The JAK/STAT signaling cascade in gastric carcinoma (Review)

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Abstract. Gastric carcinoma remains one of the most prevalent forms of cancer worldwide, despite the decline in incidence rates, increased awareness of the disease and advancement in treatment strategies. *Helicobacter pylori* infection, dietary factors, lifestyle influences and various genetic aberrations have been shown to contribute to the development and progression of gastric cancer. Recent studies on the genomic landscape of gastric adenocarcinoma have identified several key signaling molecules, including epidermal growth factor receptor family (ErbB) members, vascular endothelial growth factor receptor family (VEGFR) members and PI3K/Akt/mTOR pathway components, that have been implicated in the molecular pathogenesis of gastric cancers. However, clinical trials with compounds that target these molecules have failed to show a significant improvement in overall survival rates when supplemented with conventional therapies. Therefore, it is essential to identify effective prognostic and/or diagnostic biomarkers and develop molecular targeted therapies. The JAK/STAT cascade is a principal signal transduction pathway in cytokine and growth factor signaling, regulating various cellular processes such as cell proliferation, differentiation, migration and survival. Numerous *in vivo* and *in vitro* studies have shown that dysregulated JAK/STAT signaling is a driving force in the pathogenesis of various solid cancers as well as hematopoietic malignancies. Hence, a large number of preclinical and clinical studies of drugs targeting this pathway are currently underway. Notably, aberrant JAK/STAT signaling has also been implicated in gastric cancers. In this review, we focus on the ongoing research on the JAK/STAT cascade in gastric carcinoma and discuss the therapeutic potential of targeting JAK/STAT signaling for the treatment of gastric cancer.

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1. Introduction

Gastric cancer refers to a group of heterogeneous malignant tumors arising in any part of the stomach, with the potential to spread through the blood/lymph vessels to other tissues of the body. Gastric carcinoma continues to be one of the most predominant forms of cancer worldwide (1). Approximately 952,000 new cases of gastric cancer were reported in the year 2012, accounting for 6.8% of all cancers, and thus, making it the fifth most common cancer in the world (2). The incidence rates of gastric cancer are particularly high in East Asia, South America and East Europe, whereas lowest incidence rates prevail in North America, Africa and Eastern Mediterranean region (2). These regional differences reflect variations in dietary patterns and food habits, as well as the prevalence of *Helicobacter pylori* infection (3). Furthermore, gastric cancer accounted for 723,000 deaths in 2012, making it the third most common cause of death in both genders (4). Although the incidence of gastric carcinoma is declining, the mortality rates are alarming and the need of the hour is to develop specific and efficacious treatment options in the effort to combat this dreaded disease.

2. Gastric tumorigenesis

Gastric carcinoma: etiology and risk factors. The stomach is a part of the alimentary tract, which aids in the digestion of food by secreting hydrochloric acid and enzymes. Histologically, the stomach contains four distinct layers with the innermost layer (mucosa) containing the gastric glands (5). The most common form of gastric cancer (90-95%) is adenocarcinoma, which arises from the glandular epithelium of the innermost lining of the stomach (6). Less common forms of gastric cancer include lymphoma of the stomach, gastrointestinal stromal tumor and gastrointestinal carcinoid tumor. Approximately 4% of all gastric cancer cases are of the lymphoma type arising from immune cells found in the wall of the stomach (7,8). On the other hand, gastrointestinal stromal tumor is a rare benign or

malignant tumor arising in the connective tissue of the stomach (8). Gastrointestinal carcinoid tumor is a neuroendocrine tumor of hormone-forming cells in the stomach, accounting for around 3% of all gastric cancers (9).

Under the Lauren classification, gastric carcinoma can manifest as two main histologic forms, intestinal type or diffuse type (10-12). The intestinal type of gastric carcinoma is well differentiated with cells arranged in glandular/tubular structures, whereas the diffuse type comprises of scattered poorly cohesive cells with little or no gland formation. In certain cases, the stomach tumor may exhibit features of both cancer types (10). The Ming system of classification of gastric carcinomas is based on the growth pattern of neoplastic cells, and categorizes tumors into expanding type or infiltrative type (13,14). More recently, the WHO system of classification which has also been adopted, grades adenocarcinomas on the basis of the extent of metaplastic intestinal tissue. Under this classification system, five subtypes namely adenocarcinoma (intestinal and diffuse), papillary, tubular, mucinous and signet-ring cell are identified (6).

Since gastric cancers grow slowly, the initial cancer stages are asymptomatic and generally remain undetected (15). However, the extent of the tumor as well as outcome of disease is determined by the initial cancer-causing event. There are numerous risk factors associated with gastric cancer, ranging from *Helicobacter pylori* (*H. pylori*) infection to age, gender, geographical location and other lifestyle factors (16). Infection by *H. pylori* is the primary risk factor for gastric cancers, specifically for those arising from the distal portion of the stomach. *H. pylori* promotes gastric inflammation, clinically known as chronic atrophic gastritis, which subsequently leads to cancerous alterations to the lining of the stomach (17).

Gastric carcinoma occurs more commonly in older people, primarily above the age of 60. A combination of aging with *H. pylori* infection may have an additive role in the promotion of gastric carcinoma, and people having been exposed to *H. pylori* infection in childhood are at a high risk of developing adult gastric cancer (18,19). Concurrently, studies have shown that men are at a higher risk of developing gastric carcinoma as compared to women; particularly for *H. pylori*-induced gastric cancer, due to lifestyle disparities as well as estrogen-mediated biological differences (7,20). Geographical features also dictate incidence rates, with higher number of cases seen in East Asia, Eastern Europe and parts of South and Central America and lower rates seen in Northern and Western Africa, South Central Asia, and North America (21). Histologically, the diffuse type of gastric adenocarcinoma is uniformly distributed amongst populations while the intestinal type of gastric cancer is predominantly found in the high risk geographical regions (11). Interestingly, there is also a variation seen in the incidence rates between different ethnic groups living in the same region (22).

Furthermore, a low socioeconomic status has been associated with a high risk of developing gastric cancer (23). Diets including high intake of salt and preserved or pickled food also increase the chances of a person developing gastric cancer, and studies have shown that eating fresh vegetables and fruits may help lower these risk rates (19,24). Lifestyle factors including smoking has also been associated with gastric cancers, particularly of those arising in the upper portion of the stomach (7). An overview of gastric carcinogenesis is illustrated in Fig. 1.

Genetic aberrations and mutations associated with gastric cancer. In addition to the risk factors, studies on the genomic landscape of gastric adenocarcinoma have revealed that certain genetic alterations and/or mutations can contribute to the pathogenesis of gastric cancer (25). Advancement in molecular profiling technologies have enabled rapid whole genome sequencing, with better resolution that provides researchers the opportunity to scan for known genomic mutations, as well as identify novel genomic aberrations specific to different subsets of gastric carcinoma patients (26-28).

A high throughput screen has been conducted using 237 gastric adenocarcinoma patient tissues that led to the identification of 474 'hotspot' mutations in 41 genes (29). Specifically, it was found that 34 (14.4%) of 237 gastric cancer patients harbour mutations in *PIK3CA* (5.1%), *TP53* (4.6%), *APC* (2.5%), *STK11* (2.1%), *CTNNB1* (1.7%) and *CDKN2A* (0.8%) (29). Another study using 15 adenocarcinoma patient tissues along with matched normal tissues has identified somatic mutations in *TP53* (11/15), *PIK3CA* (3/15) and *ARID1A* (3/15) (30). Dulak *et al* also carried out genomic profiling analysis of 486 gastrointestinal cancers, including 296 esophageal and gastric cancers, and identified 64 regions of recurrent amplified/deleted somatic mutations (33). Amplified genes that were identified included kinases such as *ERBB2, FGFR1, FGFR2, EGFR*, and *MET*, as well as several novel genes not previously known to be associated with carcinogenesis were recognized. All these studies provided a foundation for the development of novel treatment options, specifically targeting genes with 'hotspot' mutations in gastric cancer. Since targeted therapy offers several advantages over the traditionally available treatment alternatives, many researchers are currently working on translating these genomic findings to clinical outcomes (Fig. 2).

Molecular profiling has shown that the most frequently mutated genes in gastric cancer patients are the members of epidermal growth factor receptor family (ErbB1-4). Of these, overexpressed ErbB1 has been implicated in 27-64% of gastric cancer patients (31-33). However, clinical trials where cetuximab, a monoclonal anti-EGFR antibody, was used along with capecitabine-cisplatin to treat patients with advanced gastric cancer have failed to demonstrate a significant improvement (34). On the other hand, 6-34% of gastric cancer patients showed increased levels of ErbB2/HER2, primarily encompassing those belonging to the intestinal type of tumor (35,36). In the ToGA trial, the inclusion of trastuzumab (an anti-HER2 monoclonal antibody) to traditional chemotherapy treatment showed a slight increase in overall survival (OS) from 11.1 to 13.8 months in patients with HER2 amplified gastric adenocarcinomas; therefore, providing the potential of molecular targeted therapy in the treatment of gastric cancer (37). Overexpression of ErbB3 has been reported to be associated with tumor progression/invasion and lower OS rates in gastric cancer patients (38). Analysis of gastric cancer tissues has shown that significantly higher levels of HER2 and HER3 are associated with late stage gastric adenocarcinoma (stage III-IV) compared to stage I-II disease (22-24% vs. 5.8%-7.7%, $p<0.05$) (39). Several ongoing clinical trials are currently

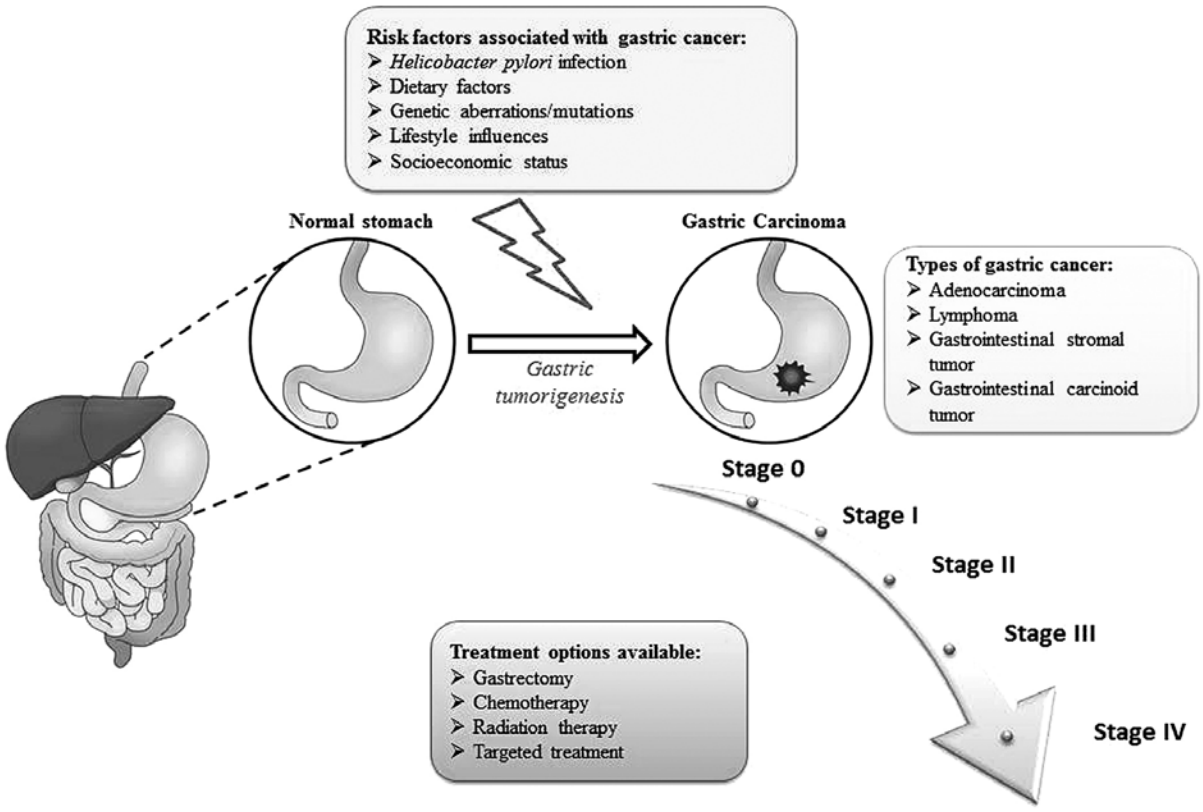


Figure 1. Gastric cancer: risk factors, types and treatment options available.

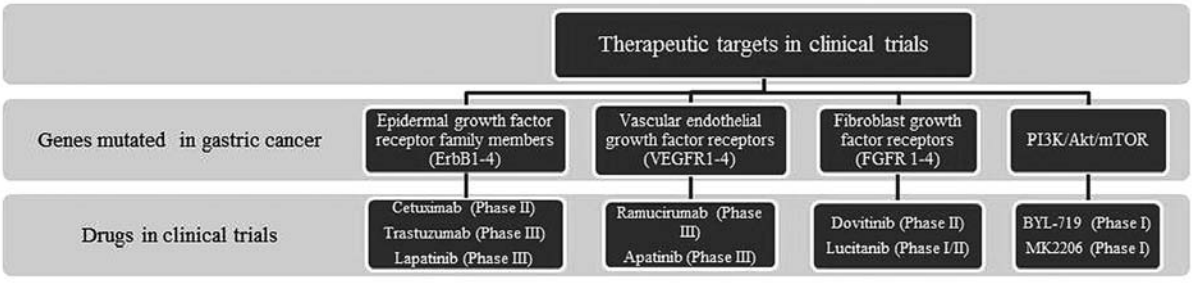


Figure 2. Genetic mutations associated with gastric cancer, and representative drugs currently in clinical trials. A complete list of drugs can be found on ClinicalTrials.gov.

evaluating the efficacy of novel EGFR-targeted treatment options in HER-2 positive/amplified gastric cancers, as well as on EGFR and HER2 co-expressing tumors (40).

An increased expression of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptors (VEGFR1-4) is known to promote angiogenesis, and is therefore associated with more aggressive forms of gastric cancer (41-43). Despite promising *in vitro* results, clinical trials with the VEGF-A monoclonal antibody bevacizumab failed to show a significant improvement in patient survival rates when supplemented with first-line chemotherapy (44,45). On the other hand, the results from the REGARD clinical trial with ramucirumab, (an anti-VEGFR monoclonal antibody) showed an increase in OS rates (5.2 versus 3.8 months, p=0.047) in patients with advanced gastric cancer after first-line chemotherapy (46).

Fibroblast growth factor receptors (FGFR1-4), another family of receptor tyrosine kinases, have also been implicated in gastric carcinoma (26). Five to eight percent of gastric patients show amplified *FGFR2* contributing to lymph node metastasis, and thus, worsening the prognosis (47). Consequently, the clinical studies of dovitinib targeting this amplified *FGFR2* are currently under phase II clinical trials as a monotherapy in patients with metastatic or unresectable gastric cancer (48).

The PI3K/Akt/mTOR is a major effector cascade of receptor tyrosine kinase signaling, and the core components of this cascade are found to be altered in gastric carcinoma. *PIK3CA* is found to be mutated in 5% of gastric cancers in which mutation of this gene leads to the constitutive activation of the pathway even in the absence of ligand (29,49,50). Poor prognosis has also been associated with gastric cancer

patients having amplified PIK3CA in advanced gastric cancer cases (51). Several clinical trials targeting molecules involved in this dysregulated signaling pathway are under investigation. Everolimus, an mTOR inhibitor, has increased progression-free survival in neuroendocrine tumors and renal cell carcinomas; however, it failed to show a significant improvement in survival rates when tested for its efficacy in previously treated advanced gastric carcinoma patients (52,53). Phase I trials in gastric cancer patients with altered *PIK3CA* or amplified *HER2* are being tested with the isoform specific p110-α inhibitor BYL719 and the heat shock protein 90 (Hsp90) inhibitor AUY922 (NCT01613950) (54). The Akt inhibitor MK2206 is also in early clinical trials for patients with gastric cancer, as well as other solid tumors (NCT01260701, NCT00963547) (54).

The treatment of early stage gastric cancer primarily includes radiation therapy/chemotherapy to reduce tumor size followed by surgical removal of the tumor mass (55). Advanced forms of gastric carcinoma are, however, more difficult to target. Several genetic alterations have been shown to be associated with gastric cancer; and thus, researchers have been trying to develop therapeutic interventions targeting these signaling molecules as a novel therapeutic approach to eradicate these aggressive forms of stomach cancer. Although targeted therapeutics against the molecules with 'hotspot'mutations have provided the potential to treat patients with gastric cancer, ongoing clinical trials with the drugs have failed to show a significant improvement in overall survival rates of patients. Therefore, more effective and promising therapeutics targeting additional molecules implicated in gastric cancer need to be designed and developed.

3. JAK/STAT signaling in gastric tumorigenesis

JAK/STAT signal transduction pathway. The JAK/STAT (Janus kinase/signal transducer and activator of transcription) cascade is a principal signal transduction pathway that is involved in a range of physiological and cellular processes, such as cellular proliferation, stem cell self-renewal and immune responses (56-58). Tightly regulated JAK/STAT signaling is of utmost importance in maintaining normal cellular homeostasis. Consequently, dysregulation of this pathway is known to be associated with a variety of pathological conditions, including immune disorders and human cancers (59).

The JAK/STAT signaling cascade is highly conserved across phyla, ranging from slime molds to humans (59). The JAK/STAT cascade was originally identified in the context of interferon-α (IFNα), IFN-γ and interleukin-6 (IL-6)-mediated signaling. The binding of these immune modulators to their receptors triggers the activation and dimerization of specific receptors, which in turn, causes the receptor-associated JAKs to come into close proximity, and subsequently leads to the auto- and/or trans-phosphorylation of the kinases (60). The cognate receptor then becomes phosphorylated by the activated JAKs and in turn, serves as a docking site for the SH2 domain-containing STAT molecules (5). STATs, which have been tyrosine-phosphorylated by JAK kinases are released from the receptor, dimerize and then translocate to the nucleus, where they act as a transcription factor to modulate the expression of downstream target genes (56). This cascade is negatively regulated by three main classes of molecules; namely protein tyrosine phosphatase (PTP), suppressor of cytokine signaling (SOCS) and protein inhibitor of activated STAT (PIAS), at different levels of signaling (62). PTPs dephosphorylate STAT, JAK or the associated receptors, consequently, inactivating them, whereas PIAS molecules inhibit the signaling by preventing activated STAT dimers from binding to their downstream targets or by interfering with their transactivation capacity (61). SOCS molecules interfere with STAT recruitment to the receptor, inhibit JAK activation, or promote the proteasomal degradation of activated JAKs or the associated receptors. Interestingly, SOCS is transcriptionally regulated by JAK/STAT signaling, and thus a negative feedback mechanism occurs (62).

In mammals, the JAK family includes four members, namely JAK1, JAK2, JAK3 and TYK2. JAK1, JAK2 and TYK2 are known to be ubiquitously expressed, whereas JAK3 expression is restricted to the hematopoietic cells, suggesting its essential role in hematopoietic development (63). On the other hand, the STAT protein family has 7 key players namely STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6, each of which is known to regulate diverse cellular processes (56). STAT proteins act as important transcription factors that regulate the transcription of many key molecules involved in cell differentiation, proliferation, inflammation and apoptosis. Recently, an indirect transcriptional role of STAT has been reported, and this non-canonical JAK/STAT signaling has been shown to be associated with heterochromatin stability and the epigenetic regulation of global transcriptional state, particularly by DNA methylation and chromatin remodelling (64).

Constitutive activation of JAK/STAT signaling is well-established in cancers. It may occur as a result of an increased cytokine/cytokine receptor production or a decreased expression of the negative regulators of the pathway (65). Activating somatic mutations in *JAK2* or *MPL* (encoding thrombopoietin receptor) have been implicated in certain cases of myeloproliferative disorders, resulting in the persistent activation of STAT3/5 (66,67). In-frame deletions in *gp130* were shown to lead to the constitutive activation of STAT3, even in the absence of a ligand during the pathogenesis of hepatocellular carcinomas (68). Furthermore, sphingosine-1-phosphate receptor-1 (S1PR1) was reported to upregulate JAK2/STAT3 signaling in different epithelial cancers via increasing STAT3 signaling, which in turn transcriptionally regulates itself, *S1PR1* and *IL-6* gene in a positive feed forward loop, contributing to the process of tumorigenesis in these cancers (69). Novel somatic mutations in *LNK*, encoding a negative regulator of the JAK/STAT pathway, was also found to be a driving force in a subset of myeloproliferative neoplasms by activating STAT signaling (70). Additionally, the tumor suppressor PTP delta, which is known to dephosphorylate STAT3, was found to be frequently mutated in human glioblastoma, head and neck cancers and lung cancers, thus, reinforcing the causative role of dysregulated STAT signaling in a wide variety of cancers (71).

The first report describing STAT3 as an oncogene was published more than a decade ago. Constitutively-active STAT3 produced by substituting two cysteine residues for alanine and asparagine respectively, in the C-terminal loop of the SH2 domain was demonstrated to have the ability to transform immortalized fibroblasts and induce tumors in nude

mice (72). This study provided the foundation for exploring the role of STAT3 as an oncogene in various human cancers. Subsequent studies have linked dysregulated JAK/STAT signaling to the tumor initiation and progression of a variety of solid cancers and hematopoietic malignancies (66-69). STAT3 has been shown to prevent apoptosis by increasing the expression levels of the anti-apoptotic proteins of Bcl-2 family proteins (73). In particular, STAT3 mediates its pro-survival functions via Survivin, which not only prevents apoptosis but also promotes the mitogenic activity of cells (73,74). Studies have also shown that STAT3 controls the expression of the master EMT (epithelial-to-mesenchymal) transcriptional regulators, thus, contributing to the process of metastasis in cancers (75). An aberrant expression of STAT3 was also shown to contribute to the tumor progression via facilitating cell motility and invasion (76). Moreover, STAT3 is also known to promote the formation of new blood vessels by increasing the levels of VEGF and hypoxia-inducible factor (HIF)-1α (77-79). Several immunomodulatory molecules are also regulated by the JAK/STAT cascade. Specifically, reduced Th1-dominated antitumor response on aberrant STAT3 activation contributes to cancer cell survival and proliferation, suggesting the role of STAT3 in the maintenance of the tumor microenvironment by contributing to the process of inflammation and angiogenesis (77,80-82).

JAK-STAT signaling in gastric carcinoma. Various *in vitro* and *in vivo* studies have implicated dysregulated JAK/STAT signaling in haematological malignancies, as well as in various solid cancers. Interestingly, aberrant activation of the JAK/STAT pathway has also been described to contribute to the process of gastric tumorigenesis (83,84). Constitutively-active STAT3 was found in various gastric cancer cell lines, such that its inhibition by the ectopic expression of dominant negative STAT3 or JAK inhibitor induced the apoptosis of these cancer cells. Inhibition of STAT3 has consistently resulted in a significant decrease in the levels of the anti-apoptotic protein Survivin, leading to a decrease in gastric cancer cell survival (85). Gong *et al* examined 86 cases of resected gastric cancers to study the association of activated STAT3 with various angiogenesis factors, including VEGF expression and microvessel density in gastric cancer. Univariate survival analysis confirmed the role of aberrant STAT3 levels in angiogenesis, which in turn, was found to contribute to the gastric cancer progression (79). Furthermore, the expression of REG Iα (a member of the regenerating gene family), an IL-6 inducible protein, was examined in cancer specimens to study the significance of STAT3 in inflammation-driven gastric cancer. REG Iα expression was found to correlate with phospho-STAT3 expression in gastric cancer tissues, suggesting the role of REG Iα in tumorigenesis by promoting anti-apoptosis (86). Moreover, in the $gp130^{757FF}$ mouse model of gastric cancer, IL-6/IL-11-dependent increase of STAT3 expression was shown to contribute to the development and progression of *H. pylori*-associated gastric adenocarcinoma (87).

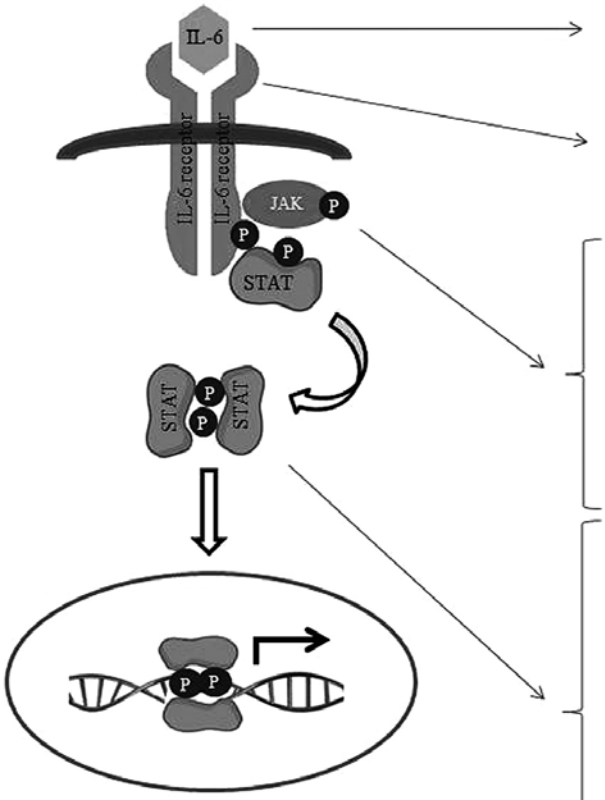
One hundred gastric adenocarcinoma patient tissues after gastrectomy were also analysed to examine the expression of STAT3 by immunohistochemical staining (88). It was found that STAT3 expression was highly associated with TNM staging and survival, thus, suggesting that it functions as a biomarker predicting poor prognosis of gastric cancer. Similarly, Deng *et al* evaluated the association of STAT3, phospho-STAT3, SOCS1 as well as other clinicopathological factors with overall survival rates in 53 gastric cancer patient tissue samples. Univariate and multivariate analysis revealed that phospho-STAT3 and lymph node metastasis are independent predictors of OS in gastric cancer, and STAT3 expression correlates with lymph node metastasis status in these patients (89). Deng *et al* also analysed 107 gastric cancer patient tissue samples by immunohistochemistry to elucidate the role of SOCS3 expression in gastric cancer, and found that SOCS3 was the best indicator for lymph node metastasis; and thus, further studies are warranted to explore its role as a predictor of lymph node metastasis in gastric cancer (90).

The role of STAT3 in inflammation-mediated gastric tumorigenesis has also been extensively explored. A study using loss- and gain-of-function of STAT3 mice in a colitis-associated cancer (CAC) model showed that gp130/STAT3 signaling cascade provides a link between inflammation and gastrointestinal cancers. STAT3 was found to function in tumor progression by promoting intestinal epithelial cell (IEC) survival and proliferation through G1 and G2/M cell-cycle progression (91). Furthermore, it was shown that low-grade intraepithelial lesions in Stat3-deficient mice progress to advanced tubular tumors, thus, affirming the critical role of STAT3 in IEC proliferation and survival in CAC carcinogenesis (92). Additionally, more aggressive tumors have been observed in relation to STAT3 activation, either by epithelial-specific SOCS3 ablation or introduction of SOCS3 binding-deficient $gp130^{Y757F}$ mutation (93,94). These reports have provided valuable insights into STAT3-driven inflammation and gastric cancer (94).

Therapeutic potential of JAK/STAT inhibitors in human cancers. Constitutive activation of JAK/STAT signaling is a common occurrence in human cancers. Tumors may arise either due to an increased autocrine/paracrine cytokine signaling via the associated receptors or due to an increased transcription of downstream STAT-dependent target genes, such as pro-survival Bcl-2 family members, angiogenic factors (HIF-1α), inflammation promoting genes (IL-10, TGF-β, COX-2) or metastasis regulators (MMP1/3/9, ICAM-1) (77,95-97).

Tocilizumab, a monoclonal antibody against IL-6 receptors, has proven to be effective in inflammatory conditions, including Rheumatoid arthritis as well as Castleman's disease, with recent clinical trials testing the efficacy of this antibody in the context of cancers (98-100). Tocilizumab has been tested for its efficacy in various IL-6-driven cancer models for large-cell carcinoma of the lung, ovarian cancer as well as pancreatic ductal adenocarcinoma (101-103). *In vitro* and *in vivo* studies have shown that treatment of these tumors with this IL-6 receptor antibody significantly decreases the size of the tumor mass as well as invasion/metastasis, and ongoing clinical trials are testing its efficacy in patients with recurrent ovarian cancer and chronic lymphocytic leukemia (104,105). In addition, the IL-6 ligand antibody CNTO-328 is currently under phase I/II clinical trials for myeloma and prostate cancer (106-108).

In myeloproliferative neoplasms involving activating somatic mutations in *JAK1/2*, clinical trials of JAK inhibi-



Drug/ Inhibitor	Mechanism of action	Disease/Cancer	Status
CNTO-328	IL-6 ligand blocking antibody	Multiple Myeloma, Prostate cancer	Phase I/II
Tocilizumab	IL-6 receptor blocking antibody	Castleman's Disease	FDA approved
Ruxolitinib	JAK1/2 inhibitor	Myelofibrosis	FDA approved
INCB018424	JAK1/2 inhibitor	Hematologic malignancies	Phase III
AZD1480	JAK1/2 inhibitor	Breast cancer, Ovarian cancer, Prostate cancer, Hematologic malignancies	Phase I
STAT3 decoy	STAT3 DNA competitor	Head and neck cancer	Phase 0
Pyrimethamine	STAT3 inhibitor	Chronic lymphocytic leukemia, Small lymphocytic leukemia	Phase I/II
AZD9150	STAT3 inhibitor	Hepatocellular carcinoma	Phase I/Ib
WP1066	STAT3 inhibitor	Glioblastoma multiforme	Phase I

Figure 3. Ongoing clinical trials of cancer drugs that target the components of the JAK/STAT pathway.

tors have demonstrated a significant improvement in patient survival rates, with the JAK1/2 inhibitor ruxolitinib becoming the first FDA approved drug for the treatment of intermediate-/high-risk myelofibrosis clinically (109,110). Moreover, the JAK inhibitor AG490 has been successful in reducing tumor growth both *in vitro* and *in vivo* models of relapsed B-cell leukemias (111). Orally administered JAK1/2 inhibitors, such as INCB018424, are currently in phase III clinical trials for myeloproliferative disorders where it has shown several clinical improvements, including reduction in splenomegaly, discomfort and night sweats (112). Additionally, the JAK1/2 inhibitor AZD1480 has shown to reduce tumor growth and aggressiveness in the xenograft models of IL6-mediated breast, ovarian and prostate cancers, and thus, ongoing clinical trials are exploring its potential in patients (113).

Due to their multifaceted roles as transcription factors, STAT family proteins are vital mediators of tumorigenesis, in the context of both solid tumors as well as hematopoietic malignancies. Hence, inhibitors abrogating STAT signaling are also extensively being studied (114-116). A STAT3 decoy, a double-stranded DNA containing STAT3-binding site, has been shown to successfully act in sequestering dimeric STAT3 away from its endogenous targets (117). Preliminary results with the STAT3 decoy in head and neck cancer showed that it successfully results in the apoptosis of cancer cells and a reduction in tumor growth; and thus, this decoy is being tested clinically in patients with head and neck squamous carcinoma (118,119). Peptidomemetics and designed small molecules specifically targeting STAT3 have also shown promising outcomes in preclinical acute cancer models for human breast cancer, pancreatic cancer, prostate cancer and non-small cell lung cancer, as well as in hematopoietic disorders such as acute myeloid leukemia (120-122). Nifuroxazide, which was initially identified as a treatment drug for diarrhea, was shown to effectively inhibit the survival of multiple myeloma cells by suppressing JAK2 and TYK2 directly (123). Similarly, the malarial drug pyrimethamine was found to inhibit STAT3, and is currently under investigation as a treatment option for chronic lymphocytic leukemia and small lymphocytic leukemia (124).

4. Conclusion

As compared to other cancer types, a large proportion of gastric carcinoma patients even after curative surgery suffer from relapse and secondary diseases. The use of histopathological features such as depth of primary tumor and lymph node metastasis status have improved prognosis in these cancers. However, the need for better and new molecular markers still exists. Ongoing studies on important signaling

molecules, including ErbB, VEGFR and PI3K/mTOR/Akt, as potential prognostic markers have not yet led to translation into clinical practices hitherto.

Studies have demonstrated dysregulated JAK/STAT signaling in patient cohorts with gastric carcinoma. In particular, aberrant STAT3 expression has been implicated in gastric adenocarcinoma patients, making STAT3 a promising candidate as a prognostic marker in gastric cancers (79,85,125,126). In gastric cancer, the abnormal STAT3 expression not only contributes to cancer cell proliferation and survival, but also functions in promoting inflammation, EMT transition and metastasis (94,97,127,128). Various *in vitro* and *in vivo* studies have confirmed the role of STAT3 in the precancerous pathology of the stomach, indicating that STAT3 may serve as a useful prognostic/diagnostic biomarker for the early detection of gastric cancer and that limiting STAT3 activity could help prevent malignancy (125). Altogether, these findings suggest that targeting the aberrant JAK/STAT signaling in gastric carcinoma may hold great potential as a novel therapeutic intervention for the treatment of patients with gastric cancer; and that the drugs/inhibitors of JAK/STAT cascade currently in clinical trials for solid tumors and hematopoietic malignancies (Fig. 3) should also be tested for their efficacy as therapeutics in gastric carcinoma.

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