads to the development of IBD and potentially CAC.

Figure 2. The colitis microenvironment

In IBD, the epithelial layer of the colon suffers damage, increased permeability, and leakage of luminal content (microbes, microbial products, metabolites, etc.), which induces local immune cell activation. The production of cytokines by responding leukocytes causes the recruitment of more leukocytes and therefore more cytokine production, causing a positive feedback loop. Other cell types, such as endothelial cells, fibroblasts, and MSCs are also recruited to the site of inflammation. Endothelial cells create new blood vessels, which directly allow more immune cells to reach the damaged area. Fibroblasts can become activated as well and secrete pro-inflammatory cytokines and proliferate out of control, creating fibrosis. Lastly, MSCs actually have a beneficial role, and attempt to regenerate the damage epithelium and secrete the appropriate cytokines.

Figure 3. The tumor microenvironment

Tumors are a complex and heterogeneous mixture of various cell types that dynamically interact with each other. A multitude of cell types, including endothelial cells, fibroblasts, stem cells, and immune cells get recruited to and support tumor progression, and cytokines are major drivers this process. The uneven distribution of the different cell types creates local environments that are dissimilar from one another, and can act as niches for certain cell types, or program cells differentially. Unlike in IBD, wound-healing processes appears to promote tumorigenesis, while they are beneficial to damaged epithelia in colitis. The heterogeneity of the microenvironment is a major therapeutic hurdle, and understanding how cytokines affect each cell type will be critical to clinical efficacy.

Table 1
Cytokines and their effects on IBD and CAC

This table identifies the role of cytokines in three potential outcomes of IBD and CAC. The examples listed demonstrate if the cytokine in question worsened IBD and CAC, improved both IBD and CAC, or had differential effects on IBD and CAC.

Model	Examples	Reference
IBD and CAC exacerbated	<ul style="list-style-type: none"> IL-22 drives intestinal inflammation and tumor formation in bacterial driven colitis model IL-1β promotes IBD and CAC IL-23 overexpression induces inflammation and CAC NLRP3, NLRC4, NLRP6 KO mice shifts towards pro-inflammatory phenotype, disrupting epithelial integrity and promoting both conditions 	104 26 44 105-108
IBD and CAC ameliorated	<ul style="list-style-type: none"> IL-22 protects against intestinal inflammation and cancer development IL-6 blockade reduces IBD and CAC TNFα inhibition reduces IBD and CAC IL-1β blockade reduces CAC IL-23 signaling inhibited in mouse models reduces intestinal inflammation and CAC IL-21 genetic ablation reduces intestinal inflammation and CAC IL-17RA KO mice display reduced colitis in mice 	51-53 16, 20, 22 12, 13, 26 63 109 110
IBD ameliorated, CAC exacerbated	<ul style="list-style-type: none"> Blockade of IL17F lessens inflammation in colitis, but accelerates tumorigenesis IL-17A expression necessary for intestinal homeostasis in IBD, but promotes inflammation in CAC 	47, 48 61, 63, 64
IBD exacerbated, CAC ameliorated	<ul style="list-style-type: none"> STAT3 KO in the epithelium reduces intestinal integrity and reduces wound healing increasing IBD severity, but limiting CAC. IKKβ KO in epithelium disrupts intestinal integrity and increases susceptibility to cell death. 	21, 52 6, 111

Table 2
Anti-cytokine therapies in the clinic

This table depicts current clinical trials on-going for anti-cytokine therapies in the treatment of IBDs, namely ulcerative colitis (UC) and Crohn's Disease (CD).

Potential therapeutics intervention		
	IBD	
	UC	CD
IL6/IL6R	-	Clinical trials stage II
IL12 and IL23	Clinical trials stage II	-
TNF	used in clinic	used in clinic
IL-13	Clinical trials stage II	?
IL-17A	-	Clinical trials stage II