Published in final edited form as:

Inflamm Bowel Dis. 2014 December ; 20(12): 2405–2411. doi:10.1097/MIB.0000000000000180.

Stat3: Friend or Foe in Colitis and Colitis-associated Cancer?

Jie Han, MS and Arianne L. Theiss, PhD

Department of Internal Medicine, Division of Gastroenterology, Baylor Research Institute, Baylor University Medical Center, Dallas, Texas

Abstract

Chronic inflammation predisposes tissue to cancer development. Individuals afflicted with inflammatory bowel diseases are at an increased risk of developing colorectal cancer depending on disease severity, duration, and management. The intestinal epithelium exhibits mitochondrial dysfunction during colitis and colitis-associated cancer. Signal Transducer and Activator of Transcription (Stat)-3 is a transcription factor involved in growth-promoting and antiapoptotic signaling pathways. In addition to its activities as a transcription factor, Stat3 resides in the mitochondria of cells where it is required for optimal electron transport chain activity and protects against stress-induced mitochondrial dysfunction. The function of mitochondrial Stat3 is not completely understood; dichotomous roles include protecting against cellular injury but also supporting malignant transformation. This review discusses the roles of Stat3 in the regulation of intestinal epithelial cell fate during colitis and colorectal cancer with an emphasis on mitochondrial dysfunction and the potential involvement of mitochondrial Stat3 during disease progression.

Keywords

inflammatory bowel disease; intestinal epithelium; cancer; mitochondria

PLEIOTROPIC STAT3

Signal Transducer and Activator of Transcription (Stat)-3 is a member of the Stat protein family, which has been shown to play key roles in cytokine signaling pathways. The Stat family comprises 7 members: Stat1, Stat2, Stat3, Stat4, Stat5a, Stat5b, and Stat6. Unlike Stat2, Stat4, and Stat6, which are activated by a few, select cytokines, Stat1, Stat3, and Stat5 are activated through multiple ligands and are involved in controlling cell-cycle progression and apoptosis.¹ Stat3 can be activated by the entire family of interleukin-6 (IL-6)-type cytokines, IL-10, IL-22, IL-17, and IL-23 epidermal growth factor, leukemia inhibitory factor, basic fibroblast growth factor, oncostatin M, and the ciliary neurotrophic factor family of cytokines.² IL-6, IL-10/IL-22, and IL-17/IL-23 have been shown to play a central role in facilitating neoplastic cell survival and proliferation through Stat3 activation

Copyright © 2014 Crohn's & Colitis Foundation of America, Inc.

Reprints: Arianne L. Theiss, PhD, Department of Internal Medicine, Division of Gastroenterology, 1053 Wadley Tower, 3600 Gaston Avenue, Baylor Research Institute, Baylor University Medical Center, Dallas, TX 75246, arianne.theiss@baylorhealth.edu.

The authors have no conflicts of interest to disclose.

(reviewed in Ref. 3). In addition to the gp130-dependent receptors, Stat3 can be activated by at least 6 other classes of receptors.² Stat3 interacts with the gp130 receptor through the cytoplasmic consensus sequence YxxQ. Ligand binding to the gp130 receptor induces gp130 receptor dimerization and activation of a Janus kinase. Stat3 is activated by phosphorylation at tyrosine 705 (Y705) and serine 727 (S727).² Phosphorylation of Stat3 at Y705 is often mediated by JAK1, epidermal growth factor receptor, or Src and is required for Stat3 homo- or hetero-dimerization, nuclear translocation, and DNA binding. Phosphorylation of Stat3 at S727 is mediated by many kinases including ERK1, ERK2, p38, and JNK that contributes to maximal transcriptional activity and is necessary for mitochondrial action of Stat3 as discussed in detail below.

Although the pleiotropic nature of Stat3 was revealed across multiple studies using Stat3 conditional knockout mice, Stat3 is generally considered a growth-promoting, antiapoptotic factor. Several target genes of Stat3 have been identified, including proteins that are involved in cell survival and proliferation, such as Bcl-2, Bcl-xL, Mcl-1, Fas, cyclin D1, cyclin E1, and p21.^{4,5} In addition, other transcription factors, including c-myc, c-jun, and c-fos are Stat3 targets.⁶ VEGF, basic fibroblast growth factor, HIF-1, TGF β , and TIMP-1 have also been shown to be targets of Stat3 and contribute to angiogenesis and fibrosis, respectively.^{7,8} Under normal conditions, Stat3 is activated in a transient manner with activation terminated by suppressors of cytokine signaling proteins. Human cancer cells exhibit constitutively activated Stat3, which can be attributed to upregulated tyrosine kinases and impairment of negative regulation by suppressors of cytokine signaling proteins.⁵ Persistent Stat3 target gene activation can stimulate cell growth, angiogenesis, cell motility, and prevent apoptosis, thereby driving tumorigenesis.

STAT3 IN COLITIS AND COLITIS-ASSOCIATED CANCER

An association between inflammatory bowel diseases (IBD), the most common forms being Crohn's disease and ulcerative colitis (UC), and colorectal cancer (CRC) has been well established with increased risk of developing CRC dependent on the extent of disease at diagnosis, disease severity and duration, and efficacy of IBD management.⁹ Recent population-based studies suggest that risk of colitis-associated cancer (CAC) in IBD has decreased over time thought to be due, at least in part, to the increased use of maintenance therapy for IBD and surveillance colonoscopy after 8 years of disease duration.¹⁰ Although evidence suggests that chronic inflammation predisposes tissue to cancer development by inhibiting apoptosis, inducing gene mutations, inducing cancer cell proliferation, and stimulating angiogenesis, the molecular mechanisms of CAC are only beginning to be elucidated. The frequency and sequence of genetic alterations in CAC differ from those that occur in sporadic CRC. Specifically, mutations in the adenomatous polyposis coli (APC) tumor suppressor gene happen late during the progression from dysplasia to CAC after earlier mutations in p53 and K-Ras.¹¹ It is thought that IBD inflammation drives DNA damage and mutations, thereby bypassing the initial APC mutation step required to initiate sporadic CRC tumorigenesis.⁹

Although Stat3 activation is transient in normal cells, constitutively activated Stat3 is associated with IBD where it modulates gut immune cell activation.¹² The *Stat3* gene is a

susceptibility loci for IBD.¹³ IL-6 is elevated in the serum and mucosa of patients with IBD, and serum IL-6 levels are predictive of disease relapse.¹⁴ Furthermore, IL-6 and soluble IL-6 receptor are increased in the lamina propria during active IBD and stimulate T cells lacking the membrane-bound IL-6 receptor, leading to Stat3 induction of antiapoptotic genes including Bcl-2 and Bcl-x_L.¹⁵ This signaling cascade leads to mucosal T-cell survival and perpetuates inflammation through the augmented production of IL-6 by activated Th1 and Th17 cells.^{15,16} Animal models using neutralizing anti-IL-6 receptor antibodies, fusion proteins that inhibit the soluble IL-6 receptor, or IL-6-deficient mice have indicated that T cells are a key source of IL-6 production during colitis.^{15,17,18} Reduction in disease severity with IL-6 blockade was associated with diminished Stat3 activation and lamina propria T-cell apoptosis.¹⁵ However, mice with disruption of the Stat3 gene specifically in macrophages and neutrophils develop spontaneous colitis and adenocarcinomas in the colon and rectum. This was attributed to involvement of the microflora and lack of IL-10 regulation on colonic macrophage and neutrophil activation in these mice.¹⁹ Collectively, these studies highlight the key role of Stat3 to regulate gut immune cell homeostasis.

Stat3 is a key factor determining intestinal epithelial cell fate during colitis and CAC. Activated Stat3 is increased in intestinal epithelial cells during active IBD and UC-associated high-grade dysplasia and cancer, with a concomitant decrease in the number of cells expressing SOCS3.²⁰ Stat3 activation in intestinal epithelial cells has been shown to be beneficial during colitis. Conditional knockout mice with intestinal epithelial cells deficient in Stat3 were highly susceptible to experimental colitis, indicating that epithelial Stat3 regulates intestinal homeostasis.²¹ Epithelial Stat3 is also essential for mucosal wound healing responses by promoting regeneration of the epithelium in response to injury, thereby mediating recovery from colitis.^{21,22} Intestinal epithelial wound healing responses of Stat3 have been linked to its activation by IL-22, in contrast to IL-6.^{21,22} IL-22 is produced predominantly by T and natural killer cells, whereas the IL-22 receptor is expressed solely on nonhematopoietic cells including intestinal epithelial cells.²³ A recent study revealed that the availability of IL-22, which is increased during intestinal tissue damage,²⁴ is regulated by the inflammasome and is crucial for tissue repair during the peak of damage but promoted tumor development if uncontrolled during the recovery phase.²⁵ The protective functions of IL-22 on intestinal epithelium such as regeneration and production of mucins and antimicrobial peptides are mediated through Stat3 activation.²⁶ Collectively, Stat3 has emerged as a protective factor during colitis, inducing intestinal epithelial cell proliferation and wound healing.

It is easily perceived how the induction of Stat3 in the intestinal epithelium to promote wound healing from injury and inflammation through enhanced cell proliferation could become detrimental if chronically induced. Using the azoxymethane/dextran sodium sulfate (AOM/DSS) murine model of CAC, IL-6 was identified as a mediator of tumorigenesis due to its stimulation of intestinal epithelial cell proliferation, thereby promoting growth of tumor-initiating cells.²⁷ Furthermore, IL-6 produced by lamina propria immune cells prevented apoptosis of normal and premalignant intestinal epithelial cells.^{28,29} A role of Stat3 acting downstream of IL-6 to promote tumorigenesis was provided by studies using mice with intestinal epithelial cell-specific deletion of Stat3, which exhibited diminished tumor growth and multiplicity during CAC despite increased susceptibility to experimental

colitis.^{28,29} These findings mimicked the phenotype of genetic deletion or pharmacological inhibition of IL-6 during CAC.²⁸ Inhibition of Stat3 signaling induces apoptosis of CRC cells through the mitochondrial pathway by modulating Bcl-2 and Bcl-x_L.³⁰ A recent study provided insight that epithelial Stat3 was essential for colonic tumor progression by coordinating immune cell recruitment by means of the sphingosine-1-phosphate receptor (S1PR1) pathway.³¹ Upregulation of sphingosine kinase 1 during colitis leads to increased sphingosine-1-phosphate (S1P), subsequently leading to IL-6/Stat3 activation, which in turn amplifies expression of S1PR1 in tumors and associated immune cells (Fig. 1).³² As a result, tumor infiltrating macrophages and dendritic cells are stimulated to produce elevated IL-6 levels during CAC, thereby promoting a proinflammatory tumor microenvironment and forming an IL-6/S1P/Stat3 amplification loop.^{32–34} In addition, IL-22 activation of epithelial Stat3 has been identified as a mediator of development and progression to CAC in a bacteria-induced model, distinct from the action of IL-6.³⁵ IL-22 induces hyperproliferation of epithelial cells during chronic colitis and therefore could perpetuate cancer through activation of pathways controlling epithelial proliferation.³⁶ Furthermore, polymorphisms in the gene encoding IL-22 are associated with an increased risk of developing CRC.³⁷ Additional insight into the role of IL-6 and Stat3 in the AOM/DSS model was provided by a recent study suggesting that Stat3 repression of miR-34a was required for epithelial-to-mesenchymal transition and progression to invasive carcinomas.³⁸ These studies suggest that epithelial Stat3 induced by IL-6 and/or IL-22 plays a critical role in CAC.

ROLE OF EPITHELIAL MITOCHONDRIAL DYSFUNCTION IN COLITIS AND CAC

Mitochondria control essential functions including adenosine triphosphate (ATP) production through oxidative phosphorylation. In addition, mitochondria are emerging as key mediators of cell homeostasis with involvement in cellular distress signaling pathways, including inflammation, autophagy, and apoptosis.³⁹ Mitochondrial dysfunction is associated with many chronic diseases, including arthritis, neurodegeneration, cardiovascular disease, and cancer.⁴⁰ Multiple studies have reported mitochondrial dysfunction in epithelial cells during IBD as evidenced by decreased ATP levels,^{41–43} increased mitochondrial-derived reactive oxygen species (ROS),⁴⁴ reduced activities of electron transport chain complexes,^{41,44} activated mitochondrial unfolded protein response,^{45,46} defective mitochondrial oxidative metabolism of butyrate, which provides >70% of the energy requirements for the colonic epithelium,^{47–49} and ultrastructural alterations of the mitochondria, including swelling and irregular and/or dissolved cristae.^{50,51} Polymorphisms in the genes encoding SLC22A5, IRGM, and UCP2, which are crucial for mitochondrial ATP production, are susceptibility loci in IBD.^{52–54} Although it remains unknown whether mitochondrial stress is a cause or consequence of IBD, recent studies suggest that it participates in disease pathogenesis.^{45,55} Ultrastructural images of epithelial cells of patients with IBD demonstrate that mitochondrial alterations are evident before endoscopic or histologic inflammation or deterioration of apical junctional complexes, suggesting that mitochondrial structural alterations are an early event in the onset of mucosal inflammation.^{50,51} UC-associated ATP depletion in the mucosa exists independently of active inflammation.^{41,42} Furthermore, cultured intestinal epithelial cells treated with dinitrophenol, an uncoupler of oxidative

phosphorylation, to induce mitochondrial stress exhibit decreased barrier function.⁵⁶ Mice deficient in dsRNA-activated protein kinase, which mediates the mitochondrial unfolded protein response in intestinal epithelial cells, fails to upregulate a mitochondrial unfolded protein response in response to DSS-induced colitis and exhibit reduced severity of inflammation.⁴⁵ This study suggests that there is a link between mitochondrial stress and the pathogenesis of intestinal inflammation in the DSS model.⁴⁵ Another study showed that mice carrying polymorphisms in mitochondrial DNA shown to modulate mitochondrial function in intestinal mucosa, thereby increasing levels of ATP and enhancing barrier integrity, are protected from experimental colitis.⁵⁵ Furthermore, mice treated with the mitochondrial-targeted antioxidant MitoQ exhibited reduced severity of experimental colitis, suggesting that mitochondrial-derived ROS are involved in disease pathogenesis.⁵⁷ Collectively, these studies demonstrate that epithelial mitochondrial function plays a role in regulating intestinal homeostasis.

It is well established that mitochondrial dysfunction is associated with tumorigenesis. However, it is not clearly understood how mitochondrial alterations contribute to cell transformation and tumor progression. The Warburg effect, first postulated in the 1950s, suggested that mitochondrial dysfunction causes cells to undergo aerobic glycolysis, a characteristic of cancer cells.⁵⁸ However, more recent studies put forth the concept that cancer metabolism is not the consequence of mitochondrial dysfunction but the result of mitochondrial reprogramming by loss-of-function mutations in tumor suppressor genes or proto-oncogenic-directed gene regulation.⁵⁹ Mitochondrial reprogramming alters cellular metabolism and enhances anabolic pathways necessary to meet the increased requirements of tumor growth.⁶⁰ These changes in cellular metabolism occur in response to exaggerated extracellular growth factor signaling because of overexpression and/or constitutive activation of growth factor receptors, causing the cell to adopt an anabolic metabolism.⁶⁰ Alteration of cellular metabolism is fundamental to transformation, selected for during tumorigenesis, and does not occur passively as a consequence of damaged mitochondria or reduction in ATP concentration.⁵⁹ It is a misconception that cancer cells do not use mitochondria to derive ATP through oxidative phosphorylation. Oxidative phosphorylation produces a significant portion of ATP in cancer cells; however, simultaneously, these cells alter use of mitochondrial enzymes to synthesize anabolic precursors such as reduced carbon, reduced nitrogen, and cytosolic NADPH for macromolecular synthesis of nucleotides, proteins, and lipids necessary for cell proliferation.⁶⁰ In a dynamic process, the function of tumor mitochondria is complemented to metabolic needs necessary to achieve rapid cell growth.

In addition to oncogenic transformation and tumor progression, alterations in mitochondria are associated with metastasis. Mutations in mtDNA that reduce activity of complex I of the electron transport chain and increase mitochondrial-derived ROS confer a high meta-static activity in tumor cells, which could be prevented by treatment with antioxidants.⁶¹ Transfer of mutated mtDNA conferring high metastatic activity into cells with low metastatic potential functionally changed the behavior of the recipient cells to resemble the high metastatic potential of the donor cells.⁶² These results suggest that ROS-generated mtDNA damage can regulate metastatic potential.

IBD-associated tumorigenesis is associated with mitochondrial alterations and an accumulation of mitochondrial DNA (mtDNA) mutations.⁶³ A recent study by Ussakli et al⁶⁴ characterized mitochondrial alterations in UC-associated tumorigenesis. The authors found that expression of cytochrome C oxidase (complex IV of the electron transport chain) and mtDNA content reflected the number of mitochondria. A reduction in the number of mitochondria was found in low-grade and high-grade dysplasia with a concomitant increase in glycolysis. At the cancer stage, glycolysis was still evident, whereas mitochondrial content was surprisingly restored (Fig. 1).⁶⁴ The authors conclude that loss of mitochondria precedes tumor progression in UC and a reduction in cytochrome C oxidase could be a potential biomarker for patients with UC progressing to cancer. The preneoplastic loss of mitochondria and neoplastic gain of mitochondria demonstrated during UC-associated tumorigenesis supports the concept that oncogene-regulated transcription might initially suppress mitochondrial biogenesis and function but later positively select for mitochondria and restore oxidative phosphorylation in cancer cells to further growth.⁶⁵

MITOCHONDRIAL STAT3

In addition to its activities as a transcription factor, a pool of Stat3 consisting of 5% to 10% of total Stat3 resides in the mitochondria of cells.⁶⁶ Although the mechanism remains unknown, common variants in the Stat3 gene have been shown to modulate mtDNA copy number, which is critical for the maintenance of normal mitochondrial function.⁶⁷ Much of our current understanding of mitochondrial Stat3 function comes from data using cardiomyocytes, hematopoietic stem cells, or mouse embryonic fibroblasts. Mitochondrial Stat3 regulates cellular respiration and is required for optimal electron transport chain activity in nontransformed cells through its interaction with complexes I and II.^{66,68–70} In the absence of Stat3, the activity of complexes III and V was also reduced.^{66,71} Cardiomyocyte-deficient in Stat3 exhibit a 50% decrease in activity of respiratory chain complexes I and II and elevated ROS levels leading to cardiac inflammation in mice and death due to congestive heart failure.⁷¹ Phosphorylation of mitochondrial Stat3 at S727, but not Y705, is crucial for optimal functioning of the respiratory chain.^{66,72} pS727-Stat3, in a manner independent of transcription, attenuates stress-induced damage to mitochondria, resulting in decreased production of ROS by the electron transport chain and retention of cytochrome c by mitochondria.⁷² It is not known whether mitochondrial Stat3 is constitutively phosphorylated. A recent study indicates that MEK/ERK signaling is involved in mitochondrial serine phosphorylation of Stat3.⁷³ S1P increases phosphorylation of Stat3 at S727 in both the mitochondria and nucleus, and this was shown to be dependent on ERK activation, indicating that Stat3 is a downstream target of S1P.⁷⁴ Furthermore, it has been shown that serine phosphorylation of Stat3 is required for the cardioprotective effect of S1P.^{75,76} These results suggest a protective role of mitochondrial Stat3 during cellular injury in nontransformed cells.

The mechanism whereby Stat3 interacts with complexes I and II of the electron transport chain has not been elucidated. Stat3 lacks a mitochondrial targeting sequence, and transport into the mitochondria has been shown to be dependent on gene associated with retinoid–interferon-induced mortality 19 (GRIM-19), which is a component of complex I of the respiratory chain.⁷⁷ GRIM-19 is capable of translocating between the mitochondria, cytosol,

and nucleus depending on stimulation by cytokines or growth factors.⁷⁸ On phosphorylation of Stat3 at S727, GRIM-19 binds to Stat3, suppresses the transcriptional activity of Stat3, and transports Stat3 into the mitochondria.⁷⁷ Relative to complexes I/II, mitochondrial Stat3 is 10⁵-fold less abundant, which suggests that Stat3 may not be a structural component of complexes I or II but likely modifies mitochondrial function indirectly through signal transduction pathways or posttranslational modifications.⁷⁹

In addition to protection against cellular injury, mitochondrial Stat3 can support malignant transformation. Stat3 can be oxidized directly by ROS and this direct regulation of Stat3 by ROS has been shown to couple intracellular redox status to respiration and cell proliferation in tumor cells.^{80,81} Specifically, mitochondrial Stat3 plays a key role in Ras- (H-, N-, and K-) activated transformation.^{73,82} The Ras family members are the only known oncogenes that stimulate the phosphorylation of Stat3 at S727 but not Y705.⁷³ Ras oncoproteins alter glycolytic and oxidative phosphorylation, resulting in increased mitochondrial ROS production characteristic of cancer cells.^{82,83} Ras-induced alteration of mitochondrial function triggers further expression of oncogenes, such as Myc.⁸⁴ Mutation of S727 to alanine renders Stat3 unable to support Ras-dependent transformation and altered mitochondrial respiratory activity.⁸² A recent study revealed that mice with loss of the mitochondrial transcription factor A (TFAM) gene exhibited less mitochondrial-derived ROS and reduced K-Ras-induced tumorigenesis, suggesting that mitochondrial metabolism and ROS production are essential for tumorigenicity induced by K-Ras.⁸⁵ Given that gain-of-function mutations of K-Ras are common in colitis-associated neoplasia and can occur early in neoplastic progression,⁸⁶ K-Ras activation of mitochondrial Stat3 may play a role in tumorigenesis during IBD. Mitochondrial Stat3 specifically has been shown to be crucial in the promotion of breast, prostate, and pituitary cancer.^{87–89} Inhibition of Stat3 in CRC cells promoted the loss of mitochondrial transmembrane potential, generation of ROS, and apoptosis.⁹⁰ Although this study did not directly target mitochondrial Stat3, it did show that cellular status of Stat3 directly impacts CRC cell fate through mitochondrial function.⁹⁰ Studies assessing the expression and role of mitochondrial Stat3 during the progression from colitis to cancer are lacking. The recent study by Ussakli et al⁶⁴ characterizing mitochondrial alterations in UC-associated tumorigenesis did not assess Stat3. We speculate that mitochondrial Stat3 is necessary for epithelial regeneration during colitis, supporting maximal respiratory chain function and cellular homeostasis. During dysplasia, loss of mitochondrial number and decreased oxidative phosphorylation could be associated with loss of mitochondrial Stat3 expression or function. As dysplasia progresses to cancer, the restoration of mitochondrial metabolism to support tumor growth is likely associated with enhanced activation of mitochondrial Stat3. Future studies are required to elucidate the role of mitochondrial Stat3 in the progression from colitis to dysplasia to cancer and its downstream effects on intestinal epithelial cell fate distinct from Stat3 transcriptional activities.

CONCLUSIONS

The transcriptional role of Stat3 in regulating cell proliferation and apoptosis influences intestinal epithelial cell fate during colitis and CAC. In addition, the nontranscriptional function of mitochondrial Stat3 in maintaining respiratory activity has begun to emerge as

protective against cellular injury but also essential for Ras-induced transformation. Given that mitochondria of intestinal epithelial cells are dysfunctional during colitis, dysplasia, and colitis-associated cancer, it is conceivable that mitochondrial Stat3 is involved in metabolic alterations during the progression to neoplasia during chronic inflammation. Mitochondrial Stat3 might provide a future target to restore mitochondrial function and intestinal epithelial cell homeostasis during colitis and to prevent the development of CRC associated with chronic inflammation.

Acknowledgments

Supported by National Institutes of Health grants: K01-DK085222 (A. L. Theiss) and R03-DK098229 (A. L. Theiss).

References

1. Santos CI, Costa-Pereira AP. Signal transducers and activators of transcription-from cytokine signaling to cancer biology. *Biochim Biophys Acta*. 2011; 1816:38–49. [PubMed: 21447371]
2. Levy DE, Lee CK. What does Stat3 do? *J Clin Invest*. 2002; 109:1143–1148. [PubMed: 11994402]
3. Ernst M, Thiem S, Nguyen PM, et al. Epithelial gp130/Stat3 functions: an intestinal signaling node in health and disease. *Semin Immunol*. 2014; 26:29–37. [PubMed: 24434062]
4. Alvarez JV, Frank DA. Genome-wide analysis of STAT target genes: elucidating the mechanism of STAT-mediated oncogenesis. *Cancer Biol Ther*. 2004; 3:1045–1050. [PubMed: 15539936]
5. Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. *Eur J Cancer*. 2005; 41:2502–2512. [PubMed: 16199153]
6. Yang E, Lerner L, Besser D, et al. Independent and cooperative activation of chromosomal c-fos promoter by STAT3. *J Biol Chem*. 2003; 278:15794–15799. [PubMed: 12600988]
7. Ogata H, Chinen T, Yoshida T, et al. Loss of SOCS3 in the liver promotes fibrosis by enhancing STAT3-mediated TGF-beta1 production. *Oncogene*. 2006; 25:2520–2530. [PubMed: 16474852]
8. Xu Q, Briggs J, Park S, et al. Targeting Stat3 blocks both HIF-1 and VEGF expression induced by multiple oncogenic growth signaling pathways. *Oncogene*. 2005; 24:5552–5560. [PubMed: 16007214]
9. Grivennikov SI. Inflammation and colorectal cancer: colitis-associated neoplasia. *Semin Immunopathol*. 2013; 35:229–244. [PubMed: 23161445]
10. Jess T, Simonsen J, Jorgensen KT, et al. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology*. 2012; 143:375–381. e371. quiz e313–e374. [PubMed: 22522090]
11. Brentnall TA, Crispin DA, Rabinovitch PS, et al. Mutations in the p53 gene: an early marker of neoplastic progression in ulcerative colitis. *Gastroenterology*. 1994; 107:369–378. [PubMed: 8039614]
12. Atreya R, Neurath MF. Signaling molecules: the pathogenic role of the IL-6/STAT-3 trans signaling pathway in intestinal inflammation and in colonic cancer. *Curr Drug Targets*. 2008; 9:369–374. [PubMed: 18473764]
13. Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet*. 2011; 43:246–252. [PubMed: 21297633]
14. Neurath MF, Finotto S. IL-6 signaling in autoimmunity, chronic inflammation and inflammation-associated cancer. *Cytokine Growth Factor Rev*. 2011; 22:83–89. [PubMed: 21377916]
15. Atreya R, Mudter J, Finotto S, et al. Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in crohn disease and experimental colitis in vivo. *Nat Med*. 2000; 6:583–588. [PubMed: 10802717]
16. Yamamoto M, Yoshizaki K, Kishimoto T, et al. IL-6 is required for the development of Th1 cell-mediated murine colitis. *J Immunol*. 2000; 164:4878–4882. [PubMed: 10779797]

17. Kitamura K, Nakamoto Y, Kaneko S, et al. Pivotal roles of interleukin-6 in transmural inflammation in murine T cell transfer colitis. *J Leukoc Biol.* 2004; 76:1111–1117. [PubMed: 15339938]
18. Noguchi D, Wakita D, Tajima M, et al. Blocking of IL-6 signaling pathway prevents CD4+ T cell-mediated colitis in a T(h)17-independent manner. *Int Immunol.* 2007; 19:1431–1440. [PubMed: 17981790]
19. Kobayashi M, Kweon MN, Kuwata H, et al. Toll-like receptor-dependent production of IL-12p40 causes chronic enterocolitis in myeloid cell-specific Stat3-deficient mice. *J Clin Invest.* 2003; 111:1297–1308. [PubMed: 12727921]
20. Li Y, de Haar C, Chen M, et al. Disease-related expression of the IL6/STAT3/SOCS3 signalling pathway in ulcerative colitis and ulcerative colitis-related carcinogenesis. *Gut.* 2010; 59:227–235. [PubMed: 19926618]
21. Pickert G, Neufert C, Leppkes M, et al. STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. *J Exp Med.* 2009; 206:1465–1472. [PubMed: 19564350]
22. Neufert C, Pickert G, Zheng Y, et al. Activation of epithelial STAT3 regulates intestinal homeostasis. *Cell Cycle.* 2010; 9:652–655. [PubMed: 20160497]
23. Witte E, Witte K, Warszawska K, et al. Interleukin-22: a cytokine produced by T, NK and NKT cell subsets, with importance in the innate immune defense and tissue protection. *Cytokine Growth Factor Rev.* 2010; 21:365–379. [PubMed: 20870448]
24. Brand S, Beigel F, Olszak T, et al. IL-22 is increased in active Crohn's disease and promotes proinflammatory gene expression and intestinal epithelial cell migration. *Am J Physiol Gastrointest Liver Physiol.* 2006; 290:G827–G838. [PubMed: 16537974]
25. Huber S, Gagliani N, Zenewicz LA, et al. IL-22BP is regulated by the inflammasome and modulates tumorigenesis in the intestine. *Nature.* 2012; 491:259–263. [PubMed: 23075849]
26. Sugimoto K, Ogawa A, Mizoguchi E, et al. IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. *J Clin Invest.* 2008; 118:534–544. [PubMed: 18172556]
27. Matsumoto S, Hara T, Mitsuyama K, et al. Essential roles of IL-6 trans-signaling in colonic epithelial cells, induced by the IL-6/soluble-IL-6 receptor derived from lamina propria macrophages, on the development of colitis-associated premalignant cancer in a murine model. *J Immunol.* 2010; 184:1543–1551. [PubMed: 20042582]
28. Grivennikov S, Karin E, Terzic J, et al. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell.* 2009; 15:103–113. [PubMed: 19185845]
29. Bollrath J, Phesse TJ, von Burstin VA, et al. gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell.* 2009; 15:91–102. [PubMed: 19185844]
30. Du W, Hong J, Wang YC, et al. Inhibition of JAK2/STAT3 signaling induces colorectal cancer cell apoptosis via mitochondrial pathway. *J Cell Mol Med.* 2012
31. Nguyen AV, Wu YY, Liu Q, et al. STAT3 in epithelial cells regulates inflammation and tumor progression to malignant state in colon. *Neoplasia.* 2013; 15:998–1008. [PubMed: 24027425]
32. Liang J, Nagahashi M, Kim EY, et al. Sphingosine-1-phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. *Cancer Cell.* 2013; 23:107–120. [PubMed: 23273921]
33. Lee H, Deng J, Kujawski M, et al. STAT3-induced S1PR1 expression is crucial for persistent STAT3 activation in tumors. *Nat Med.* 2010; 16:1421–1428. [PubMed: 21102457]
34. Lee H, Herrmann A, Deng JH, et al. Persistently activated Stat3 maintains constitutive NF-kappaB activity in tumors. *Cancer Cell.* 2009; 15:283–293. [PubMed: 19345327]
35. Kirchberger S, Royston DJ, Boulard O, et al. Innate lymphoid cells sustain colon cancer through production of interleukin-22 in a mouse model. *J Exp Med.* 2013; 210:917–931. [PubMed: 23589566]
36. Kamanaka M, Huber S, Zenewicz LA, et al. Memory/effector (CD45RB(lo)) CD4 T cells are controlled directly by IL-10 and cause IL-22-dependent intestinal pathology. *J Exp Med.* 2011; 208:1027–1040. [PubMed: 21518800]

37. Thompson CL, Plummer SJ, Tucker TC, et al. Interleukin-22 genetic polymorphisms and risk of colon cancer. *Cancer Causes Control*. 2010; 21:1165–1170. [PubMed: 20339910]
38. Rokavec M, Oner MG, Li H, et al. IL-6R/STAT3/miR-34a feedback loop promotes EMT-mediated colorectal cancer invasion and metastasis. *J Clin Invest*. 2014; 124:1853–1867. [PubMed: 24642471]
39. Rath E, Haller D. Mitochondria at the interface between danger signaling and metabolism: role of unfolded protein responses in chronic inflammation. *Inflamm Bowel Dis*. 2012; 18:1364–1377. [PubMed: 22183876]
40. Lopez-Armada MJ, Riveiro-Naveira RR, Vaamonde-Garcia C, et al. Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*. 2013; 13:106–118. [PubMed: 23333405]
41. Santhanam S, Rajamanickam S, Motamarri A, et al. Mitochondrial electron transport chain complex dysfunction in the colonic mucosa in ulcerative colitis. *Inflamm Bowel Dis*. 2012; 18:2158–2168. [PubMed: 22374887]
42. Sifroni KG, Damiani CR, Stoffel C, et al. Mitochondrial respiratory chain in the colonic mucosal of patients with ulcerative colitis. *Mol Cell Biochem*. 2010; 342:111–115. [PubMed: 20440543]
43. Kameyama J, Narui H, Inui M, et al. Energy level in large intestinal mucosa in patients with ulcerative colitis. *Tohoku J Exp Med*. 1984; 143:253–254. [PubMed: 6474455]
44. Santhanam S, Venkatraman A, Ramakrishna BS. Impairment of mitochondrial acetoacetyl CoA thiolase activity in the colonic mucosa of patients with ulcerative colitis. *Gut*. 2007; 56:1543–1549. [PubMed: 17483192]
45. Rath E, Berger E, Messlik A, et al. Induction of dsRNA-activated protein kinase links mitochondrial unfolded protein response to the pathogenesis of intestinal inflammation. *Gut*. 2012; 61:1269–1278. [PubMed: 21997551]
46. Rath E, Haller D. Unfolded protein responses in the intestinal epithelium: sensors for the microbial and metabolic environment. *J Clin Gastroenterol*. 2012; 46(suppl):S3–S5. [PubMed: 22955354]
47. Roediger WE. The colonic epithelium in ulcerative colitis: an energy-deficiency disease? *Lancet*. 1980; 2:712–715. [PubMed: 6106826]
48. Chapman MA, Grahn MF, Boyle MA, et al. Butyrate oxidation is impaired in the colonic mucosa of sufferers of quiescent ulcerative colitis. *Gut*. 1994; 35:73–76. [PubMed: 8307454]
49. Ramakrishna BS, Roberts-Thomson IC, Pannall PR, et al. Impaired sulphation of phenol by the colonic mucosa in quiescent and active ulcerative colitis. *Gut*. 1991; 32:46–49. [PubMed: 1991638]
50. Delpre G, Avidor I, Steinherz R, et al. Ultrastructural abnormalities in endoscopically and histologically normal and involved colon in ulcerative colitis. *Am J Gastroenterol*. 1989; 84:1038–1046. [PubMed: 2773897]
51. Hsieh SY, Shih TC, Yeh CY, et al. Comparative proteomic studies on the pathogenesis of human ulcerative colitis. *Proteomics*. 2006; 6:5322–5331. [PubMed: 16947118]
52. Barrett JC, Hansoul S, Nicolae DL, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet*. 2008; 40:955–962. [PubMed: 18587394]
53. Singh SB, Ornatowski W, Vergne I, et al. Human IRGM regulates autophagy and cell-autonomous immunity functions through mitochondria. *Nat Cell Biol*. 2010; 12:1154–1165. [PubMed: 21102437]
54. Yu X, Wiczorek S, Franke A, et al. Association of UCP2 -866 G/A polymorphism with chronic inflammatory diseases. *Genes Immun*. 2009; 10:601–605. [PubMed: 19387457]
55. Bar F, Bochmann W, Widok A, et al. Mitochondrial gene polymorphisms that protect mice from colitis. *Gastroenterology*. 2013; 145:1055–1063. e1053. [PubMed: 23872498]
56. Lewis K, Lutgendorff F, Phan V, et al. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. *Inflamm Bowel Dis*. 2010; 16:1138–1148. [PubMed: 20024905]
57. Dashdorj A, Jyothi KR, Lim S, et al. Mitochondria-targeted antioxidant MitoQ ameliorates experimental mouse colitis by suppressing NLRP3 inflammasome-mediated inflammatory cytokines. *BMC Med*. 2013; 11:178. [PubMed: 23915129]
58. Warburg O. On respiratory impairment in cancer cells. *Science*. 1956; 124:269–270. [PubMed: 13351639]

59. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even warburg did not anticipate. *Cancer Cell*. 2012; 21:297–308. [PubMed: 22439925]
60. Ward PS, Thompson CB. Signaling in control of cell growth and metabolism. *Cold Spring Harb Perspect Biol*. 2012; 4:a006783. [PubMed: 22687276]
61. Ishikawa K, Imanishi H, Takenaga K, et al. Regulation of metastasis; mitochondrial DNA mutations have appeared on stage. *J Bioenerg Biomembr*. 2012; 44:639–644. [PubMed: 22895836]
62. Ishikawa K, Koshikawa N, Takenaga K, et al. Reversible regulation of metastasis by ROS-generating mtDNA mutations. *Mitochondrion*. 2008; 8:339–344. [PubMed: 18727959]
63. Brentnall TA, Pan S, Bronner MP, et al. Proteins that underlie neoplastic progression of ulcerative colitis. *Proteomics Clin Appl*. 2009; 3:1326. [PubMed: 20098637]
64. Ussakli CH, Ebaee A, Binkley J, et al. Mitochondria and tumor progression in ulcerative colitis. *J Natl Cancer Inst*. 2013; 105:1239–1248. [PubMed: 23852949]
65. Smolkova K, Plecita-Hlavata L, Bellance N, et al. Waves of gene regulation suppress and then restore oxidative phosphorylation in cancer cells. *Int J Biochem Cell Biol*. 2011; 43:950–968. [PubMed: 20460169]
66. Wegrzyn J, Potla R, Chwae YJ, et al. Function of mitochondrial Stat3 in cellular respiration. *Science*. 2009; 323:793–797. [PubMed: 19131594]
67. Gianotti TF, Castano G, Gemma C, et al. Mitochondrial DNA copy number is modulated by genetic variation in the signal transducer and activator of transcription 3 (STAT3). *Metabolism*. 2011; 60:1142–1149. [PubMed: 21310444]
68. Bernier M, Paul RK, Martin-Montalvo A, et al. Negative regulation of STAT3 protein-mediated cellular respiration by SIRT1 protein. *J Biol Chem*. 2011; 286:19270–19279. [PubMed: 21467030]
69. Mantel C, Messina-Graham S, Moh A, et al. Mouse hematopoietic cell-targeted STAT3 deletion: stem/progenitor cell defects, mitochondrial dysfunction, ROS overproduction, and a rapid aging-like phenotype. *Blood*. 2012; 120:2589–2599. [PubMed: 22665934]
70. Szczepanek K, Chen Q, Lerner AC, et al. Cytoprotection by the modulation of mitochondrial electron transport chain: the emerging role of mitochondrial STAT3. *Mitochondrion*. 2012; 12:180–189. [PubMed: 21930250]
71. Elschami M, Scherr M, Philippens B, et al. Reduction of STAT3 expression induces mitochondrial dysfunction and autophagy in cardiac HL-1 cells. *Eur J Cell Biol*. 2013; 92:21–29. [PubMed: 23102833]
72. Szczepanek K, Chen Q, Derecka M, et al. Mitochondrial-targeted Signal transducer and activator of transcription 3 (STAT3) protects against ischemia-induced changes in the electron transport chain and the generation of reactive oxygen species. *J Biol Chem*. 2011; 286:29610–29620. [PubMed: 21715323]
73. Gough DJ, Koetz L, Levy DE. The MEK-ERK pathway is necessary for serine phosphorylation of mitochondrial STAT3 and ras-mediated transformation. *PLoS One*. 2013; 8:e83395. [PubMed: 24312439]
74. Frias MA, Lecour S, James RW, et al. High density lipoprotein/sphingosine-1-phosphate-induced cardioprotection: role of STAT3 as part of the SAFE pathway. *Jakstat*. 2012; 1:92–100. [PubMed: 24058758]
75. Frias MA, Lang U, Gerber-Wicht C, et al. Native and reconstituted HDL protect cardiomyocytes from doxorubicin-induced apoptosis. *Cardiovasc Res*. 2010; 85:118–126. [PubMed: 19700468]
76. Somers SJ, Frias M, Lacerda L, et al. Interplay between SAFE and RISK pathways in sphingosine-1-phosphate-induced cardioprotection. *Cardiovasc Drugs Ther*. 2012; 26:227–237. [PubMed: 22392184]
77. Tammineni P, Anugula C, Mohammed F, et al. The import of the transcription factor STAT3 into mitochondria depends on GRIM-19, a component of the electron transport chain. *J Biol Chem*. 2013; 288:4723–4732. [PubMed: 23271731]
78. Shulga N, Pastorino JG. GRIM-19-mediated translocation of STAT3 to mitochondria is necessary for TNF-induced necroptosis. *J Cell Sci*. 2012; 125:2995–3003. [PubMed: 22393233]

79. Phillips D, Reilley MJ, Aponte AM, et al. Stoichiometry of STAT3 and mitochondrial proteins: implications for the regulation of oxidative phosphorylation by protein-protein interactions. *J Biol Chem*. 2010; 285:23532–23536. [PubMed: 20558729]
80. Li L, Cheung SH, Evans EL, et al. Modulation of gene expression and tumor cell growth by redox modification of STAT3. *Cancer Res*. 2010; 70:8222–8232. [PubMed: 20807804]
81. Shaw PE. Could STAT3 provide a link between respiration and cell cycle progression? *Cell Cycle*. 2010; 9:4294–4296. [PubMed: 20962592]
82. Gough DJ, Corlett A, Schlessinger K, et al. Mitochondrial STAT3 supports Ras-dependent oncogenic transformation. *Science*. 2009; 324:1713–1716. [PubMed: 19556508]
83. Leslie K, Gao SP, Berishaj M, et al. Differential interleukin-6/Stat3 signaling as a function of cellular context mediates Ras-induced transformation. *Breast Cancer Res*. 2010; 12:R80. [PubMed: 20929542]
84. Kamp DW, Shacter E, Weitzman SA. Chronic inflammation and cancer: the role of the mitochondria. *Oncology (Williston Park)*. 2011; 25:400–410. 413. [PubMed: 21710835]
85. Weinberg F, Hamanaka R, Wheaton WW, et al. Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. *Proc Natl Acad Sci U S A*. 2010; 107:8788–8793. [PubMed: 20421486]
86. Redston MS, Papadopoulos N, Caldas C, et al. Common occurrence of APC and K-ras gene mutations in the spectrum of colitis-associated neoplasias. *Gastroenterology*. 1995; 108:383–392. [PubMed: 7835579]
87. Tateno T, Asa SL, Zheng L, et al. The FGFR4-G388R polymorphism promotes mitochondrial STAT3 serine phosphorylation to facilitate pituitary growth hormone cell tumorigenesis. *PLoS Genet*. 2011; 7:e1002400. [PubMed: 22174695]
88. Zhang Q, Raje V, Yakovlev VA, et al. Mitochondrial localized stat3 promotes breast cancer growth via phosphorylation of serine 727. *J Biol Chem*. 2013; 288:31280–31288. [PubMed: 24019511]
89. Mackenzie GG, Huang L, Alston N, et al. Targeting mitochondrial STAT3 with the novel phospho-valproic acid (MDC-1112) inhibits pancreatic cancer growth in mice. *PLoS One*. 2013; 8:e61532. [PubMed: 23650499]
90. Du W, Hong J, Wang YC, et al. Inhibition of JAK2/STAT3 signalling induces colorectal cancer cell apoptosis via mitochondrial pathway. *J Cell Mol Med*. 2012; 16:1878–1888. [PubMed: 22050790]

FIGURE 1.

Mitochondrial alterations and the role of Stat3 during the progression from colitis to cancer. Inflammation is associated with mitochondrial dysfunction and ulceration of the epithelium. IL-6 produced by lamina propria T cells activates Stat3 in T cells, enhancing their survival, and activates Stat3 in epithelial cells, promoting proliferation and expression of S1P. IL-22 induction of Stat3 is essential for wound healing responses of the epithelium. Inflammation-associated ROS can damage DNA and mtDNA in epithelial cells and act as intracellular signaling molecules, promoting the transition to dysplasia. Dysplastic epithelium exhibits increased Stat3, thereby perpetuating activation of S1P signaling in the epithelium and

mucosal immune cells, forming an IL-6/Stat3/S1P amplification loop. UC-associated dysplastic epithelium displays loss of mitochondria and cytochrome C oxidase expression, decreased oxidative phosphorylation, and increased glycolysis. p53 mutation, K-Ras activation, and later APC mutation are involved in the progression from dysplasia to colitis-associated cancer. The IL-6/Stat3/S1P amplification loop and dysregulated IL-22 activation of epithelial Stat3 play a central role in tumor progression. The number of mitochondria and oxidative phosphorylation are restored during the cancer stage, coupled with glycolysis to meet the requirements of tumor growth. NK, natural killer cell.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript