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Short Communication

A meta-analysis on the role of IL-6 associated JAK/STAT3 signaling pathway modulation in the inflammatory bowel disease complicated colonic cancer development

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The signaling pathway of Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) is suggested to be involved in various pathophysiological processes, including immune function, cell growth, differentiation, hematopoiesis and more importantly oncogenesis of distinct tumoral conditions. Interleukin (IL) 6 is a proinflammatory cytokine produced by antigen-presenting cells and non-hematopoietic cells in response to external stimuli and considered to be a key player in the development of the microenvironment of malignancy by promoting tumor growth and metastasis by acting as a bridge between chronic inflammation and cancerous tissue. In tumor cells, JAK/STAT3 hyperactivation can occur as a result of elevated IL-6 levels in the serum and/or in the tumor microenvironment, owing to signals from other growth factors and/or their receptors, activation by non-receptor tyrosine kinases, or loss-of-function mutations affecting negative regulators of STAT3. Ulcerative colitis (UC) and Crohn's disease (CD) are subtypes of inflammatory bowel disease (IBD) in which abnormal reactions of the immune system cause inflammation and ulcers on the distinct segments of the gastrointestinal system with a significant risk of colorectal cancer development. Recent studies suggest that aberrant interleukin IL6/JAK/STAT3 signaling pathway exists in both IBD and inflammation-related gastrointestinal cancers. In the present meta-analysis, we aimed to analyze the relationship between IL-6/JAK/STAT3 and IBD associated colorectal carcinogenesis and the effect of the inhibition of this system on disease follow-up and management.

A systematic literature review was carried up to January 2021 to identify all primary studies examining the role of IL-6 associated JAK/STAT3 system in IBD associated colorectal carcinogenesis. Studies related with the rest of other interleukins other than IL-6 was excluded.

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Table 1. Studies evaluating IL6 associated JAK/STAT3 pathway activation in colitis associated cancer

Reference	Result	Proposal
Li et al. (2009)	In dysplasia and cancer, epithelial cells of UC patients expressed significantly more IL6 and p-STAT3 compared with controls	This study demonstrated the importance of IL6/p-STAT3 in patients with inflammation-induced colorectal cancer. Moreover, cytokine signaling 3 may be involved in UC pathogenesis and the absence of cytokine signaling 3 seems critical for colorectal cancer progression.
Grivennikov et al. (2010)	IL-6 is found to be a critical tumor promoter during early colitis associated cancer tumorigenesis. In addition to enhancing proliferation of tumor initiating cells, IL-6 produced by lamina propria myeloid cells protects normal and pre-malignant intestinal epithelial cells (IEC) from apoptosis.	The proliferative and survival effects of IL-6 are largely mediated by transcription factor STAT3, whose IEC-specific ablation has profound impact on colitis associated tumorigenesis. Thus, the NF-κB-IL-6-STAT3 cascade is an important regulator of the proliferation and survival of tumor initiating IEC.
Yang et al. (2013)	The IL-6/STAT3 signaling pathway was attenuated in oroxylin A-treated mice. Oroxylin A effectively inhibited IL-6/STAT3 pathway in human HCT-116 cells.	The result of this study demonstrated that oroxylin A inhibits colitis-associated cCRC via modulating IL-6/STAT3 pathway in AOM/dextran sodium sulfate mouse model and in HCT-116 cells.
Chakilam et al. (2013)	It was found that death-associated protein kinase (DAPK)-induced conformational changes in the STAT3 dimer masked its nuclear localization signal. Alternatively, pharmacological inactivation of STAT3 resulted with an increase in DAPK mRNA and protein levels.	This study revealed that DAPK as a negative regulator of STAT3 emerges as therapeutic option in the treatment of UC and UC associated CRC.
Kim et al. (2013)	It has been found that shRNA-mediated galectin-4 silencing increases cell proliferation and, concomitantly, activates NF-κB and STAT3 signaling along with IL-6 up-regulation in CRC patients.	Authors proposes that abrogation of galectin-4 expression promotes cancer cell proliferation and provide s evidence that down-regulation of galectin-4 elicits tumor promotion in vitro and in vivo through activation of IL-6/NF-κB/STAT3 signaling.
Dai et al. (2014)	Embelin suppressed colonic IL-6 expression and secretion, and subsequently STAT3 activation in vivo. Moreover, embelin protected mice from AOM/DSS induced colitis before tumor development.	Embelin suppresses colitis-associated cancer, and its antitumor effect is partly mediated by limiting IL-6/STAT3 activation and Th17 immune response. It may be a potential agent in the prevention and treatment of colitis- associated cancer
Saadatdous t et al. (2015	Cocoa significantly decreased the tumor incidence and size in colitis-associated colorectal cancer in a rat IBD model of azoxymethane/dextran sulfate sodium. Moreover, cocoa suppressed colonic IL-6 expression and resulted in activation of STAT3.	This study demonstrated that cocoa may be a potential agent in the prevention and treatment of colitis-associated colorectal cancer by suppressing IL-6 secretion
Chen et al. (2015)	In UC model + empty vector group, IL6 and STAT3 expression was increased as lesion degree increased ($P < 0.05$). The expression of cytokine signaling 3 was weakened and the degree of activation decreased ($P < 0.05$)	The expression and activation of IL6 and STAT3 expression were enhanced in ulcerative colitis carcinogenesis, and their expression increased with the lesion degree increased, reflecting the disease progression to a certain extent
Do et al. (2016)	The total numbers of tumors in the Balsalazide and probiotic agent VSL#3 groups were significantly low compared with the colitis-associated carcinogenesis group	The results of this study demonstrated that Balsalazide and probiotic agent VSL#3 have chemo preventive effects against colitis-associated carcinogenesis through IL- 6/STAT3 suppression. Balsalazide and VSL#3 could be suitable options for chemoprevention of colorectal cancer.
Zhang et al. (2018)	IL-6 treated cells stimulated inflammatory microenvironment and found that glucose uptake, lactate production and lactate dehydrogenase activity elevated dramatically.	This study revealed that metabolic disruptions triggered by inflammatory signaling are associated with tumorigenesis via the STAT3/c-Myc axis in rat model of DSS induced colitis.
Ye at al. (2019)	Retinoid X receptor-alpha (XRα) is abnormally cleaved in tumor cells and tissues, producing a truncated RXRα (tRXRα) and transgenic expression of tRXRα in mice accelerates the development of colitis-associated colon cancer. The tumorigenic effect of tRXRα is primarily dependent on its expression in myeloid cells, which results in IL-6 induction and STAT3 activation.	Results of this study provides new insight into tRXRα action and identify a promising tRXRα ligand for treating colitis associated cancer.
Huangfu et al (2020)	Transcriptomic sequencing indicated that modified Pulsatillae decoction treatment downregulated the IL-6/STAT3 signaling pathway, and reduced the levels of p-NF-κB, IL-1β and NLRP3, which were confirmed by western blot.	This study propose that modified Pulsatillae decoction could efficiently relieve clinical signs and inflammatory mediators of UC, providing evidence of the anti-colitis effect of modified Pulsatillae decoction, which might provide novel strategies for therapeutic intervention in UC, which may be applied to the prevention of IBD-related colorectal cancer

All articles were critically appraised with regard to methodological quality and risk of bias. Twelve clinical trials that fulfilled the inclusion criteria were further pooled into a meta-analysis.

Twenty-two studies met initial selection criteria but only 12 were eligible for inclusion in the meta-analysis. The majority of studies demonstrated a significant role of IL6 associated JAK/STAT3 in the pathophysiology of UC related carcinogenesis. Table 1 summarizes the clinical trials that shows the potential role of IL6/JAK/STAT3 pathway in UC associated colorectal cancer development.

In light of the small number of studies able to be included in the meta-analysis, evidence strongly proposed that JAK/STAT3 signaling especially via the IL-6/STAT3 axis is involved in the transition of inflammatory lesions to tumoral diseases and leading to UC associated colorectal cancer. For this reason, based on the evidence presented in this meta-analysis it is reasonable to suggest that targeting components of the IL-6/JAK/STAT3 signaling pathway can inhibit tumor cell growth and relieve immunosuppression in the UC associated colonic tumoral microenvironment.

Conflict of Interests

Authors declare that there are none.

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