REVIEW PAPER

Targeting JAK-STAT signal transduction pathways in human carcinomas

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Abstract

Cancer is the second most common cause of death in the United States and the leading cause of deaths worldwide and thus remains a global problem to the human population. Since the discovery of the JAK-STAT pathway over two decades ago, research investigations have clearly demonstrated that the JAK-STAT pathway plays a major role in many biological processes including proliferation, immunity, cellular activation, and differentiation to name just a few. While the JAK-STAT pathway is indispensable for normal cellular functions, it was also discovered that abnormal activation of the JAK-STAT signaling pathway significantly contributes to the formation and progression of many human carcinomas. By examining dysfunctional intracellular activation events researchers may identify specific molecular regulators of disease and develop interventions to prevent and treat particular diseases. JAK-STAT signaling mechanisms during pathogenesis and cancer development are continually being explored for potential therapeutic benefit. The following review explores novel molecular therapeutic strategies.

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Introduction

The JAK-STAT pathway was initially discovered over 20 years ago (Darnell et al., 1994). Since that time there have been many reviews and research articles regarding the nature of the canonical mechanisms of the JAK-STAT signaling pathway (Leonard and O'Shea, 1998; Kotenko and Pestka, 2000; Kisseleva et al., 2002; Flowers, 2012; Kaushal and Chorawala, 2012; Stark and Darnell, 2012). Briefly, the JAK-STAT pathway primarily contains two main components: Janus kinase proteins (JAK) and signal transducers and activators of transcription proteins (STAT). JAKs are tyrosine kinases containing two functional sites.

One functional site binds to the cytosolic domain on a specific cytokine receptor subunit. The other functional site on JAK molecules has catalytic activity (e.g., kinase activity). Four members of the JAK kinase family have been identified: JAK1, JAK2, JAK3, and Tyk-2. STAT proteins are transcription factors that bind to phosphorylated tyrosine cytokine receptors and upon nuclear localization mediate gene transcription by binding to the promoter regions of cytokine-specific genes. Seven members of the STAT transcription factor family have been identified: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Activation of the JAK-STAT signaling pathway proceeds following ligand (e.g. cytokine) binding with unique cytokine receptors. Binding of cytokine to cytokine receptor subunits result in cytokine receptor dimerization. Dimerization leads to reciprocal phosphorylation and subsequent activation of JAK proteins. Activated JAK proteins phosphorylate specific tyrosine residues on the receptor creating docking sites for STAT proteins.

STAT-receptor binding is mediated by STAT-specific SH2 domains. During a brief docking period STAT transcription factors are phosphorylated and activated by JAK proteins. Following JAK-mediated activation, STAT proteins form dimers and translocate to the nucleus where they promote gene transcription of important genes for a given cell type. Analysis using Ingenuity Pathways Analysis (IPA) software revealed genes that have been shown to interact with JAKs (Figure 1 [JAK - center]) and STAT molecules (Figure 2 [STAT - center]).

Recently, however, analysis of Drosophila melanogaster demonstrated a non-canonical method of JAK-STAT signaling that results in modifications to heterochromatin stability indicating that activation of the JAK-STAT pathway may also affect genes that are not under control of STAT proteins (Li, 2008).

The JAK-STAT signaling pathway has been shown over the past two decades to contribute to a variety of normal biologic processes such as cellular differentiation, angiogenesis, cell growth, innate and adaptive immunity, and apoptosis and therefore serves as an attractive target for chemotherapeutic interventions.

Human Carcinomas and the JAK-STAT Pathway

A carcinoma is a malignant tumor caused by multistage transformative biological processes involving mutated genes, altered proteins, overactive proteins, and oncogenic chemicals. Human carcinomas typically arise from both endodermal and ectodermal tissue. Carcinomas can form in many areas in the human body such as the brain, bladder, breast, cervix, colon, esophagus, liver, lungs, prostate, and stomach. Despite recent advances in early screening and therapeutic intervention, human carcinomas remain a leading cause of death of the human populace worldwide. Specifically, recent data from the American Cancer Society reveal that approximately 1.7 million new cancer cases are expected this year that will lead to approximately 600,000 deaths in the US alone (American Cancer Society, 2013). Based on the epidemiologic statistics above, there exist a critical need for the continued development and investigation of novel targeted molecular strategies for the treatment of human carcinomas. Discussions regarding early detection methods, cancer symptoms, and cancer-related risk factors are equally important issues, however, those issues are not the focus of this review.

Constitutively activated JAK-STAT signaling components have long been implicated to play a role in the progression and prognosis of cancer and its resistance to conventional treatments.
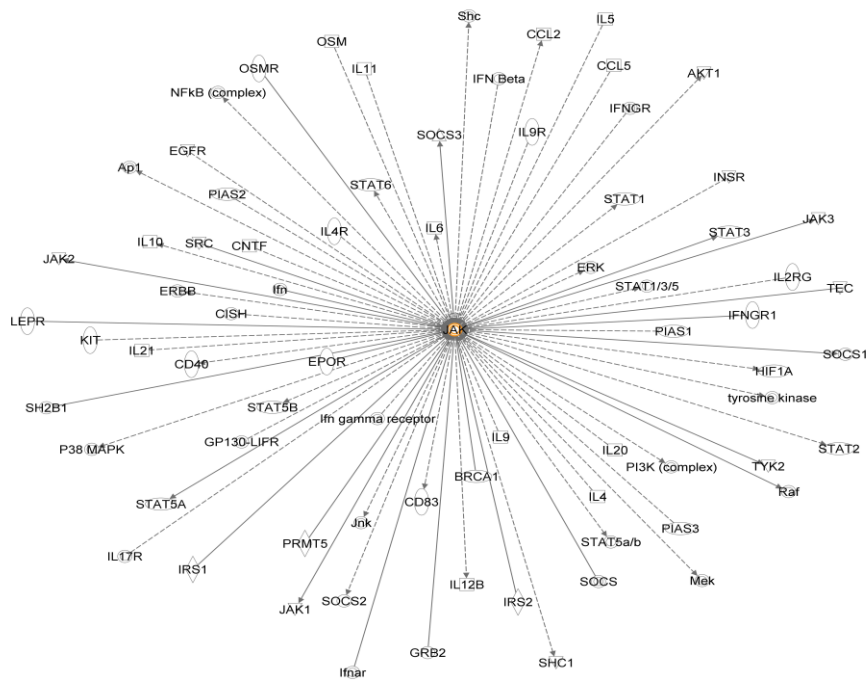
Fig. 1. Gene network for JAK generated using Ingenuity Pathway Analysis (IPA). Shapes denote different cellular molecules: cytokines (□), kinase (▽), phosphatase (△), peptidase (◇), transcription regulator (▭), transcription receptor (0), complex (◎), and other (○). Arrows correspond to the following relationships: acts on (A➜B), inhibits (A—IB), direct interaction (——), and indirect interaction (----).

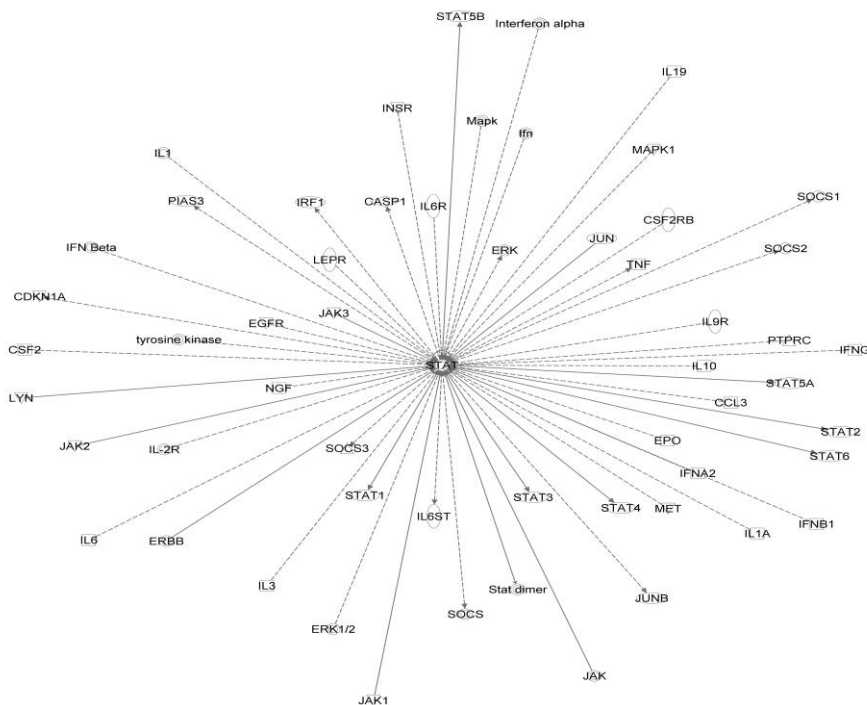**Fig. 2.** Gene network for STAT generated using Ingenuity Pathway Analysis (IPA). Shapes denote different cellular molecules: cytokines (□), kinase (▽), phosphatase (△), peptidase (◇), transcription regulator (▭), transcription receptor (0), complex (◎), and other (○). Arrows correspond to the following relationships: acts on (A➜B), inhibits (A—IB), reaction (A➜B), direct interaction (——), and indirect interaction (----).

The primary objective of this review article is to explore the role of the JAK-STAT pathway in the production of human cancers and to examine current literature that focuses on cancer therapeutic agents that target the JAK-STAT pathway. Previous research has provided insight into the effects of the inactivation of key molecules in the JAK-STAT pathway on cytokine signaling events (Leonard and O'Shea, 1998; Imada and Leonard, 2000). Specifically, inactivation or inhibition of JAK and STAT proteins produce cells and animals that are completely unresponsive to the cytokines that rely on these proteins for cellular activity (Darnell *et al.*, 1994; Leonard and O'Shea, 1998; Imada and Leonard, 2000). Early knockout mice studies involving members of the JAK and STAT protein families offered key insights into the function of these molecules and also elucidated interesting information regarding the relationship between JAK and STAT molecules in human disease. For example, based on early studies, JAK3 deficiency was implicated in the extremely fatal severe combined immunodeficiency (SCID) in human patients. SCIDs are diseases primarily observed in children. The most prevalent form of SCIDs is associated with the X chromosome and results in severe T cell deficiency and B cell abnormalities. Since T cells and B cells are fundamental to proper functioning of the immune system, individuals with SCIDs are susceptible to simple infections that would otherwise be eliminated by a healthy immune system (Aringer *et al.*, 1999). Additionally, hyperactivated JAK and STAT proteins have been implicated in cancer or inflammatory diseases (Darnell *et al.*, 1994; Darnell, 2002; You *et al.*, 2012).

Mutated JAK proteins have also been known to lead to an abnormal increase in the number of leukocytes in body tissues. Several forms of leukemias such as acute lymphoblastic leukemia, chronic myelogenous leukemia, and adult T-cell leukemia have been reported to arise in part due to unregulated JAK proteins (Verma *et al.*, 2003). Previous research has also demonstrated the involvement of JAK proteins in the activation of MAP kinases in B cells suggesting that JAK plays a pivotal role in important kinases in cell division (Kumar *et al.*, 1994). The significance of JAK proteins on cellular transformation was also shown by Sakia and coworkers (1997) who demonstrated that activation of JAK2 was sufficient to sustain B cell survival and mediate the induction of bcl-2, an integral membrane protein that negatively regulates proteins involved in apoptosis. Moreover, JAK kinase participation in the development of cancer usually involves chromosomal translocations of JAK kinase genes. These abnormal translocations produce constitutively activated JAK kinases that have very dramatic and malignant consequences in the human body. The best observed example of this phenomenon is the TEL-JAK2 fusion protein. Constitutively activated STAT proteins have also been implicated in a variety of human carcinomas including breast cancer and prostate cancer. Of the seven identified STAT molecules STAT3 and STAT5 have recently been implicated to be major players in the development of oncogenesis in a variety of hematopoietic and cancer cell lines (Dhir *et al.*, 2002; Spiekermann *et al.*, 2002; Verma *et al.*, 2003; Cotarla *et al.*, 2004). STAT3 has been shown by many investigators to promote cell proliferation and cell survival by regulating apoptosis or inducing cellular transformation. Earlier it was shown in experiments using electrophoretic mobility shift assays (Yu *et al.*, 1995) that there was increased STAT3 DNA-binding activity and constitutive tyrosine phosphorylation of STAT3 in fibroblasts transformed with v-src oncogene suggesting an association between STAT3 activation and v-src induced cellular transformation. Moreover, it has been shown by several investigators that elevated STAT3 expression is correlated with prostate cancer cell survival and reduction in cellular apoptotic signals. Antisense Stat3 nucleotides were used to inhibit the growth of human prostate cancer cell lines and reduce their level of STAT3 phosphorylation (Mora *et al.*, 2002). Recently, elevated protein levels of nuclear localized phosphorylated STAT5a were observed in primary breast adenocarcinomas (Cotarla *et al.*, 2004) using immunohistochemistry and immunoblotting analysis.

These experiments demonstrate the importance of constitutively activated STAT3 and STAT5a in cancer cell growth. These experiments also offer insights into potential molecular targets for anticancer therapeutics.

Targeted approach to cancer therapy

A new prevailing paradigm for cancer chemotherapy is aimed at specifically targeting cellular processes, signal transduction pathways, and mutated proteins that give rise to uncontrolled cell proliferation. The goal of the targeted therapeutic approach is to identify critical molecular components that lead to tumorigenesis and to design specific inhibitors to control their effects. There are a variety of targeted approaches designed to regulate specific tyrosine kinases associated with cancer and inflammatory disorders like arthritis. These involve receptor-specific antibodies, decoy receptors to bind and inactivate ligands, small molecules with specificity towards the ATP-binding sites, and small molecules that block kinase function by unknown mechanisms. Several novel anticancer drugs have been developed to treat cancer employing this targeted approach. Gleevec and Herceptin were among the first examples of drugs identified for the treatment of chronic myelogenous leukemia (Gleevec) and breast cancer (Herceptin). Chronic myelogenous leukemia is a form of cancer that affects white blood cells of the myeloid lineage. The increase in cell proliferation of myelogenous cells in the bone marrow, blood, and tissues give rise to the clinical effects associated with the disease. Chronic myelogenous leukemia is primarily caused by generation of a constitutively active tyrosine kinase known as Bcr-Abl. The genetic basis for the Bcr-Abl tyrosine kinase stems from the formation of the Philadelphia chromosome (present in 95% of CML patients). This mutated chromosome results from a translocation between human chromosomes 22 (Bcr) and 9 (Abl). The Bcr-Abl gene gives rise to the fusion of the Bcr protein and the Abl tyrosine kinase, resulting in constitutive activation of the kinase activity of Abl. The Bcr-Abl fusion tyrosine kinase thus promotes the unregulated cellular proliferation of certain white blood cells.

Gleevec binds to the ATP-binding site of Bcr-Abl and inhibits tyrosine kinase activity (Shawver *et al.*, 2002; May, 2003) resulting in dramatic control of chronic myelogenous leukemia (CML) and a rare form of stomach cancer where this Bcr-Abl oncogene is the determining factor for oncogenesis. Gleevec has also been demonstrated to inhibit lung cancer cell growth *in vitro.* Zhang (2003) demonstrated that Gleevec effectively inhibited cell proliferation in the human lung cancer cell line A549 in a dose dependent manner. The optimal concentration (IC50) of Gleevec was shown to be 2-3 µM.

Breast cancer is a major problem affecting women around the world. Although a specific cause for this type of carcinoma has not been identified, several factors have been purported to be consistent with the development of breast cancer such as genetic disposition, family history, and obesity (Key *et al.*, 2004). Metastatic forms of breast cancer cells often overexpress the epidermal growth factor receptor 2 (HER2, erb2) on their cell surface. HER2 is a receptor tyrosine kinase that when activated by growth factor binding relays cellular signals that lead to cellular proliferation. Overexpression of HER2 causes cells to be abnormally stimulated resulting in increased cell growth and tumuriogenesis. HER2-related cancers proliferate at a faster rate than cancer cells in which HER2 is found at normal levels (Baselga and Hammond, 2002). The classic and original demonstration of a monoclonal antibody that blocked tyrosine kinase function is Herceptin, which is a humanized monoclonal antibody specific for the HER2 receptor (Shawver *et al.*, 2002). Herceptin which is administered intravenously to patients binds to the extracellular binding domain of HER2 and prevents downstream growth-promoting signals. This discovery has resulted in the treatment of aggressive forms of breast cancer where the cancer cells overexpress HER2. It seems clear from the anticancer approaches described above that an understanding of the molecular basis of specific cancers may lead to the production of more powerful chemotherapeutic drugs to treat cancer.

Novel JAK inhibitors and STAT inhibitors

Chemotherapeutic agents in use today are both synthetic drugs, i.e., pharmacologic agents prepared in the laboratory or natural products isolated from plants, trees, minerals, or other natural products. One such natural product, Brevilin A, a compound derived from medicinal herbs, is a molecule that has been recently shown to exhibit a robust inhibition of STAT1 and STAT3 tyrosine phosphorylation and expression of STAT1 and STAT3 target genes (e.g., interferon regulatory factor 1) in human lung cancer cells (Chen *et al.*, 2013). Overexpression construct studies also demonstrated that Brevilin A may mediate STAT1 and STAT3 inhibition by binding to the JH1 domains (tyrosine kinase domain) of all four JAK family members (JAK1, JAK2, JAK3, and Tky2). The proclivity of Brevilin A to block the activation of all four JAK family members suggest that Brevilin A may also be capable of blocking the downstream activation events of many cytokines and growth factors. AZD1480 is an orally active pharmacologic compound and inhibits activation of both JAK1 and JAK2 via ATP-competitive inhibitory mechanisms (Yan *et al*., 2013).

AZD1480 was shown to reduce STAT3 activation and attenttuate tumor growth in neuroblastoma and pediatric sarcomas (rhabdomyosarcoma and the Ewing sarcoma family tumors) *in vitro* and *in vivo*. Functional biologic experiments employed to evaluate intracellular and extracellular activity revealed that AZD1480 precipitated tumor growth inhibition and caspase-dependent apoptosis as well as inhibition of STAT3 target genes including cyclin D1 and CDC25A. Cyclin D1 was previously shown to be a key factor in controlling cellular growth of prostate cancer cell lines DU145 and LNCap (Flowers *et al*., 2005). Interestingly, AZD1480 was also shown to decrease TIMP-1 (tissue inhibitors of metalloproteinases), a gene that plays a role in metastatic potential of tumor cells.

Ashizawa and associates (2013) recently provided critical insight into a small molecular STAT3 inhibitor, STX-0119. STX-0119 exerts its inhibitory action by blocking STAT dimerization, a critical step during JAK-STAT signaling mechanisms.

STX-0119 was extremely effective in inhibiting the growth of glioblastoma multiforme stem-like cell (GBM-SC) lines. Additionally, following treatment with STX-0119, GBM stem cell lines showed a decrease in cell cycle genes and an increase in apoptotic genes mediated by activated STAT transcription factors. Evodiamine, a chemical plant extract, was recently shown to exert antitumor activity on hepatocellular carcinoma cells (HCC). Evodiamine, like many other chemotherapeutic tumor suppressors, specifically targets STAT3.

Numerous research studies have linked STAT3 to a variety of properties that promote tumor development and progression including angiogenesis, unregulated tissue growth, immunosuppressive signaling pathways, and induction of immunosuppressive cytokines, for example IL-10 (Kawakami *et al.,* 2013).

In one report evodiamine abolished constitutive and IL-6-induced activation of STAT3 via a JAK2-dependent mechanism. In this same study it was shown that evodiamine-specific antitumor effects on HCC cells were also dependent on SHP-1, a SH2-containing phosphatase. Confirmation of a phosphatase dependent anticancer mechanism was demonstrated when investigators treated HCC cells with the protein tyrosine phosphatase inhibitor, sodium pervanadate. Treatment of carcinoma cells with sodium pervanadate blocked STAT3 activation induced via IL-6 signaling. Studies involving short interfering RNA (siRNA) that specifically targeted SHP-1 gene expression demonstrated the important role SHP-1 plays in mediating evodiamine-specific suppression of HCC cells (Yang, 2013). OPB-31121, another novel therapeutic molecule, exhibits similar characteristics as the SOCS-1 mimetic, TKIP (tyrosine kinase inhibitor peptide) that has been previously described by the author and associates (Flowers *et al*., 2004). Like TKIP, OPB-31121, successfully inhibited JAK2 phosphorylation leading to inactivated STAT

molecules and a subsequent reduction in gastric cancer cell proliferation (Kim *et al.*, 2013).

The induction of apoptosis following OPB-31121 treatment indicates that OPB-31121 mediates up-regulation of essential apoptotic genes and down-regulation of antiapoptotic proteins. Studies involving AG490, a small molecule that inhibits JAK2, further substantiate the functional role of STAT3 in laryngeal carcinoma cells. In their study, Zhang and others (2010) treated the human laryngeal cancer cell line Hep-2 with AG490 and observed a significant reduction in laryngeal carcinoma cell proliferation due to cell cycle arrest and apoptosis as measured by flow cytometry. Immunoblotting experiments also demonstrated a decrease in STAT3 phosphorylation in Hep-2 cells as a result of AG490 treatment. Experimental evidence provided by many investigators over the last ten years regarding molecular inhibitory agents renews the optimism for the beneficial therapeutic outcomes and the continued focus to develop novel pharmacologic JAK and STAT signaling inhibitors. Indeed, targeted molecular therapies represent an extremely promising future in the treatment of a wide variety of cancers, especially cancers with a high mortality rate.

Conclusion

The future of targeted cancer therapies lies in the exciting field of individualized or personalized medicine (Schweiger *et al.* 2013). The fundamental premise behind individualized medicine is the understanding that multifactorial, multistep diseases such as cancer arise and progress via unique processes that differ for each patient. Moreover, since oncogenes behave in a unique manner in cancer patients it is equally likely that there must also be unique or personalized therapies to treat specific patients. Personalized medicine strategies seek to employ genomic and epigenomic experimental methods in order to determine a patient's precise genetic information (e.g., gene expression patterns), genetic variation, and potential genetic risk factors; this type of molecular understanding leads to customization of a particular treatment strategy for that individual.

The exponentially expanding fields of genomics, proteomics, and genetic testing are providing new insight into disease transmission, development, and progression as it relates to individual patients. To that end, new technologies such as single nucleotide polymorphisms, genome-wide association studies, DNA microarray technology, and tissue microarray technology coupled with the enormous insight that is currently being generated as a result of completion of the Human Genome Project have paved the way for the current state of individualized medicine as well as provided monumental insight into defective signal transduction pathways associated with disease and cancer genomics (Bubendorf, 2001; Nakagawa, 2013).

The sophisticated high-throughput genotyping technology to study genes and genetic variants and the impetus to utilize this beneficial technology for cancer research investigations is not entirely new to scientists and has been discussed previously (Anzick and Trent, 2002; Baselga and Hammond, 2002). Undoubtedly, the use of DNA microarrays and tissue microarrays, and genome-wide association studies will lead to enhanced diagnosis and precise cancer treatment options and thereby continue to revolutionize cancer biology research leading to significant decreases in mortality rates associated with human carcinomas.

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