HHS Public Access

Author manuscript

Mol Cell Endocrinol. Author manuscript; available in PMC 2018 August 15.

Published in final edited form as:

Mol Cell Endocrinol. 2017 August 15; 451: 80–87. doi:10.1016/j.mce.2017.02.023.

STAT3 activation in infection and infection-associated cancer

Rong Lu, **Yong-guo Zhang**, and **Jun Sun**

Division of Gastroenterology and Hepatology, Medicine, University of Illinois at Chicago, Chicago, IL, USA

Abstract

The Janus kinase/signal transducers and activators for transcription (JAK/STAT) pathway plays crucial roles in regulating apoptosis, proliferation, differentiation, and the inflammatory response. The JAK/STAT families are composed of four JAK family members and seven STAT family members. STAT3 plays a key role in inducing and maintaining a pro-carcinogenic inflammatory microenvironment. Recent evidence suggests that STAT3 regulates diverse biological functions in pathogenesis of diseases, such as infection and cancer. In the current review, we will summarize the research progress of STAT3 activation in infection and cancers. We highlight our recent study on the novel role of STAT3 in *Salmonella* infection-associated colon cancer. Infection with bacterial AvrA-expressing *Salmonella* activates the STAT3 pathway, which induces the β-catenin signals and enhances colonic tumorigenesis. STAT3 may be a promising target in developing prevention and treatment for infectious diseases and infection-associated cancers.

Keywords

Bacteria; colon cancer; inflammation; Infection; JAK; *Salmonella*; STAT; STAT3; STAT5; virus

1. Introduction

The Janus kinase/signal transducers and activators for transcription (JAK/STAT) families are composed of four JAK family members (JAK1, JAK2, JAK3 and TyK2) and seven STAT family members (STATs 1, 2, 3, 4, 5a, 5b, and 6). STAT family members act as transcription factors and are activated by JAK proteins. The JAK/STAT pathway plays crucial roles in regulating cell proliferation, differentiation, the inflammatory response and apoptosis[1]. Notably, among STAT proteins, STAT3 is a key player in inducing and maintaining a pro-carcinogenic inflammatory microenvironment. Recent evidence suggests that STAT3 regulates diverse biological functions at the initiation of malignant transformation and in the

Corresponding Authors: Jun Sun, PhD, AGA Fellow, Associate Professor, Division of Gastroenterology and Hepatology, Medicine, University of Illinois at Chicago, 840 S Wood Street, Room 704 CSB, MC716, Chicago, IL, 60612, USA, Tel: 312-996-5020; junsun7@uic.edu.

Declaration of financial interests

No financial interests

pathogenesis of many cancers[2–7]. STAT3 is essential for host immune and inflammatory responses during cancer progression[8]. Therefore, STAT3 is a potential target to regulate inflammation for cancer treatment[9–13]. A number of bacteria and viruses are known to regulate STAT3 pathway[14–16]. In the current review, we will discuss the research progress of STAT3 activation in infection and cancers. We will highlight our recent study on the novel role of STAT3 in infection-associated colon cancer. Finally, we will discuss the potential for using STAT3 as a target in developing new treatment for infectious diseases and cancers.

2. STAT3 pathway in regulating inflammatory responses and bacterial infection

The STAT3 pathway has been shown to play a central role in the inflammatory signaling cascades triggered by LPS, INFγ and other cytokines. Binding of IL-6, IL-10 and IL-11 to specific receptors activates phosphorylation of the receptor-associated JAK1 and Tyk2. Then STAT3 is phosphorylated by JAK1. Activated STAT3 translocates into the nucleus, where it binds to specific promoter sequences and regulates transcription of target genes, such as Bcl-XL, Bcl-2, MYC and BIRC5. STAT3 also promotes transcription of SOCS3. SOCS3 inhibits endotoxin-inducible expression of TNF-alpha, IL-6, and IL-1β and is considered a negative feedback regulator of JAK1/STAT3 signaling.

STAT3 regulates the host response to bacterial infection to maintain intestinal epithelial barrier function by controlling bacterial growth and suppressing apoptosis. Wittkopf *et al.* demonstrated that Intestinal epithelial STAT3 conditional knockout ($STAT3^{\Delta IEC}$) mice are hypersusceptible to gastrointestinal infections and develop severe colitis[15]. Accordingly, breakdown of the intestinal epithelial barrier and impaired expression of antimicrobial peptides (AMPs) are found in $STAT3^{\Delta IEC}$ mice. The activation of STAT3 leads to impaired transcription of antimicrobial peptides thereby facilitating overgrowth of intestinal bacteria. *C. rodentium* induces transcription of IL-6 which depends on STAT3 activation in intestinal epithelial cells. *C. rodentium* infection induces expression of several AMPs, such as Pla2g2a and REG3γ, which are associated with activation of STAT3[15]. Gene ontology analysis indicates that STAT3 links IL-22 signaling to mucosal wound healing in intestinal epithelial cells[17]. IL-22 is important for production of AMPs which is crucial to defend against most intestinal infections[18]. IL-22 also induces activation of STAT3 in the intestine[15]. Thus, STAT3 activation plays a critical role in host-bacterial interactions.

2.1 *Helicobacter pylori*

Helicobacter pylori is a gram-negative, microaerophilic bacteria which colonizes the gastric mucosa. It was identified in a patients with gastritis and ulcers in 1982 by Australian scientists Barry Marshall and Robin Warren. The majority of people infected with *Helicobacter pylori* are asymptomatic. *H. pylori* infection represents a key risk factor for chronic gastritis. Moreover, accumulated research supports that *H. pylori* significantly increases the risk of duodenal ulcers and gastric cancer and it has been classified as a group I biological carcinogen by the World Health Organization.

Helicobacter pylori induces a host cell response and triggers various signaling pathways (e.g. JAK/STAT3, Wnt/β-catenin, NF-κB, Ras/Erk and PI3K/Akt) in gastric epithelial cells[8, 19–21]. STAT3 affects the epithelial and immune compartments of the gastric mucosa. STAT3 activation is an important factor in the progression of gastric cancer. *H. pylori*-positive gastritis patients exhibit a high level of STAT3 phosphorylation[22]. p-STAT3^{Tyr705}, an active form of STAT3, mainly exists in the nucleus and is confirmed to be related to the pathogenesis and TNM stage of gastric cancer. After eradication treatment of *H. pylori*, the expression of p-STAT3^{Tyr705} is markedly decreased in these individuals, suggesting the important role of p-STAT3^{Tyr705} in *H. pylori*-associated disease[23].

CagA is one of the most studied pathogenicity factors of *H. pylori* and delivered to host cells via a type IV secretion system. It is considered as an oncogenic protein. CagA induces secretion of AMP REG3γ from gastric epithelial cells by activating STAT3 signaling[24]. Overproduction of reactive oxygen species (ROS) caused by *H. pylori* infection is detected in gastric carcinogenesis, which may contribute to proliferation and resistance to apoptosis[25]. *H. pylori* infection promotes ROS production, which can activate IL-6-STAT3 signaling in gastric cancer cells[23]. Aberrant expression of TMEFF2 contributes to *H. pylori*-associated gastric disease. *H. pylori*-downregulation of TMEFF2 is also dependent on constitutive activation of STAT3[26].

2.2 *Salmonella*

Salmonella is an enteric bacterial pathogen infecting a broad range of hosts. It can cause a systemic infection in mice similar to typhoid fever in humans. An early increase in the activation of STAT3 is demonstrated *in vivo* and *in vitro* following *Salmonella* infection. Increased STAT3 activation was also found in macrophages and lymphoid organs of mice deficient in IL-10 or IL-6 production following infection[27]. Increased activation of STAT3 was observed in the spleens and mesenteric lymph nodes 6h post-infection. CD11b+ cells isolated from the mesenteric lymph nodes revealed elevated STAT3 activation in *Salmonella*-treated mice. Phosphorylation and nuclear translocation of STAT3 were detected in cultured bone-marrow derived macrophages isolated from mice 30min after *Salmonella* infection.

2.3 Mycobacterium tuberculosis

Tuberculosis (TB) is a severe chronic bacterial infection caused by the bacterium *Mycobacterium tuberculosis* (MTB). Tuberculosis generally affects the lungs, but can also affect other parts of the body. STAT3 is a key factor for MTB intracellular establishment in the early stages of infection[28]. Consititutively activated STAT3 occurs in MTB infected cells and is mediated by IL-10. Activation of STAT3 also inhibits TNF-α, IL-6, MIP-1β and IFN-γ. Queval *et al.* have demonstrated that STAT3 can repress iNOS expression and NO synthesis[28]. Consequently, the inhibition of STAT3 is detrimental for MTB intracellular replication. Matrix metalloproteinase-1 (MMP-1) is a collagenase. Type I collagen provides the lung's tensile strength and is cleaved by MMP-1. O'Kane *et al.* have reported that STAT3 is key in driving fibroblast-dependent, unopposed MMP-1 production and may be an important factor in tissue destruction in patients with tuberculosis[29]. STAT3 inhibitors might be useful in patients with TB infection[30].

3. Involvement of STAT3 in the pathogenesis of virus infection

Several studies have reported the involvement of STAT3 in the pathogenesis of viral infections in humans and animals[31–35]. Viruses are known to regulate STAT3, including both DNA viruses (HBV, EBV, KSHV etc.) and RNA viruses (HIV-1, HCV, IAV etc.). STAT3 can be upregulated or downregulated in viral infections, depending on the type of virus involved. For example, EBV, HIV-1, HBV and HCV activate STAT3 phosphorylation, whereas IAV and hMPV inhibit STAT3 phosphorylation[16].

3.1 Hepatitis virus

Viral hepatitis is liver inflammation caused by a viral infection. It may present in acute or chronic forms. The most widespread causes of viral hepatitis are the five unrelated hepatotropic viruses: hepatitis A, B, C, D and E. HBV X protein (HBx) is a multifunctional protein which activates multiple signal transduction and transcription pathways in different types of cells. HBx has a critical role in HBV replication and regulates the process of cell apoptosis. He *et al.* demonstrated that HBX protein modulates cell apoptosis by activating the JAK2/STAT3 signaling pathway[36]. Most cases of hepatocellular carcinoma (HCC) are associated with HBV or Hepatitis C virus infection. Hepatitis C virus core protein regulates NANOG expression via the STAT3 pathway. Overexpression of NANOG has been observed in many types of human malignancies. Core-induced NANOG expression was accompanied by constitutive activation of STAT3 and was attenuated by inhibition of STAT3 phosphorylation[37]. Blocking STAT3 signaling by shRNAs promotes HBV-positive HCC cell apoptosis and induces cell cycle arrest, resulting in HCC cell growth inhibition. STAT3-shRNAs effectively reduce the level of HBV replication, which would minimize virus-derived stimulation to STAT3 signaling and increase the STAT3-shRNAs-mediated anti-HCC effect. Moreover, this STAT3-shRNAs-mediated anti-HBV-positive HCC effect was shown effective in xenograft nude mice[38].

3.2 Human papillomavirus

Human papillomavirus (HPV), a DNA virus from the papillomavirus family, is a viral infection that is passed between people by skin-to-skin contact. Most HPV infections resolve spontaneously and are asymptomatic. In some patients they persist and result in warts or precancerous lesions. The precancerous lesions increase the risk of several types of cancer[39].

Nearly all cervical cancer is due to two types of HPV: HPV16 and HPV18. Several studies have analyzed the expression and activation of STAT3 in cervical cancer in respect to HPV infection during carcinogenesis[40–42]. Shukla *et al.* reported high STAT3 expression in cervical precancerous and cancerous lesions compared to normal tissue. Consistent activation of STAT3 was found in HPV-positive cervical cancer cell lines, whereas it was absent in HPV-negative cells. Meanwhile, expression and activity of STAT3 were specifically high in cervical precancerous and cancerous lesions in HPV16-positive tissue. Expression of active pSTAT3 was associated with severity and progression of cervical lesions from precancerous changes to cancer[43].

HPV infection is correlated with STAT3 signaling activities in breast cancer. Zhang *et al.* examined HPV infection by GenChip technology in breast cancer tissues and found that high-risk HPV infections were correlated with both active p-STAT3 and its downstream IL-17 levels. There may be a complicated relationship among HPV infection, constitutive STAT3 activity and IL-17 levels. Combination of these factors induces a proinflammatory microenvironment in breast tissue and promote scancer progression[44]. Another correlation implicating the HPV-STAT3 mechanism was also found in the pathogenesis of colon cancer. HPV infection is highly associated with constitutive STAT3 activity in colon cancer tissues[40].

3.3 Epstein–Barr virus

The Epstein–Barr virus (EBV), a virus in the herpes family, is one of the most common viruses in humans. It is associated with several types of cancer, such as Hodgkin's lymphoma, gastric cancer, Burkitt's lymphoma and nasopharyngeal carcinoma (NPC). Latent membrane protein 1 (LMP1) encoded by EBV functions as an essential factor in EBV-induced cell transformation and is expressed in many of the malignancies associated with EBV. LMP1 protein is detected in most of tissue samples from NPC patients[45]. Induction of STAT3 by LMP1 may contribute to the invasion of NPC[46]. Epidermal growth factor receptor (EGFR), which is expressed at high levels in NPC, is induced by LMP1 through a p50 NFκB1-Bcl-3 complex. Consistent activation of STAT3 induces the expression of Bcl-3[47].

3.4 Others

Microbial pathogens are responsible for its pathogenesis in related with STAT3 expression and activation. STAT3 regulates proliferation and survival of CD8+ T cells which enhance effector responses to HSV-1 infection in autoimmune uveitis[48]. Cai reported that STAT3 mediates a prosurvival pathway by upregulating miRNAs, leading to inhibition of host cells with *Toxoplasma* infection. Thus, the function of STAT3-binding miRNAs is considered to be an essential apparatus in *Toxoplasma* biology[49]. Liu *et al.* revealed a heterozygous mutation of the STAT3 gene in a patient with multiple serious *Staphylococcus aureus* infections[50]. HIV-1-infected/activated monocyte-derived macrophages (MDM) induce human neural progenitor cell (NPC) via the STAT3 pathway[51].

4. STAT3 activation in cancer

STAT3 is a functional signaling protein and constitutive activation of STAT3 has been implicated in the progression of inflammation and inflammation-associated caners.

4.1 STAT3 abnormal activation in tumorigenesis and development

STAT3 is expressed in a variety of cells and tissues, and plays an important role in the regulation of cell proliferation, differentiation, survival and apoptosis.[52] Its activation is transient and precisely regulated in normal cells and tissues. STAT3 gene homozygous knockout mice die in the embryonic period, which suggests that STAT3 plays a vital role in embryonic development.[53] In addition, mice with tissue-specific deletion of the STAT3 gene in intestinal epithelial cells are not only susceptible to DSS-induced colitis, but also exhibit

slower healing rate of lesions.[54] In tumor cells, STAT3 is highly expressed due to the loss of precise negative regulation and persistent activation. STAT3 induces the accumulation of IL-6/JAKs,[55] EGFR,[56] Src[57] and many transcription factors and oncoproteins due to the inhibition or deletion of negative regulatory proteins, as well as over-stimulation of intracellular and extracellular factors.

4.1.1 STAT3 promotes tumor cell proliferation and suppresses apoptosis— Apoptosis is a programmed cell death, thereby maintaining the stability of the internal environment and the removal of genetic mutation and unstable cells. But in tumors, this process is inhibited, which leads to the accumulation of various genetically unstable cells. STAT3 exerts its anti-apoptotic effect via directly up-regulating the expression of Bcl-xl/Mcl-1/Bcl-w directly, or indirectly induce the apoptosis of Hsp70/RegIIIβ by the induction of the expression of heat shock protein Hsp70/RegIIIβ.[58] Persistent STAT3 activation is closely related to the hyperproliferation and anti-apoptosis in tumor cells. In addition, activated STAT3 can induce immediate anti-apoptosis by inducing the production of p100/p52. It has been found that activated STAT3 suppresses p53-mediated apoptosis by binding to the promoter of p53 and inhibiting the transcription of p53. STAT3 can promote tumor cell proliferation by up-regulating the expression of the cyclinB1/cdc-2/c-myc/cyclinD1/c-jun/c-fos complex and down-regulating the expression of the cyclinB1 kinase inhibitor CDK1 in p21/p27 expressing cells, which drives rapid progression through the G1/S checkpoint[59–61].

STAT3 has been shown to up-regulate cyclinD1, a proliferation regulator. However, STAT3 expression is suppressed in HepG2 cells with high cyclinD1 expression. This finding is also verified in artificially inducible breast cancer cells with high cyclinD1 expression. It suggests that over-activated cyclinD1 can negatively regulate the activity of STAT3.[62]

4.1.2 Role of STAT3 in tumor invasion and metastasis—Tumor invasion and metastasis are closely associated with angiogenesis and are regulated by STAT3. Nuclear translocation of p-STAT3 leads to altered transcription of related target genes and induces tumor angiogenesis. Vascular endothelial growth factor (VEGF), a key protein in angiogenesis, also plays a key role in the carcinogenesis of various tumors. In breast cancer, VEGF protein expression is closely correlated with microvessel density and lymph node metastasis. VEGF is regulated by a variety of factors. STAT3 and hypoxia-inducible factor-1α (HIF-1α) have been confirmed to be regulators of VEGF. In hypoxic conditions, STAT3 is activated which further promotes HIF-1α expression and tumor vascular proliferation.[63, 64] P-STAT3 induces HIF-1α transcription in tumor cells and in tumor-surrounding inflammatory cells. HIF-1α protein is known to induce expression of survivin, a protein involved in angiogenesis and inhibition of apoptosis. HIF-1α also promotes expression of erythropoietin, which inhibits the apoptosis of cancer cells under hypoxia and leads to tumor growth, invasion and metastasis. Additionally, HIF-1α can promote the transcription and expression of VEGF, participate in tumor angiogenesis, and tumor invasion and metastasis. STAT3 also directly regulates the expression of VEGF in tumor angiogenesis.[65, 66] Gong *et al.* found that activated STAT3 promotes the over-expression of VEGF, and obvious vascular proliferation in gastric cancer, which plays an important role in

the development, invasion and metastasis of gastric cancer.[67] STAT3 can directly bind to the promoter of VEGF, and promotes VEGF expression. Thus, STAT3 plays a critical role in the invasion and metastasis of malignant tumors, and may also be involved in the malignant transformation of cells.

4.1.3 STAT3 and immune escape—The role of STAT3 in tumor immune escape was first found in a gene therapy study. Wang *et al.* found infiltration of macrophages, neutrophils and T cells in a B16 tumor tissue transfected with STAT3β plasmid. Further biochemical analysis showed that STAT3β or STAT3 antisense oligonucleotides could block the activation of STAT3 in tumor cells and increase the expression of proinflammatory mediators, including interferon, tumor necrosis factor, IL6, RANTES and IP10. [68, 69] In contrast, persistent activation of STAT3 in Src-transformed fibroblasts inhibits the expression of proinflammatory mediators and cytokines induced by IFN and lipopolysaccharide.

Furthermore, in mice with transplanted tumors, blocking the STAT3 signaling pathway with small molecule inhibitors significantly enhances the anti-tumor immune activity of tumor-associated immune cells such as NK cells and neutrophils.[70] JAK inhibition impacts NK cell differentiation and can contribute to enhanced metastasis.[71–73]

4.2 STAT3 in various cancers

Multiple signaling pathways converge on STAT3 activation, such as IL-6/JAKs, EGFR, Src, and is overexpressed in a variety of tumor cells and tissues. Studies have confirmed that STAT3 is constitutively activated in tumors, including colon, liver, breast gland, prostate, lung, pancreas, brain, stomach and ovarian tumors and also in head and neck squamous cell carcinoma (HNSCC), melanoma, lymphoma, leukemia.

4.2.1 STAT3 and colon cancer—STAT3 plays an important role in regulating the cell cycle and inhibiting apoptosis of colorectal carcinoma. After screening 45 cases of colon cancer specimens, Ma *et al.* found that p-STAT3 was highly expressed in 57.8% (26/45) tumor tissues. P-STAT3 expression was 2.6 times higher in tumors compared to adjacent normal mucosa. Expression was closely correlated with lymph node metastasis and higher in Stages III and IV cancer but lower in Stages I and II.[74] Kusaba *et al.* found that p-STAT3 was not expressed in 15 cases of normal colonic epithelium but was expressed in 69 of 95 cases of colon adenocarcinoma; the level of expression was positively correlated to the depth of tumor invasion, co-invasion, and Dukes' stage, but not related to the degree of differentiation of colon cancer.[75] Lassmann *et al.* demonstrated that STAT3 mRNA expression was positively correlated with cyclin D1, survivin and Bcl-xl mRNA expression, but not related to age, sex or tumor location in invasive colorectal cancer.[76] Fan *et al.* found that in the HT29 cell line transfected with STAT3 siRNA the expression of p-STAT3 was weakly positive, the expression of anti-apoptotic genes Bcl-xL and survivin was significantly decreased, and the activity of STAT3 DNA binding domain was also decreased.[77]

4.2.2 STAT3 and breast cancer—Studies indicate that constitutively activated STAT3 is widely present in breast cancer cell lines, tumor models, and human tumor samples. Both the IL-6/GP130/JAK pathway and SRC kinase mediate the activation of STAT3. Inhibition of either pathway leads to reduced levels of activated STAT3.[78] The occurrence of breast cancer is more likely due to the synergistic effect of EGFR, SRC, JAKs and STAT3. Inhibition of kinases SRC and JAK can prevent STAT3 activation and induce apoptosis of breast cancer cells. In addition, persistent STAT3 activation might also be involved in the anti-apoptotic effect of metastatic breast cancer cells.[78–80] Selander et al. further found that the overall transplant rate was 72% in breast cancer cell line MDA-231 transplanted animals. The tumor was large with rich blood supply. About 50% of metastases was observed in transplanted animals, including the chest wall, abdominal metastasis, bloody ascites. The metastatic tumor size is same as the original.[81]

STAT5 was originally identified in mammary epithelium of lactating animals as a latent cytoplasmic transcription factor which drives the expression of milk proteins in response to the lactogenic hormone prolactin.[82, 83] STAT5 has been found to be constitutively activated in breast cancer.[84] Overexpression of upstream activators of STAT5, like Jak2, or a constitutively activated form of STAT5 induces development of mammary tumors.[85, 86] The activated form of STAT5 (p-STAT5) is detected in 20% to 70% of human breast cancers.[87, 88] Activated STAT5 can regulate a series of downstream target genes, such as pro-survival genes Bcl-xl, Bcl-2, β-casein and whey acidic protein.[89–91] Activated STAT5 in breast cancer also regulates cyclin D1/cyclin D2/p21WAF/Cip1/p27kip.[92,93] STAT5 has been demonstrated to contribute to oncogenesis by stimulating proliferation and preventing apoptosis in breast tumor cells.

4.2.3 STAT3 and other tumors—Constitutive STAT3 activation promotes tumor cell growth and malignancy, and is also found in in human liver cancer, pancreatic cancer, ovarian cancer, lung cancer, renal cancer, esophageal cancer, and gastric cancer. In a variety of liver cancer cell lines and tissues, constitutively activated STAT3 is detected.[94, 95] In pancreatic cancer, ovarian cancer. etc, the activation of STAT3 might be induced by growth factor receptor and non-receptor tyrosine kinase.[96] In melanoma, activated STAT3 can promote the growth of melanoma cells. Persistent STAT3 activation promotes *in vivo* angiogenesis and invasion and metastasis by inducing the expression of VEGF and MMP-2.[97, 98]

5. Novel role of bacterial activation of STAT3 in infection-associated colon cancer

Salmonella infection in humans can become chronic, which leads to low-grade persistent inflammation. These chronic infections increase the risk of several gastrointestinal diseases, including colon cancer. *Salmonella* AvrA is a multifunctional protein that influences eukaryotic cell pathways by regulating ubiquitination and acetylation[99–101]. AvrA is secreted through the *Salmonella* Type Three Secretion System and upregulates the STAT3 signaling pathway[14]. Mice were colonized with *Salmonella* AvrA-sufficient or AvrA-deficient bacterial strains in the AOM+DSS model of colon cancer. We have showed the

pathological changes associated with chronic *Salmonella* infection and differences in tumor development (adenoma versus carcinoma) and between AvrA− and AvrA+ AOM/DSS experimental groups. Infection with AvrA-expressing *Salmonella* activated the STAT3 pathway and enhance colonic tumrigenesis Transcriptional activity of STAT3 and its target genes were upregulated by *Salmonella* expressing AvrA, thus promoting proliferation and intestinal tumorigenesis. We have also found that AvrA induces both β-catenin and STAT3 signals which enhance colonic tumorigenesis. This effect may be through deubiquitination[14, 102].

Many cytokines and chemokines are produced by activated stromal and immune cells during chronic inflammation in tumor development. The local inflammation in the infected colon was associated with the AvrA expression level in *Salmonella*. We assessed several lymphocyte markers in normal colon and colonic tumors. Levels of CD4, CD14, CD45, and CD3 significantly increased in tumors. AvrA expression caused differential effects on these markers but had no influence on CD11.

STAT3 has a dual and self-perpetuating role in inflammation. At early stages of infection, STAT3 activation promoted inflammation; in contrast, at later stages, sustained STAT3 activation suppressed inflammation and promoted proliferation[122]. Our data also reflect the different roles of STAT3 in the progression of colon cancer. At early stages of infection (1–15 weeks) in the AOM/DSS mice, STAT3 activation may promote inflammation, whereas at later stages (45 weeks), sustained STAT3 activation suppressed inflammatory responses and promoted proliferation. As activators of transcription, the STATs upregulates the expression of genes, thus being involved in all steps of tumor development, including the induction and maintenance of an inflammatory microenvironment, as well as the malignant transformation and progression due to the maintenance of a proinflammatory state.

Our findings provide new insights regarding a STAT3-dependent mechanism by which the bacterial product AvrA enhances the development of infection-associated colon cancer. These insights might suggest future biomarkers to risk assessment and early detection of infection-related cancer.

6. Conclusion

STAT3 is crucial for both the extrinsic and the intrinsic pathways underlying infection and cancer- related inflammation. Manipulating the activity of STAT3 in infection, inflammation, and cancer have emerged as attractive targets for prevention and therapy relevance to drug development and therapeutic strategies (summarized in Table 1). STAT3 activation in various diseases models also suggests future biomarkers for risk assessment and early detection of infection-related cancer.

Acknowledgments

This work was supported by the NIDDK 1R01DK105118-01 and the UIC Cancer Center to Jun Sun. We thank Dr. Danika Bakke for making grammatical edits.

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Table 1

Effects of STAT3 inhibitors

Name	Description	function
S3I-201	S3I-201 shows potent inhibition of STAT3 DNA-binding activity and low activity towards STAT1 and STAT5.	In vitro: STAT3 DNA-binding activity↓, STAT3-dependent transcriptional activity↓, cells growth↓, apoptosis↑, cyclin D1↓, Bcl-XL↓, survivin↓ In vivo: tumor growth ↓, STAT3 phosphorylation↓[103, 104]
Stattic	Stattic inhibits STAT3 activation and nuclear translocation, highly selectivity over STAT1.	In vitro: STAT3 DNA-binding activity↓, STAT3 phosphorylation↓, apoptosis↑[105–107]
Niclosamide	Niclosamide inhibits DNA replication and inhibit STAT in a cell-free assay.	In vitro: DNA replication↓, STAT3 phosphorylation↓, nuclear translocation↓ STAT3-dependent transcriptional activity↓Wnt3A-stimulated beta-catenin↓ NF-κB activity↓ G0/G1 arrest ↑ apoptosis↑ In vivo: tumor growth ↓[108, 109]
Nifuroxazide	Nifuroxazide effectively suppresses the activation of cellular STAT1/3/5 transcription activity against IL-6-induced STAT3 activation.	In vitro: STAT3 phosphorylation↓, Jak2 and Tyk2 phosphorylation↓ Mcl-1↓ [110]
APTSTAT3-9R	APTSTAT3-9R is a specific STAT3-binding peptide with addition of a cell-penetrating motif.	In vitro: STAT3 phosphorylation↓ cell viability↓ proliferation↓ In vivo: tumor growth ↓[111]
STA-21	STA-21 is a selective STAT3 inhibitor.	In vitro: STAT3 DNA binding activity↓ Stat3 dimerization↓ Stat3-dependent luciferase activity↓ tumor growth ↓ cell viability↓ apoptosis ↑ In vivo:Th17 cells↓ Treg cells↑[112–114]
SH-4-54	SH-4-54 is a potent STAT inhibitor for STAT3 and STAT5.	In vitro:STAT3 phosphorylation↓ STAT3-dependent transcriptional activity↓ In vivo: tumor growth↓[115, 116]
Napabucasin	Napabucasin is an orally available Stat3 and cancer cell stemness inhibitor.	In vitro: self-renewal of stemness-high cancer cells↓ In vivo: tumor growth↓, relapse↓ metastasis↓[117]
Cryptotanshinone	Cryptotanshinone strongly inhibits phosphorylation of STAT3 Tyr705, with a small effect on STAT3 Ser727, but none against STAT1 nor STAT5.	In vitro: STAT3-dependent luciferase activity↓, STAT3 Tyr705 phosphorylation↓, dimerization ↓, JAK2 phosphorylation↓, proliferation↓, cyclin D1↓, Bcl-xL↓, survivin↓ In vivo: serum triglycerides and cholesterol levels↓, AMPK activity↑, blood glucose levels↓[118, 119]
HO-3867	HO-3867, an analog of curcumin, is a selective STAT3 inhibitor.	In vitro: G(2)-M cell cycle arrest↑, apoptosis↑ In vivo: tumor growth ↓, STAT3 phosphorylation↓, PTEN↑[120, 121]