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JAK/STAT Pathway in Gastric Cancer and its Potential Therapeutic Implications

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Abstract

Normal functioning of Gastric epithelial cells needs continuous check over multiple signaling pathways. Dysrhythmic behavior of any of the pathways at any of the steps can lead to unleashing of devastating effects. Tracking these abnormal steps can be a way forward for controlling the aggressiveness of these cells. Here in this review we have summed up various studies in order to link different hierarchies of the key pathway leading to gastric cancer. Out of all, JAK/STAT pathway is considered to be a master regulator for cell signaling. Abnormal functioning of JAK/STAT pathway at any of the steps ranging from inflammation caused by *Helicobacter pylori* to its negative regulator SOCS-1 can bring about the devastating nature of this pathway which ultimately leads Gastric Carcinoma. However in this review we have tried to track different steps of this pathway to find out the possible means of impeding the aggressiveness caused due to any abnormality.

Keywords: *H. pylori* • IL-6 • Inflammation • Smoking • Chemotherapy

Introduction

Gastric cancer

Gastric cancer is a group of diverse range of malignant tumors arising anywhere in the stomach with the capability of spreading through circulating blood and lymph to different body tissues [1]. Out of the four histological layers of stomach, adenocarcinoma is the most common (90%-95%) form of gastric cancers arising from the epithelial glands of the intimate gastric lining [2]. Involvement of the immune cells in the development of gastric cancer which is usually known as the lymphoma of the stomach comprises of around 4% of all cases, gastrointestinal stomal tumor arising from the connective tissue of the stomach is a rare benign or malignant tumor, another rare form of gastric cancer of neuroendocrine nature known as gastrointestinal carcinoid tumor (3%) develops from the hormone-forming cells in the stomach [3,4].

Literature Review

Incidence

Gastric cancer is the sixth most prominent cancer in the world, accounting for 5.7% of all cancers and has affected 1033701 people worldwide in the year 2012. Gastric cancer prevalence on the whole is higher in East Asia, South America and east Europe, and is less frequent in North America, Africa and eastern Mediterranean region [5]. This region wise variation relies in the diversity in eating practices, and the occurrence of *Helicobacter pylori infection* [6]. In 2012 gastric cancer took a death toll of 723,000 ranking it third prevalent reason for death world over without gender disparity [7].

Indian prevalence of gastric cancer

Stomach cancer is second notorious for cancer related deaths in India among both genders [8]. India is having lesser gastric cancer rates compared to the western population, being dominant in males (male-to-female ratio, 2:1) with 34,000 new number of gastric cancer cases. However the new figure of gastric cancer cases may rise up to 50,000 annually by the year 2020. As per the study carried out in Karnataka reports, gastric cancer amongst the five most common cancers even among young Indian men and women (aged 15-44 years). Incidence is higher in southern India mainly Chennai, however most recent data reports gastric cancer rate highest in north-eastern region, with Aizwal having incidence rate of 57.3 in men and 33.6 in women [9].

According to the study by Qureshi et al. on 1598 cancer patients at GMC Srinagar for a period of 6 years stated that gastric cancer was most prominent cancer among Kashmiri males (25.2%) and ranks third among Kashmiri females (10.4%) [10].

Mustafa et al. conducted a study on 330 gastric cancer patients for a period of 4 years and concluded that majority of the patients were males and 70% of these males belonged to rural areas with farming as their main occupation [11].

An analysis of 11213 cancer patients for a period of 3 years carried out by Iqbal et al. discovered the gastric cancer to be third (8.6%) most prevalent cancer among Kashmiri population for both the genders [12].

Classification

As per the Lauren classification, the two histological divisions of gastric carcinoma include intestinal type and diffuse type. In intestinal type cells are well differentiated and having the glandular or tubular appearances, in contrast to the diffuse type consists of poorly cohesive scattered cells with lesser or no formation of glands. In some cases of gastric cancers both features may be present. Ming system classifies gastric cancer on the basis of neoplastic cellular growth and forms two groups of expanding type or infiltrative type tumors [13]. Recently, WHO system of classification has divided adenocarcinomas into five subtypes namely adenocarcinoma (intestinal and diffuse), papillary, tubular, mucinous and signet-ring cell on the basis of the extent of metaplastic intestinal tissue [14].

Risk factors

Slow growing nature of gastric cancer make them undetected during the initial cancer stages, but the degree of tumor and the effect of the disease is

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dependent on initial cancer-causing event [15].Various risk factors leading to gastric cancer range from simple infection by *Helicobacter pylori* (*H. pylori*) to age, gender, geographical location and other lifestyle habits. Infection by *H. pylori* the major threat for gastric cancers, especially developing in the distal portion of the stomach [16]. Kamangar et al. described that gastric malignancies because of *H. pylori* mostly depend on the anatomic location of stomach [17]. Gastric inflammation caused by *H. pylori*, clinically known as chronic atrophic gastritis, eventually leads to tumorous modifications of the mucosal epithelium of the stomach [18]. Asenjo and Gisbert reviewed 38 studies containing 1844 pts infected with *H. pylori* where in MALT lymphoma was present in 79% and the rate was higher in less infectious (79%) than in highly infectious (60%) cases [19].

Linz et al. proposed that human infections by *H. pylori* is possibly an essential threat for gastric cancer mostly adenocarcinomas accounting 90% of all gastric malignancies, and is presently well thought out as the main infection causing agent cancers which represents 5.5% of the world wide cancer burden. Among infected persons, nearly 10% build-up peptic ulcer disease, about 1%–3% advance to gastric cancer, and around 0.1% develops Mucosa-Associated Lymphoid Tissue (MALT) lymphoma [20].

Old aged individuals mainly above 60 having *H. pylori* infection and occasionally individuals with childhood exposure are more prone to gastric carcinoma. *H. pylori* induced gastric cancer occurs more often in male gender compared to females and this benefit can be credited to estrogen-mediated biological differences [21]. Regional variations also describe the prevalence of gastric cancer with more number of cases seen in East Asia, Eastern Europe and parts of South and Central America and lower rates seen in South Central Asia, Northern and Western Africa, and North America and among the different regions there is the uniform distribution of diffuse type of gastric adenocarcinoma while as intestinal type of gastric cancer mostly observed in the high risk regions globally [22]. Despite the generalization, different ethnic groups show variations within the same inhabited region [23].

Moreover, population with lower socioeconomic status has been linked with a greater threat of developing gastric cancer. Taking excess salt and consumption of canned or pickled food also enhance the probability of an individual for the development of gastric cancer, and studies have illustrated that consuming fresh vegetables and fruits may help lessen the disease risk [24]. Routine living standards which include smoking have also been correlated with gastric cancer development, particularly originating in the upper region of the stomach [3].

Possible gene mutations and abnormalities linked with gastric cancer development

Besides above stated threats and possibilities, various types of genetic alterations and mutational abnormalities can proceed to the development of gastric cancer [25]. With the help of latest molecular profiling technologies like fine resolution of whole genome sequencing, aids the researchers to scrutinize known genetic mutations or any genetic abnormality specific for different types of gastric carcinoma [26,27].

A study investigated 237 gastric adenocarcinoma patient tissues and identified 474 hotspot mutations in 41 genes. Out of 34(14.4%) of 237 gastric cancer patients mutations were found in PIK3ca (5.1%), TP53 (4.6%), APC (2.5%), STK11 (2.1%), CTNNB1 (1.7%) and CDKN2A (0.8%) [28], another study on 15 gastric cancer patient tissues and adjacent normal tissues recognized somatic mutations in genes like TP53 (11/15), PIK3ca (3/15) and ARID1a (3/15) [29]. Genomic profiling analysis carried out by Dulak et al. on 486 gastrointestinal cancer patients, including 296 esophageal and gastric cancers, and acknowledged 64 recurrent regions of amplifications like EGFR,FGFR1, FGFR2, ERBB2, and MET and also some deleted somatic mutations [30]. These studies provide a basis for alternative treatment choices specifically targeting the 'hotspot' gene mutations in gastric cancer, over which many researchers are working for their clinical use.

Epidermal growth factor receptor family (ERBB1-4) has been studied as one of the frequently mutated gene, with the mutation rate of 27%–64% among gastric cancer patients [30]. However increased intensity of ERBB 2/HER2 was found in 6%-34% of intestinal type of tumor. Increase levels ERBB 3, HER2 and HER3 may be linked with late stages of gastric cancer [31]. A number of clinical trials are presently underway for evaluating the effectiveness of targeted treatment options in HER-2 positive or amplified gastric cancers, and also on HER2 and EGFR co-expressing in tumors [32].

Vascular Edothelial Growth Factor (VEGF) and vascular endothelial growth factor receptors (VEGFr1-4) promotes angiogenesis, thus linked with violent forms of gastric cancer [33,34]. However ramucirumab, (an anti-VEGFr monoclonal antibody) in comparison to bevacizumab (VEGF-a monoclonal antibody) revealed an increase in OS rates (5.2 versus 3.8 months, p=0.047) in patients with advanced gastric cancer after taking first dose chemotherapy [35].

Another family of receptor tyrosine kinases like fibroblast growth factor receptors (FGFR1-4) and FGFR2 are also associated with lymph node metastasis and thus worsening the prognosis of gastric cancer [36]. However monotherapy with dovitinib currently under phase II of clinical trials can target amplified FGFR2 [37].

Core components of PI3K/AKT/mTOR are found to be modified in gastric cancer. In 5% of advancer gastric cancer cases PIK3ca show mutation in 5% which is also linked to the poor prognosis of the disease [38]. Trials on mTOR inhibitor everolimus has found success in renal cell carcinomas and neuroendocrine tumors; though, it didn't show any success of substantial improvement in enduring rates when tested for its effectiveness in earlier treated advanced gastric carcinoma patients [39]. Studies have shown that AKT inhibitor MK2206 is also in initial clinical trials for patients with gastric cancer, and also with other solid tumors [33].

The treatment of early stage gastric cancer principally includes radiotherapy or/and chemotherapy to shrink this usually followed by surgical elimination of the tumor mass [40]. Aggressive forms of gastric carcinoma are, however, more complex to treat. Numerous gene abnormalities have been depicted to be linked with gastric carcinoma; and therefore, investigators have been attempting to get progress in therapeutic interventions aiming for the innovative therapeutic approach to eliminate these destructive forms of gastric cancer. However therapies for the targeted molecules besides the genes with 'hotspot' mutations offer a potential for treating patients with gastric cancer, clinical trials with the therapies currently under practice haven't shown a noteworthy progress in overall survival rates of gastric cancer patients. Hence, extra efficient and promising therapeutic treatments targeting additional molecules associated with gastric cancer need to be designed and established.

H. pylori induced JAK/STAT signaling pathway in gastric cancer

Gastrointestinal malignancies usually follow chronic inflammation. It is a well-known fact that inflammatory bowel diseases lead to colorectal cancer, barrett's esophagus is a precursor of esophageal adenocarcinoma and *Helicobacter pylori* causes gastric cancer [41]. Ferrand et al. proved on animals that chronic inflammation triggered by *H. pylori* in the gastric mucosa can provoke the recruitment, differentiation and transformation of Bone marrow derived dendritic cells, suggestive of gastric cancer stem cells may play a role in the *H. pylori* induced gastric cancer. Judd et al. illustrated that chronic infection by *Helicobacter pylori* induce STAT-3 activity following ligand and receptor binding, however only JAK1 and JAK-2 account for STAT-3 phosphorylation upon binding with IL-11/gp130 receptor complex. These observations suggest that JAK-2 and STAT-3 can be taken as

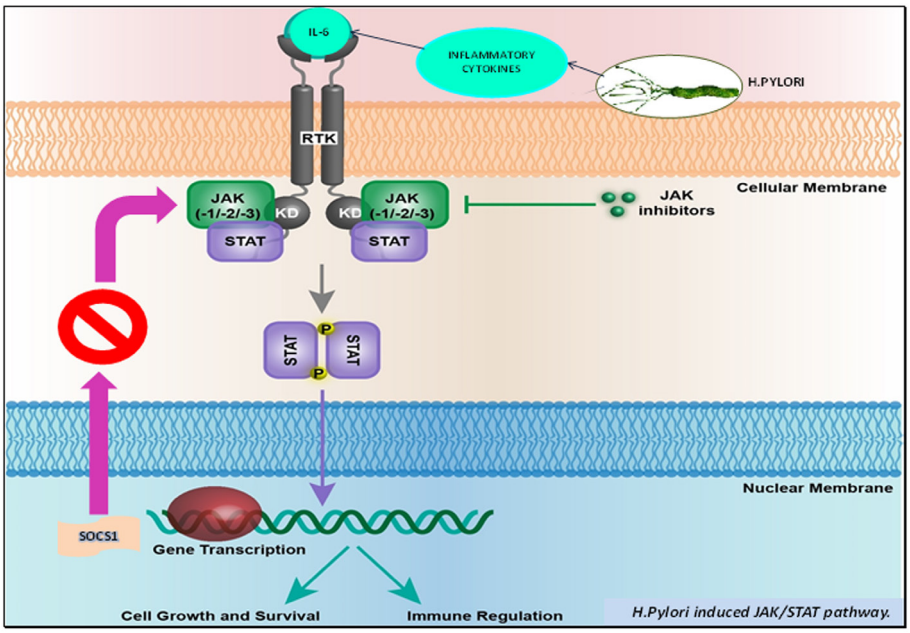

Figure 1. *H. pylori* induces JAK/STAT pathway in gastric cancer

promising targets for designing antagonistic therapies for suppressing IL-11/STAT-3 signaling in human gastric carcinoma [42,43] (Figure 1).

Although decreasing the risk for any allergic disease Cag A-positive *H. pylori* strains upsurges the threat for atrophic gastritis, peptic ulcer disease, and gastric carcinoma upon gastric colonization [44]. Hayashi T and Boquet et al. in separate studies showed that neoplastic transformation because of various virulence factors mostly Cag A (cytotoxin-associated gene a) and its pathogenicity island (cag PAI), and Vac A (vacuolating cytotoxin a) of *H. pylori* deregulate host intracellular signaling pathways . Sánchez-zauco et al. finds out that *H. Pylori* infected gastric tissues along with increased levels of IL-1β, IL-6, IFN-γ, and IL-10 and lesser levels of MCP-1 can significantly differentiate patients with GC from healthy normal. This study is supported by the research done by Salim et al. elucidating that mRNA expression levels of IL-6, IL-10, IL-17a, IFN-γ, TNF-α were amplified in the *H. pylori* infected chronic active gastritis group and those of IL-6, IL-10, IL-17a, TGF-β, TNF-α mRNA were boosted in the gastric cancer group with reference to *H. pylori*-infected normal gastric mucosa group. This study also showed that the immune response of gastric mucosa to infection of *H. pylori* differs from patient to patient. Stages of expression levels of different cytokines may be tracked in patients for tumor treating therapy. Kim et al. with the help of tissue microarrays and immune histochemical staining techniques showed that P16, P21, IL-1β, IL-6, and IL-17 protein expression was significantly higher in EBV and *H. pylori* infected gastric adenocarcinomas compared to that of IL-10, TNF-α, and TNFr1, thus suggesting that IL-17 and IL-6 linked with gastric carcinogenesis and might act as prognostic features [45-49].

Lamb et al. proposed that in gastric epithelium and the immune cells in circulation are recruited to the site of infection. *H. pylori* initiates an inflammatory process through multiple pathways up-regulating several pro inflammatory cytokines such as interleukin TNF-α, NF –κb, IL-1, IL-6, IL-8. Buchert et al. described that inflammatory cytokines like interleukin IL-6/IL-11, IL-10/IL-22 and IL-12/IL-23 families in the tumor microenvironment which share their common receptor lead to excessive activation of the JAK family and their accompanying transcription factors STAT-3 and STAT5. Various types of JAK inhibiting and JAK/STAT-3 interfering small molecules for treating solid cancers (stomach and colon) in mice are under trial in preclinical applications. Inhibitory molecules for JAK/STAT-3 pathway which is usually stimulated by cytokine activation may also afford orthogonal treatment chances for other oncogene addicted cancer cells that are usually drug resistant [50].

The bifunctional domains of IL-6 receptor gp130 can receive the activating signals either from JAK/STAT or SHP2/ERK pathways and the studies shows that gp130 receptor is phosphorylated by CagA factor of *H. pylori* [51]. Eraky et al. in one their recent study showed that 58% of the Egyptian gastric cancer population was found to have CagA +ve *H. pylori* infection. *H. pylori* disturb gp130 regulated signal transduction from the interior of gastric mucosal epithelium in addition to gp130 induction by IL-6 in the human gastric epithelial cells [52].

Many studies have found that eradication of *H. pylori* in the stomach can diminish the risk of gastric carcinoma. This study provides the insight regarding the mechanism that *H. pylori*-mediated cytokine expression enhanced tumour progression in a subset of gastric cancer where SOCS-1 was hypermethylated. Inhibition of JAK/STAT pathway by demethylation treatment or by applying specific JAK-2 inhibitor may possibly exposea novel therapeutic approach against gastric carcinoma [53]. Blocking the entry of IL-6 into inflammation induced T-cells in gp-130 knockout mice promoted the conversion of CD4+T cells into FOX P3+ T cells. These experiments clearly demonstrate chronic inflammation in cells can be prevented by targeting gp-130 entry point [54].

Several of physiological and cellular processes, such as stem cell self-renewal, cellular proliferation, and immune responses are carried out predominantly by JAK/STAT cascade [55]. Chung-min et al. in a recently studied that Janus Kinase (JAK), is activated upon ligation of IL-6 to its transmembrane receptor, which is followed by phosphorylation and dimerization of STAT-3 which then trans locates to the nucleus in order to transcribe specific target genes. STAT-3 phosphorylation and dimerization is prominent in gastric cancer patients infected with Cag A-positive *H. pylori*, even though the exact role of JAK/STAT signaling in gastric carcinoma is notcompletely understood [56].

The JAK/STAT signaling cascade can be triggered by various signaling cytokines, hormones and growth factors, such as interferon-α,β,γ, IL's23,(2, 4, 6, 7, 9, 10, 12, 15, 19, 20, 21, 22, 23) erythropoietin , growth hormone, prolactin, thrombopoietin, granulocyte colony-stimulating factor, epidermal growth factor, platelet-derived growth factor, and leptin [57]. Subsequent binding of the signaling molecule to its transmembrane receptor, activation the cytoplasmic domain of the JAK receptor takes place. Upon activation, JAK lead to phosphorylation of cytokine receptors, which lets STAT monomer domains in the cytoplasm to ligate to the JAK-receptor complex and form homoor/ and heterodimers due to phosphorylation of tyrosine. Then transcription of target genes take place upon binding of activated

STATs to the nucleus of the cell [58].

Activation by phosphorylation of JAK/STAT signaling pathway is well established in cancers. This activation can be a consequence of increased cytokine or cytokine receptor production or down regulation of the negative regulators of the JAK/STAT signaling pathway [59]. Zhao et al. worked on various gastric cancer cell lines and confirmed that increased expression of IL-6 and gp130 were capable of promoting proliferation, invasion and lymphangiogenesis *via* the JAK/STAT-3 signaling pathway [60]. Furthermore, certain other receptors like sphingosine-1-phosphate receptor-1 (S1PR1) was reported to up regulate JAK-2/STAT-3 signaling pathway in different cancers of epithelium by increasing STAT-3 signaling, which leads to its self-regulation , where S1PR1 and IL-6 gene in this positive feedback loop, contributes to the process of tumorigenesis in these cancers [61]. Recently Erdong et al. reported that increased expression of tumor hepcid in was associated with the up regulation of the JAK/STAT-3 signaling pathway in the pathogenesis of human gastric cancer, where IL-6 mediation can play a role [62]. Oncogenic nature of STAT-3 was published a decade ago, where active STAT-3 was described to be 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 [63]. A number of studies have associated deregulated JAK/STAT signaling to the initiation of tumors and development of various solid and hematopoietic malignancies [64]. STAT-3 prevents cellular apoptosis by increasing the expression anti-apoptotic proteins of BCL-2 family and promotes survival functions with the aid of surviving, which in turn helps in promoting mitogenic cellular activity [65]. Studies revealed that STAT-3 is involved in epithelial-to-mesenchymal cell transition, angiogenesis by increasing levels of VEGF and hypoxia-inducible factor (HIF)-1α, enabling cellular motility and invasion thus overall contributes to the metastatic process in cancers [66,67].

Firm regulation of JAK/STAT pathway is of chief significance in normally maintaining cellular homeostasis. Subsequently, deregulation of this pathway can be linked to a number of pathological disorders, which include immunological diseases and various cancers [68].

The involvement of STAT-3 in cancer initiation, development, metastasis, and drug resistance make it a suitable target for therapeutics. A list of STAT-3 inhibitors, which consists of oligonucleotides, peptide mimetics, and small molecules [69]. *In vitro* or clinical measures based on pSTAT-3 and STAT-3 gene regulation may assist in choosing reliable drugs and approaches targeting the STAT-3 pathway.

Balance of excessive phosphorylation of STAT-3 is kept under check by its negative regulator SOCS-1 and the same statement was proven by Natatsuka et al. when they observed that phosphorylation of STAT-3 were effectively increased in MKN-45 and AGS cells when treated with SOCS-1 inhibitor. Enforced expression of SOCS-1 was linked with increased expression of cleaved caspase-3, which increased the ratio of cells in the G2 and M phase in these GC cell lines [70]. Chan et al. in one of their study showed that down regulation of SOCS-1 was found in human hepatocellular carcinoma and multiple myeloma because of its promoter hypermethylation and one of their previous study also found that promoter region of SOCS-1 was hypermethylated in human gastric cancer cell line where methylation was detected in 5 of the 6 serum samples from gastric cancer patients and only 1 of the 6 serums samples from normal individuals had SOCS-1 methylation detected [71]. Yiping et al. illustrated that methylation of SOCS-1 is significantly linked with advanced tumor stage and lymph node metastasis in gastric carcinoma and suggested that SOCS-1 methylation can be a useful marker in detecting and evaluating the progression and development gastric cancer metastasis [72]. Guanghua et al. verified low SOCS-1 mRNA expression in 80 gastric cancer patients when compared with their clinic pathological features revealed their poor prognosis [73]. Neuwirt et al. demonstrated the altered expression of SOCS-1 and SOCS3 in head and neck cancer, gastric carcinoma, chronic myeloid leukemia, melanoma, and prostate cancer [74]. In order to investigate the significances of SOCS-1 dysfunction in JAK/STAT pathway, a group of researchers investigated the phosphorylation status of STAT-3 protein in AGS cells. Upon inactivation of SOCS-1 by methylation, STAT-3 was in hyperphosphorylated state. Reestablishing SOCS-1 expression by treatment of cells with demethylating agent, phosphorylation of STAT-3 was efficiently restored. However, obstructing the endogenous IL-6 by anti-IL-6 antibody can fractionally restrain STAT-3 activity. Besides, recombinant IL-6 restores STAT-3 phosphorylation in demethylated-AGS cell, which is suggestive of IL-6 to be responsible for STAT-3 activation. These results suggest that SOCS-1 to bevital for the down regulation of JAK/STAT signaling. Methylation leading to SOCS-1 inactivation enhances IL-6 mediated activation of STAT-3 in AGS cell. Continuing the same experiments on human gastric cancer samples showed SOCS-1 to be methylated and down regulated in 30% of primary tumor tissues and 10% of adjacent normal tissues. A noteworthy observation in the study was that SOCS-1 was hypermethylated in 10% of adjacent normal tissue and these findings imply that methylation of SOCS-1 may complicate the process of early gastric carcinogenesis [75].

Conclusion

The JAK/STAT pathway is very well known for its role in cellular proliferation. The abnormal functioning of JAK/STAT pathway can be because of its own fault or due to the faulty signals received from outside. Excessive stimulation by inflammation due to *H. pylori* switches on the JAK/STAT pathway in abnormal way. Exploring the main route of JAK/STAT action is necessary in order to track the pathway at different levels. In this review we have attempted to link the main components of inflammatory pathway leading to gastric cancer. Also we tried to locate the various steps where aggressiveness of this pathway can be targeted. It would be better to check for earlier *H. pylori* infections in order to stop inflammation. Controlling inflammatory cytokines mainly IL-6 levels can be next step from letting the inflammation to proceed inside the cell. After that hyper activation of JAK's and STAT's can be managed by using their perfect antagonists. Finally negative regulator of JAK/STAT pathway mainly SOCS-1 can be bought up in action by checking its genetic and epigenetic activity. Furthermore study is needed to find the accurate links and targets of the JAK/STAT pathway in order to stop the deadly disease from taking millions of lives every year.

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