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Role of TH17 cytokines in the control of colorectal cancer

Veronica De Simone, Francesco Pallone, Giovanni Monteleone, and Carmine Stolfi*

Department of Systems Medicine; University of Tor Vergata; Rome, Italy

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Immune/inflammatory cells infiltrate almost all human solid tumors and affect all stages of carcinogenesis as they produce different cytokine subsets. The overproduction of T_H17 cytokines marks the early stages of colorectal carcinoma (CRC) and negatively influences the prognosis of CRC patients. Studies with murine models of CRC have delineated the mechanisms by which T_H17 cytokines, notably, interleukin (IL)-17A, IL-17F, IL-21, and IL-22, regulate oncogenesis and tumor progression, paving the way to the development of novel anticancer drugs. In this review article, we discuss experimental data supporting the role of T_H17 cytokines in the modulation of colorectal tumorigenesis.

Introduction

Colorectal carcinoma (CRC) is one of the most common forms of malignancy and the second leading cause of cancer-related death in the western world.[1] The development of CRC is a multistage process characterized by a complex interaction between environmental carcinogens, genetic alterations, and the host immune system, ultimately resulting in the uncontrolled growth of transformed cells.[2] Like other common malignancies (e.g., hepatocellular carcinoma, prostate carcinoma, gastric cancer), chronic inflammation is an independent risk factor for the development of CRC.[3] Approximately 2% of CRC cases arise in patients with long-standing and extensive ulcerative colitis,[4] one of the 2 major forms of inflammatory bowel disease (IBD) in humans, while the majority of CRCs develops in individuals who are not affected IBD. However, even in these latter patients, the neoplastic tissue is massively infiltrated with immune/inflammatory cells, including $CD4^+$ and $CD8^+$ T lymphocytes, B cells, macrophages as well as natural killer (NK) cells, which can either foster or suppress the survival and growth of CRC cells, mostly through the production of cytokines.[5,6] In this context, the production of interferon γ (IFNγ) by T_H1 $CD4^+$ cells, $CD8^+$ cells, and NK cells has been demonstrated to limit tumor growth by activating cytotoxic immunity,[6] and the presence of T_H1 polarization markers positively correlates with reduced tumor recurrence among CRC patients.[7] In contrast, cytokines produced by T_H17 cells appear to exert pro-tumorigenic effects, and the presence of a T_H17 immune cell infiltrate negatively influences the prognosis of CRC patients.[8,9]

In this article, we review data supporting a role for T_H17 cytokines in the control of CRC.

*Correspondence to: Carmine Stolfi; Email: carmine.stolfi@uniroma2.it
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T_H17 Cells in Cancer

T_H17 cells produce high amounts of interleukin (IL)-17, also termed IL-17A, and their developmental program is controlled by the transcription factor retinoic acid receptor-related orphan receptor (ROR)γt.[10] T_H17 cells also synthesize IL-17F, IL-21, IL-22 and IL-26.[11,12] However, not all T_H17 cells secrete this cytokine cocktail, probably reflecting the heterogeneity of the T_H17 cell subset. Moreover, some T_H17 cytokines can be synthesized by other immune cell types, including innate lymphoid cells, NKT cells, $CD8^+$ T lymphocytes and macrophages.[13-16]

In mice, T_H17 cells differentiate from naïve T cells following activation in the presence of transforming growth factor β1 (TGFβ1) and IL-6, 2 cytokines that are sufficient to promote the expression of both RORγt and RORα, another transcription factor critical for T_H17 differentiation.[17,18] There is also evidence that the optimal expansion and maintenance of the T_H17-cell response require IL-23 and the activation of the transcription factor signal transducer and activator of transcription 3 (STAT3).[19] The mechanism by which T_H17 cells differentiate in humans is not yet fully understood, even though in vitro studies indicate that the activation of $CD4^+$ T cells in the presence of either IL-1β and IL-6, or TGFβ1 and IL-21 induces the secretion of IL-17A.[20,21] However, the T_H17 cell lineage displays a great degree of context-dependent plasticity and can acquire functional features of T_H1 cells in response to IL-12 signaling.[22,23]

Beside an important role in the host defense against extracellular microorganisms, T_H17 cells participate in the pathogenesis of diverse immune-mediated diseases, including IBD, psoriasis and rheumatoid arthritis.[24] Compelling evidence indicates that T_H17 cells are also involved in the control of tumorigenesis and T_H17 cytokines have been ascribed with either a positive or a negative effect on the survival and growth of malignant cells depending on the experimental model.[25,26] The reason why T_H17

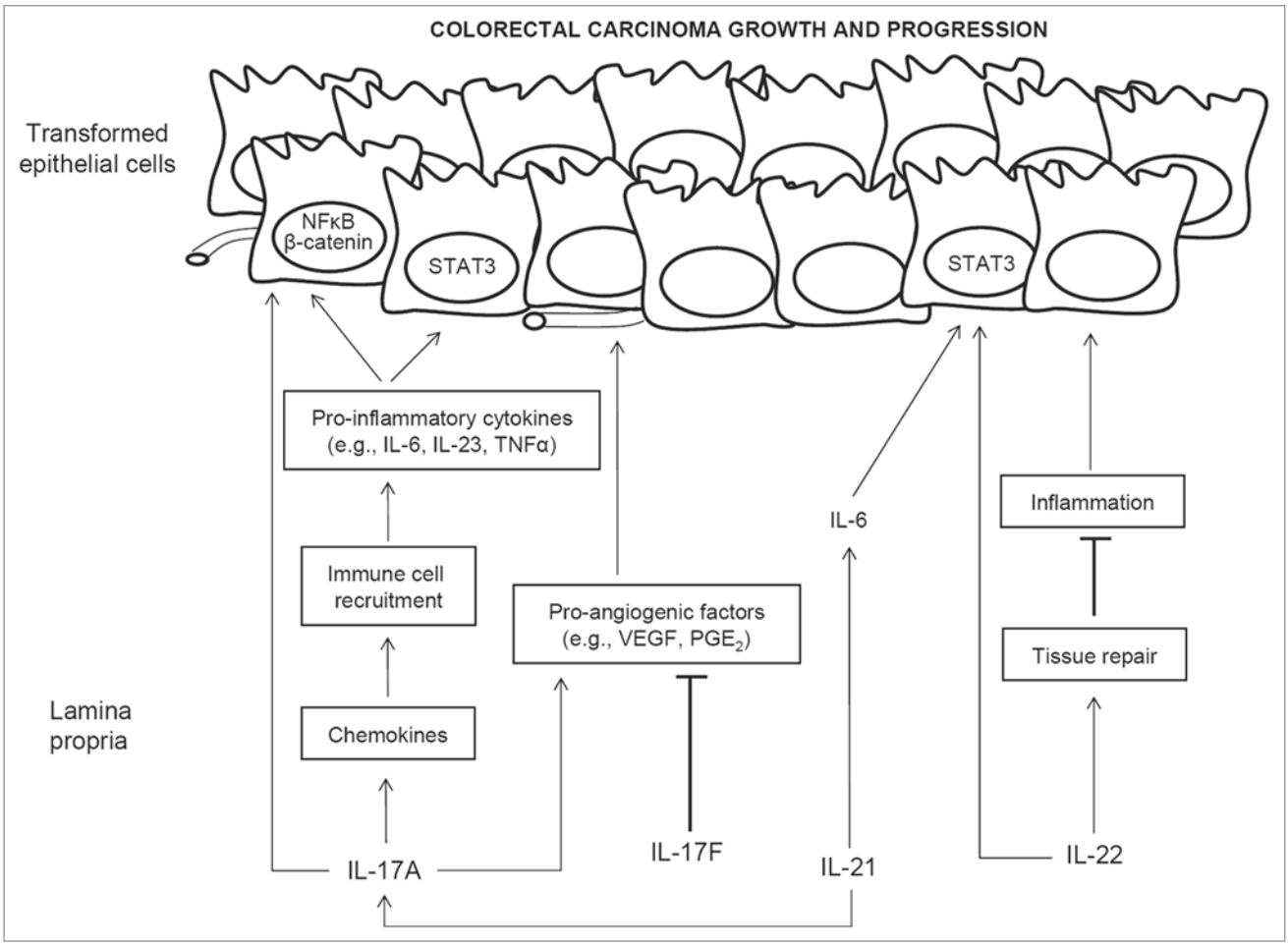

Figure 1. Overview of the role of T_H17 cytokines and downstream signaling pathways in colorectal carcinoma. Abbreviations: IL, interleukin; STAT3, signal transducer and activator of transcription 3; PGE_2, prostaglandin E_2; VEGF, vascular endothelial growth factor; TNFα, tumor necrosis factor α

cells have a dual role in the control of tumorigenesis is unknown, even though it is conceivable that their capacity to differentiate into tumoricidal T_H1-like cells under specific conditions can contribute to the antitumor effect mediated by T_H17 cells in some settings.

Role of T_H17 Cytokines in CRC

IL-17A-producing $CD4^+$ T lymphocytes and macrophages infiltrate human CRCs and the density of these cell type correlates with a poor prognosis.[27] $CD4^+$ T cells co-expressing RORγt and the regulatory T cell-associated transcription factor forkhead box P3 (FOXP3) and producing IL-17A are abundant in human CRCs as well as in the intestine of polyp-ridden *Apc*$^{min/+}$ mice.[28] These cells exert potent immunosuppressive functions and are supposed to sustain oncogenesis and tumor progression.[28] Consistently, many studies have shown that IL-17A, IL-17F, IL-21, and IL-22 are overexpressed at both the mRNA and protein level in human CRCs as compared with the non-transformed, adjacent colonic mucosa.[29-32] Moreover, CRC patients harboring elevated levels of IL-17A and RORγt in neoplastic tissues exhibit a drastic reduction in disease-free survival.[33] Studies in mouse models of CRC support the pro-tumorigenic role of T_H17 cytokines. However, as discussed below, IL-17A, IL-17F, and IL-22 can also exert anti-tumorigenic effects under specific circumstances (**Fig. 1**; **Table 1**).

IL-17A and IL-17F

IL-17A and IL-17F can be produced by immune cells other than T_H17 cells, including innate lymphoid cells, γδ T cells, NKT cells, neutrophils, and eosinophils.[16] Both IL-17A and IL-17F signal through the IL-17 receptor A (IL-17RA), an ubiquitously expressed type I transmembrane protein[34] that triggers the mitogen activated protein kinase (MAPK) and NFκB signaling pathways, hence stimulating the production of pro-inflammatory cytokines, chemokines, and prostaglandins.[34]

Early studies in mice subjected to the subcutaneous implantation of CRC cells showed opposite roles of IL-17A in the modulation of tumor growth in vivo. Numasaki et al. reported that IL-17A ectopically overexpressed by the murine CRC cell line MC38 enhances the growth of cancer cells in vivo and increases tumor vascularity by promoting the production of pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and prostaglandin E_2 (PGE_2).[35] In contrast, Kryczek and coworkers revealed an increased growth and enhanced metastatic potential

Table 1. Role of T_H17 cytokines in mouse models of colorectal carcinoma

Cytokine	Model	Effects	Ref.
IL-17A	Subcutaneous inoculation of MC38 cells	IL-17A ectopically overexpressed in MC38 cells enhances the growth of cancer cells and tumor vascularity	35
IL-17A	Subcutaneous inoculation of MC38 cells	Increased growth and enhanced lung metastasis of MC38 cells following implantation in IL-17A-deficient mice	36
IL-17A*	Subcutaneous inoculation of MC38 cells	No difference in tumor growth between wild-type and IL-17A-deficient mice	37
IL-17A	*Apc*$^{min/+}$ mice	IL-17A-deficient mice show reduced tumor formation and decreased production of pro-inflammatory cytokines (e.g., IL-6, IL-23), as compared with wild-type mice	38
IL-17A	*Apc*$^{min/+}$ mice infected with ETBF	Blockade of IL-17A inhibits ETBF-induced colitis and tumor formation	39
IL-17A	AOM/DSS-induced colitis-associated CRC	IL-17A-deficient mice express reduced levels of IL-6, STAT3, TNFα and IFNγ and develop milder colitis as well as fewer and smaller tumors than wild-type mice	40
IL-17A, IL-17F	CPC-APC mice	IL-17RA-deficient mice show upregulation of IL-17A and IL-17F and reduced tumor growth as compared with wild-type mice	42
IL-17F	HCT-116 cell xenografts in immunodeficient mice	IL-17F-overexpressing CRC cells proliferate less than control CRC cells	30
IL-17F	AOM/DSS-induced colitis-associated CRC	IL-17F-deficient mice develop more tumors than wild-type mice and this effect is associated with increased tumor angiogenesis	30
IL-21	AOM/DSS-induced colitis-associated CRC	IL-21-null mice have reduced colonic inflammation and limited tumor burden as compared with wild-type mice. These effects are associated with reduced $CD4^+$ T-cell infiltration, increased production of IL-6 and IL-17A, as well as enhanced STAT3 activation	29
IL-21	AOM/DSS-induced colitis-associated CRC	IL-21-deficient mice show decreased IL-17A expression, increased IFNγ content, low epithelial cell proliferation and prominent epithelial cell death in intestinal tumors as compared with wild-type mice	48
IL-22	HCT-116 cell xenografts in immunodeficient mice	IL-22 promotes the growth of HCT-116-derived xenografts and this effect is associated with STAT3 activation	31
IL-22	AOM/DSS-induced colitis-associated CRC	IL-22BP-deficient mice develop more and larger tumors than wild-type mice	55
IL-22	AOM/DSS-induced colitis-associated CRC	IL-22-null mice develop an elevated tumor load compared with wild-type mice	55
IL-22	*Apc*$^{min/+}$ mice	IL-22BP-null *Apc*$^{min/+}$ mice show an exacerbation in intestinal tumorigenesis compared with *Apc*$^{min/+}$ mice	55
IL-22	*Apc*$^{min/+}$ mice	IL-22-deficient *Apc*$^{min/+}$ mice exhibit a reduced tumor burden compared with *Apc*$^{min/+}$ mice	55
IL-22	Colitis-associated CRC induced by infection with *Helicobacter hepaticus* and AOM in 129SvEv.RAG-deficient mice	Antibody-mediated neutralization of IL-22 selectively decreases STAT3 activation in epithelial cells and reduces tumor burden	56

White background = pro-tumorigenic effect; gray background = anti-tumorigenic effect; * = no effect. Abbreviations: AOM, azoxymethane; DSS, dextran sodium sulfate; CPC-APC mice, ApcF/wt mice that harbor a Cdx2-Cre transgene; CRC, colorectal carcinoma; ETBF, enterotoxigenic Bacteroides fragilis; IFNγ, interferon γ; IL, interleukin; STAT3, signal transducer and activator of transcription 3; TNFα, tumor necrosis factor α

for MC38 cells implanted in IL-17A-deficient mice as compared with wild-type mice.[36] These effects were associated with reduced numbers of interferon γ (IFNγ)-producing NK cells and $CD8^+$ T cells within neoplastic lesions and tumor-draining lymph nodes.[36] Different results were obtained by Ngiow and colleagues, who showed that MC38 cells proliferate to similar extents in IL-17A-deficient and -proficient mice.[37] More recent studies have investigated the role of IL-17A in genetic, chemical-driven or microbial CRC models. Bothwell's group showed that the ablation of *Il17a* reduces tumor formation in mice bearing a heterozygote mutation in the adenomatous polyposis coli (*Apc*) gene (*Apc*$^{min/+}$ mice) and this effect is accompanied by a decrease of intratumoral immune cells and pro-inflammatory cytokines (e.g., IL-6, IL-23).[38] Wu and colleagues showed that the infection of *Apc*$^{min/+}$ mice with the human colonic bacterium enterotoxigenic *Bacteroides fragilis* (ETBF) induces colitis and causes oncogenesis in association with a marked T_H17 response and activation of STAT3 in malignant cells. Blockade of IL-17A inhibits ETBF-induced colitis and tumor formation without affecting the activity or subcellular localization of STAT3, suggesting that STAT3 activation precedes the induction of IL-17A in the tumorigenic cascade of events activated in this model.[39]

Using a model of colitis-associated CRC as induced by the sequential administration of the carcinogen azoxymethane (AOM) and dextran sodium sulfate (DSS), Hyun et al. showed that IL-17A-deficient mice express reduced levels of IL-6, STAT3, IFNγ and tumor necrosis factor α (TNFα) and develop milder colitis as well as fewer and smaller tumors than wild-type mice. Moreover, IL-17A-deficient mice exhibit reduced numbers of β catenin$^+$ cells within the intestinal crypts as well as reduction of key cell-cycle regulators (e.g., cyclin D1, cyclin-dependent kinase 2), suggesting a role for IL-17A not only in oncogenesis but also in tumor progression.[40] In contrast, IL-17F-deficient mice appear to develop more neoplastic lesions than wild-type mice upon the administration of AOM and DSS.[30] In this latter model, the lack of IL-17F is associated with the upregulation of VEGF and an increase in CD31$^+$ cells. Altogether, these data suggest that IL-17A exerts pro-tumorigenic functions while IL-17F has a protective role in colitis-associated colon carcinogenesis. The hypothesis that IL-17F mediated antitumor effects is also supported by the observation that IL-17F-overexpressing CRC cells proliferate less vigorously than control cells when transplanted into immunodeficient mice.[30]

Of note, *Apc$^{min/+}$* mice can be genetically modified to develop tumors primarily in the distal colon (CPC-APC model).[41] The neoplastic lesions that develop in CPC-APC mice exhibit a marked upregulation of IL-17A and IL-17F and both tumor multiplicity and growth are reduced in mice lacking IL-17RA.[42] As mentioned above, both IL-17A and IL-17F signal via IL-17RA. Thus, the precise mechanism whereby IL-17A and IL-17F contribute to colorectal carcinogenesis remains unclear.

IL-21

IL-21 is a pleiotropic cytokine produced by activated CD4$^+$ T cells, T_H17 cells, NKT cells and follicular helper T cells. IL-21 signals through a receptor comprising the γ chain subunit (shared with IL-2, IL-4, IL-7, IL-9, and IL-15) and the private IL-21 receptor (IL-21R) chain.[15] The binding of IL-21 to its receptor complex, which is expressed by epithelial cells and monocytes, activates STAT3 and to a lesser degree STAT1 and STAT5, MAPK, and NFκB.[43] Pre-clinical and clinical studies have shown that IL-21 exerts potent antitumor effects owing to its ability to expand cytotoxic immune responses.[44] Conversely, IL-21 has been attributed a pathogenic role in many immune-mediated diseases, including IBD.[43,45] Indeed, IL-21 is overproduced in the colonic mucosa of both ulcerative colitis and Crohn's disease patients, where it positively regulates T_H1 and T_H17 responses.[46,47] Increased IL-21 production is also found in the neoplastic tissues of patients with both sporadic and ulcerative colitis-associated CRC.[29] We showed that IL-21 production is increased in neoplastic lesions of AOM/DSS-treated mice while IL-21-null mice display reduced colonic inflammation and limited tumor burden compared with wild-type mice.[29] The analysis of the mechanisms underlying this effect revealed that IL-21 sustains the infiltration of neoplastic lesions by CD4$^+$ T cells, the local production of IL-6 and IL-17A, as well as STAT3 activation.[29] In line with these observations, Jauch and coworkers reported a reduced expression of IL-17A, increased IFNγ levels, limited epithelial cell proliferation and consistent degrees of apoptosis in the intestinal tumors of IL-21-deficient mice subjected to AOM/DSS administration compared with wild-type mice.[48] Interestingly, the neutralization of IL-21 after the induction of colitis still reduces tumor burden, suggesting that the tumor-promoting effect of IL-21 in this model is not dependent on the inhibition of inflammation.[29] At present, it remains unclear whether IL-21 also regulates the development of sporadic CRC.

IL-22

IL-22 is produced by T_H17 cells, T_H22 cells as well as innate lymphoid cells, and binds to a heterodimeric receptor complex composed of IL-22 receptor 1 (IL-22R1) and IL-10 receptor 2 (IL-10R2), resulting in the activation of STAT1, STAT3, and STAT5.[13] IL-22 can also activate multiple MAPK family members, at least in some circumstances.[49] While IL-10R2 is ubiquitously expressed, IL-22R1 is only found on epithelial cells, including human CRC cells.[50] Notably, IL-22 can be neutralized by a soluble IL-22 receptor known as IL-22 binding protein (IL-22BP), which prevents the binding of IL-22 to membrane-bound IL-22R1.[51-53] IL-22 not only promotes the secretion of mucous and defensins but also stimulates cell proliferation and is supposed to play a major role in tissue repair and oncogenesis in the gut.[54] Jiang et al. showed that high levels of IL-22 promote the growth of human CRC cells (i.e., HCT-116) transplanted into immunodeficient mice, and linked this effect to STAT3 activation and the upregulation of STAT3 downstream effectors like cyclin D1.[31]

Huber and colleagues documented accelerated AOM/DSS-driven tumorigenesis (increased number and size of lesions) in IL-22BP-deficient mice as compared with wild-type mice.[55] Time-course experiments in mice lacking either IL-22 or IL-22BP demonstrated that the negative effect of IL-22BP on CRC cell growth is strictly dependent on the inhibition of IL-22.[55] Surprisingly, IL-22-null mice developed a higher tumor load than wild-type mice.[55] This latter finding might reflect the fact that IL-22 deficiency delays colonic repair and increases intestinal inflammation, thereby accelerating tumor progression. A different scenario emerged in *Apc$^{min/+}$* mice, as the lack of IL-22BP enhanced intestinal tumorigenesis, while IL-22-deficient *Apc$^{min/+}$* mice showed a reduced tumor burden as compared with their IL-22-proficient counterparts.[55]

A pro-tumorigenic role of IL-22 has also been reported in genetically susceptible 129SvEv.RAG-deficient mice, in which chronic colitis is caused by infection with *Helicobacter hepaticus* and colorectal tumorigenesis is stimulated with AOM. In these mice, the antibody-mediated neutralization of IL-22 selectively decreases STAT3 activation in epithelial cells and reduces tumor burden.[56] Altogether, these observations are consistent with a recent findings suggesting an association between a genetic polymorphism in *IL22* and an increased risk of developing CRC.[57]

Conclusions

Elevated levels of pro-inflammatory T_H17 cytokines are found in human CRCs, and numerous studies in mice show a key role for these cytokines in facilitating the survival and growth of CRC cells Accordingly, T_H17 cytokine blockers have

been ascribed with robust antineoplastic effects in several CRC models. In this context, it is noteworthy that T_H17 cytokines may have redundant effects on the activation of pathways that sustain colorectal carcinogenesis and tumor progression, suggesting that the inhibition of downstream effector molecules such as STAT3 could be more advantageous, from a therapeutic perspective, than the blockage of individual T_H17 cytokines. This hypothesis is further supported by the observation that STAT3 is activated by other cytokines that are overexpressed by human CRCs[58,59] and are known to exert pro-tumorigenic effects in mouse models of colon cancer, such as IL-6 and IL-11.[60-63]

In designing therapeutic interventions targeting T_H17 cytokines, one should take into consideration that, at least in mice, IL-17A, IL-17F, and IL-22 can mediate antitumor effects, at least in specific circumstances, raising the possibility that the neutralization of such cytokines may have deleterious, rather than beneficial, effects. Moreover, since T_H17 cytokines are key players in the host defense against intracellular pathogens, T_H17 cytokine inhibitors can enhance the risk of infection. Further work is needed to clarify these issues as well as to ascertain which T_H17 cytokine is specifically upregulated in patients affected by specific types of CRC (e.g., sporadic vs. colitis-associated) and whether this occurs at specific stages of the disease (e.g., early vs. advanced disease). It would be also relevant to determine whether the excessive production of T_H17 cytokines in CRC is linked to genetic polymorphisms and if the genotyping of T_H17 cytokine-coding genes can be useful to identify individuals at high risk for developing CRC and/or to monitor the course of disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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