

## Janus Kinase-Signal Transducer and Activator of Transcription in target therapy of cancer

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Manuscript received August 07, 2019; revised manuscript September 05, 2019

### Abstract

**Background:** Janus kinase-signal transducer and activator of transcription (JAK-STAT) is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine-mediated signals. In the beginning of 20th century, it was named “just another kinase” but by some reasons ultimately it was published as “Janus kinase”. The name Janus was taken from the two-faced Roman god of beginnings, endings and duality, because the Janus kinases (JAKs) possess two near-identical phosphate-transferring domains, one domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first one. The article describes JAK-STAT in many aspects such as general definition, mechanism of action, biochemical qualities and the relation to cancer. Eventually the article will explain the role of JAK-STAT pathway in carcinogenesis and summarize the article through future direction in clinical medicine and research.

**Conclusions:** Understanding JAK-STAT pathway can help physicians, medical students and teachers apply this into clinical practice. By discovering more about the JAK-STAT pathway, many cancer diseases could be halted or treated due to their connection to cancer therapy.

**Key words:** Janus Kinase-Signal Transducer and Activator of Transcription, cytoplasm receptors, mutation, cancer.

### Introduction

Janus kinases (JAKs) are a family of cytoplasmic receptors associated with protein tyrosine kinases required for cytokine signaling and signal transducer activators of transcription (STAT) are transcription factors which regulate some genes required for cellular proliferation, differentiation and survival. Aberrant activation of intracellular signaling of JAK-STAT pathways resulting from mutations is associated with many types of cancers. Targeting intracellular signaling pathways has been a productive strategy for drug development, with several drugs acting on signaling pathways already in use and more continually being developed. The STATs form dimers that translocate to the nucleus when phosphorylated on highly conserved tyrosine residues (termed pSTAT) by JAKs or other tyrosine kinases. The STAT dimers bind specific promoter sequences and modulate transcription of genes controlling cellular processes including proliferation, differentiation and apoptosis. In addition to the established role of the JAK-STAT signaling pathway, cytokine traditionally signals the noncoding ribonucleic acid (RNA) [1]. Understanding the crosstalk of non-coding RNA with JAK-STAT signaling in cancer is of critical importance and may result in better patient stratification not only in terms of prognosis but also in the context of therapy.

The JAK-STAT pathway is important in cytokine-mediated immune responses. Research in the JAK-STAT field has elucidated its roles in various cellular processes such as proliferation, apoptosis and migration, and has found frequent dysregulation of the JAK-STAT pathway in diverse types of cancer. A similar interaction occurs in human cells, where

unphosphorylated STAT5A interacts with heterochromatin protein 1 $\alpha$  (HP) and acts as a tumor suppressor. Nuclear JAK2 however, functions as a histone tyrosine kinase, displacing HP1 $\alpha$  from chromatin. These data have important implications for human cancer: They suggest new drug therapies, which could target the not canonical functions of JAK and STAT [2, 3].

The (JAK-STAT) pathway plays a major role in transferring of signals from cell-membrane receptors to the nucleus. The JAKs are now recognized as an integral component of the cytokine receptor subunits, and enzyme activation, as the initiating step in a signaling cascade required for embryonic development, tissue growth, haemopoietic development and differentiation, innate and adaptive immunity and the inflammatory response. There is a reciprocal interaction between external actions and internal reactions that enables a cell to live. Each receptor like a sentinel senses stimulus and starts to transfer corps of signals to the 3d castle of the nucleus in order to provoke vital responses. The result of this process may be proliferation, differentiation (polarization), activation/inhibition and survival/apoptosis [4]. The role of JAK-STAT signalling in the pathogenesis, prognosis and treatment of solid tumours is divided into many aspects. The JAK-STAT pathway regulates embryonic development and is involved in the control of processes such as stem cell maintenance, haematopoiesis and the inflammatory response. The pathway transduces signals from cytokines, interleukins and growth factors that act through a number of transmembrane receptor families. Type I receptors include the erythropoietin receptor and the granulocyte colony-stimulating factor receptor. The granulocyte-

macrophage colony-stimulating factor receptor is a type IIa receptor and the type IIb subfamily includes the receptors for interleukin-6 and leukaemia inhibitory factor. The intracellular tails of these receptors are constitutively associated with inactive kinases named Janus kinases. While cellular overexpression studies suggested JAKs could signal promiscuously downstream of many cytokine receptors, it is evident from genetic deletion studies that cytokine receptors have clear preferences for the JAK family members which they utilize as signaling effectors. In light of this fact, here we have focused our attention on the genetic deletion studies that have illuminated which JAKs couple with which cytokine receptors. The first insights into the specificity of JAKs within each signaling pathway arose from early cell-based genetic screens to identify components of the IFN $\alpha$ / $\beta$  and IFN $\gamma$  signaling pathways [5, 6, 7].

The JAK-STAT pathway has been known for many years as a key pathway for the vitality functions of many cells in our body both in the blood system and even in the respiratory system or reproductive system. The role of JAK-STAT has been increasingly growing over the past year while more researches were published. In this article are considered many important studies that were conducted in the recent years. We will try to explain the mechanism of this apparatus, and what happens if the apparatus fails and leads to dysregulation of some cells. It is exclusively important to explain what medicines are found today on the pharmaceutical markets, their significance in different types of cancer and their function on the JAK-STAT pathway [8].

### The role of the JAK-STAT pathway in carcinogenesis

The JAK-STAT pathway plays a major role in transferring of signals from cell-membrane receptors to the nucleus. Cancer involves abnormal and uncontrollable cell growth in a part of the body. Therefore, since JAK-STAT signaling can allow the transcription of genes involved in cell division, one potential effect of excessive JAK-STAT signaling is cancer formation. High levels of STAT activation have been associated with cancer; in particular, high amounts of STAT3 and STAT5 activation are mostly linked to more dangerous tumors [9, 10]. For example, too much STAT3 activity has been associated with increasing the likelihood of melanoma (skin cancer) returning after treatment and abnormally high levels of STAT5 activity have been linked to a greater probability of patient's death from prostate cancer [11, 12]. Altered JAK-STAT signaling can also be involved in developing breast cancer. JAK-STAT signaling in mammary glands (located within breasts) can promote cell division and reduce cell apoptosis during pregnancy and puberty, and therefore if excessively activated, cancer can form. High STAT3 activity plays a major role in this process, as it can allow the transcription of genes such as B-cell lymphoma 2 and c-Myc Oncogene, which are involved in cell division.

Mutations in JAK2 can lead to leukemia and lymphoma [13]. Specifically, mutations in exons 12, 13, 14 and 15 of the JAK2 gene are supposed to be a risk factor in develop-

ing lymphoma or leukemia. Additionally, mutated STAT3 and STAT5 can increase JAK-STAT signaling in natural killer and T cells, which promotes very high proliferation of these cells, and increases the likelihood for developing leukemia [14, 15, 16]. Also, a JAK-STAT signaling pathway mediated by erythropoietin, which usually allows the development of red blood cells, may be altered in patients with leukemia. Early evidence that JAK-STAT signaling is activated in solid tumors was derived from cancer cell lines [16, 17]. There is now substantial data demonstrating tyrosine phosphorylation and nuclear localization of STATs, indicative of STAT activation, in tumor tissue derived from many patients across a range of tumor types. A relationship between JAK-STAT activation and prognosis has been observed in many of these tumor types. In general, activation of STAT3 or STAT5 is associated with a worse prognosis, although in breast cancer and in some studies of colorectal cancer and head and neck squamous cell carcinoma it appears to be associated with more favorable outcomes. In breast cancer, this relationship is consistent with the role of pSTAT5 in normal physiology – constitutive phosphorylation of STAT5 is a feature of normal breast epithelial cells, where it is thought to promote differentiation [18, 19, 20].

For other tumor types, differences in the strategies are used to quantify STAT phosphorylation, which vary across all the studies described below, may account for the apparently conflicting associations between STAT phosphorylation and outcome. Interestingly, there is some evidence that in Myeloproliferative Neoplasms STAT3 may oppose malignant proliferation, suggesting this may also occur in certain situations in solid tumors. Activation of STAT1, in contrast, is generally associated with better outcomes across all tumor types (tab. 1) [21-28].

In conclusion, the table 1 shows different types of cancer in human body which relates to the STAT activation. By understanding the source of the problem and using immunohistochemistry, we can pinpoint the mechanism that elicits those cancers. As the clinical medicine will use those methods for cancer detection, it will be easier to prevent, treat and halt many malignant diseases.

In some research papers [29, 30, 31], we found that STAT5A/B is an important immunohistochemical marker for prostate cancer as in other research studies [21, 22, 23] were found identical findings for the assesment of the progression of prostate cancer by simple immunohistochemistry. While understanding this phenomena, we can assess this marker in specific people and direct it for patient's management such as prostatectomy. In those researches was also found association with this STAT activation and the risk for developing non-small lung cancer.

In addition, the presence of pSTAT3 in immunohistochemistry examination was associated with the decrease in overall survival in patients with prostate cancer [32]. After getting to know this mechanism of cancer some researches work on therapy. In 2013 a research about JAK-STAT blockage did not succeed in proving that Siltuximab (JAK-

Table 1

## Types of cancers associated with the JAK-STAT pathway

Cancer type	STAT activation, tissue sample	Clinical implications of STAT activation
Non-small cell lung cancer	STAT3 and pSTAT3 detection with immunohistochemistry	Positivity for STAT3 or pSTAT3 associated with reduced overall survival
Prostate	Nuclear STAT5A/B, immunohistochemistry on tissue microarrays from prostatectomy	Presence of nuclear STAT5 associated with early recurrence. Presence of nuclear STAT5 associated with prostate cancer-specific death
Breast	Immunohistochemistry for pSTAT3 on tissue microarrays  Immunohistochemistry and immunofluorescence for nuclear pSTAT5 on tissue microarrays	Presence of pSTAT3 associated with improved overall survival in patients receiving adjuvant chemotherapy (10-year survival 79% for pSTAT3 positive, vs 61.5% for pSTAT3 negative). Absence of activated STAT5 associated with decreased cancer-specific survival
Rectal/colorectal	Immunohistochemistry for nuclear pSTAT3	Presence of activated STAT3 associated with better overall survival. Presence of activated STAT3 associated with worse overall survival
Oral squamous cell carcinoma	Immunohistochemistry for nuclear pSTAT3. Automated quantitative analysis immunohistochemistry for nuclear STAT3	Nuclear pSTAT3 associated with shorter median disease-free survival (13 months vs 64 months). High nuclear STAT3 associated with improved overall survival (Mean 119 months vs 57.3 months)
Cervical squamous cell carcinoma	Immunohistochemistry for nuclear pSTAT3	Nuclear pSTAT3 associated with reduced overall survival (5-year survival 79.2 months vs 95.3 months)
Malignant melanoma	Immunohistochemistry for pSTAT1 and pSTAT3	In patients with lymph node metastases, higher rates of recurrence with high pSTAT3. Lower rates of recurrence with high pSTAT1 staining in lymph node and brain metastases
Renal cell carcinoma	Immunohistochemistry for nuclear pSTAT3	Nuclear pSTAT3 associated with shortened cancer-specific survival
Glioblastoma	Immunohistochemistry for pSTAT3 on tissue microarrays	High or very high number of cells positive for pSTAT3 associated with reduced overall survival

STAT inhibitor) can halt prostate disease. Another research in 2012, found out that interleukin-6 antibody, was able to halt several types of cancer such as multiple myeloma, non-small cell lung cancer, colorectal cancer, renal cell carcinoma and prostate cancer [33].

Patients with oral squamous cell carcinoma pSTAT3 positive with special immunohistochemistry detection which is called automated quantitative analysis, had shorter disease-free survival in comparison with other patients (13 months vs 64 months) [34, 35]. But high nuclear STAT3 was surprisingly associated with improved overall survival (mean 119 months vs 57.3 months) in patients with oral squamous cell carcinoma.

Cervical squamous cell carcinoma has similar perspective with oral squamous cell carcinoma, while using immunohistochemistry for nuclear pSTAT3 associated with reduced overall survival (5-year survival 79.2 months vs 95.3 months) [34, 35].

The role of JAK-STAT signaling in the pathogenesis, prognosis and treatment of solid tumours that was described above on several types of cancer is supposed to be fascinating phenomena in biochemistry and oncology.

Finally, the prospects for treating solid tumours are analyzed using strategies targeting JAK-STAT signalling, including what can be learned from haematological malignancies and the extent to which results in solid tumours might be expected to differ [36, 37, 38].

## Conclusions

1. According to recent studies JAK-STAT pathway has a significant role in the control of immunity, cell proliferation and apoptosis.
2. Many studies showed that defects which activate JAK-STAT pathway can lead to different types of cancer. Finding defected components of this pathway can help to understand the mechanism of tumor genesis.
3. Finding defected components of this pathway can help us diagnose various cancer diseases.
4. Also, we can use these defected proteins as a target to inhibit the progression of the disease and produce new drugs.
5. After many researches, we still must continue to learn more about different components of the JAK-STAT apparatus.
6. Cancer progression might be in the future less accelerated after discovering more about JAK-STAT.

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