REVIEW ARTICLE

Jak 2 and Stat Proteins; a Mini Review

Qamar K.[1] and Saboor M.[2]
[1]*Department of Haematology, University of Health Sciences Lahore.*
[2]*Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Jazan University, Jazan*

ABSTRACT
JAK-STAT pathway transduces a multitude of signals for many cellular activities like hemopoiesis, lactation, fertility and development of immature embryo, immunity & mammary gland, etc. Jaks are cytoplasmic tyrosine kinases. There are several types of cytokines and growth factors which activates Jak tyrosine kinases. Jak activation depends upon ligand induced receptor multimerization. Alteration in JAK-STAT pathway confers hematological as well as non-hematological malignancies. The most common hematological malignancy is the myeloproliferative neoplasms (i.e chronic myeloid leukemia, polycythemia vera, essential thrombocythemia and primary myelofibrosis) in which abnormal stimulation of JAK-STAT pathway occurs. Therefore, this review not only presents the Anatomy, Physiology and Pathological effects of Jak 2 and STAT proteins but also deliberately assesses JAK-STAT signaling role in normal cellular events and in hematological neoplasms.

Keywords: Jak 2, STAT pathway, tyrosine kinase.

INTRODUCTION

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) is the most significant intracellular cascade pathway. It transduces a multitude of signals for many cellular activities like hemopoiesis, lactation, fertility and development of immature embryo, immunity & mammary gland etc.[1,2,3]

Structure and Functions of Jak

Janus is a Latin word. Jak gene has two domains i.e. JH1 and JH2 that resembles the two faces of the Roman God "Janus" from which their name is derivated.[3] Jaks are cytoplasmic tyrosine kinases. These kinases are capable of binding with a certain type of cell surface receptors that in turn cause transfer of extracellular signals to the nucleus which automatically stimulate or inactivate transcription of the target genes.[2,3]

There are four cytoplasmic tyrosine kinases which are Jak 1, Jak 2, Jak 3 and TYK 2. There are several types of cytokines and growth factors that activates Jak tyrosine kinases e.g. erythropoietin, thrombopoietin, granulocyte–monocyte colony stimulating factor, interleukins, interferon, etc. Jak activation depends upon ligand induced receptor multimerization.[2-5] When a ligand binds with its receptor, two Jak molecules come into close vicinity. This binding leads to the dimerization of the surface receptor subunit. Upon activation, tyrosine kinases auto-phosphorylate or trans-phosphorylate cytoplasmic domains of receptor complex. These activated Jak receptor complexes subsequently phosphorylate cytoplasmic transcriptional factors such as STATs, PI3k etc. Consequence of phosphorylation of STAT proteins is in the form of dimerization. Eventually STAT dimer enters in nucleus and attack with the DNA molecule on promoter region. As a result, translation of specific sequence leads to the for-mation or activation of specific proteins as shown in figure 1.[1,4,5,6]

Each Jak molecule comprises of seven defined homology regions known as Janus homology domains (JH) 1 to 7. N-terminal (JH 7) of Jak molecule has a receptor binding site while C-terminal (JH 1) is responsible for catalytic activity.[1,3] These regions have four functional domains, which includes a FERM (band 4.1, ezrin, radixin, moesin), an SH2 (Src homology 2) like domain, a tyrosine kinase and kinase-like pseudokinase domain.[4,6-8]

JH 5 to JH 7 (along with part of JH 4) regions encompass FERM domain. It is responsible for the regulation of catalytic activity and also brings about an association with cytokine receptor. SH2 domain constitutes the JH 3 and part of JH 4 regions as shown in figure 2.[4,6,7,9] Although the exact function of SH2 domain is not clear, some studies suggest that it acts as scaffolds. JH 1 domain has tyrosine kinase activity so it is called as kinase domain. JH 2 domain has a considerable structural similarity with JH 1, but it does not have enzymatic activity. This is the reason naming the JH 2 as pseudokinase domain.[4] Among all Jaks, Jak 2 shows an important role in stem cell production and hematopoiesis. By contrast Jak1 and Jak3 are helpful in the regulation of lymphopoiesis.[1,6]

Corresponding Author: Khansa Qamar, Lecturer, Department of Haematology
University of Health Sciences Lahore. Mobile # 03343125778

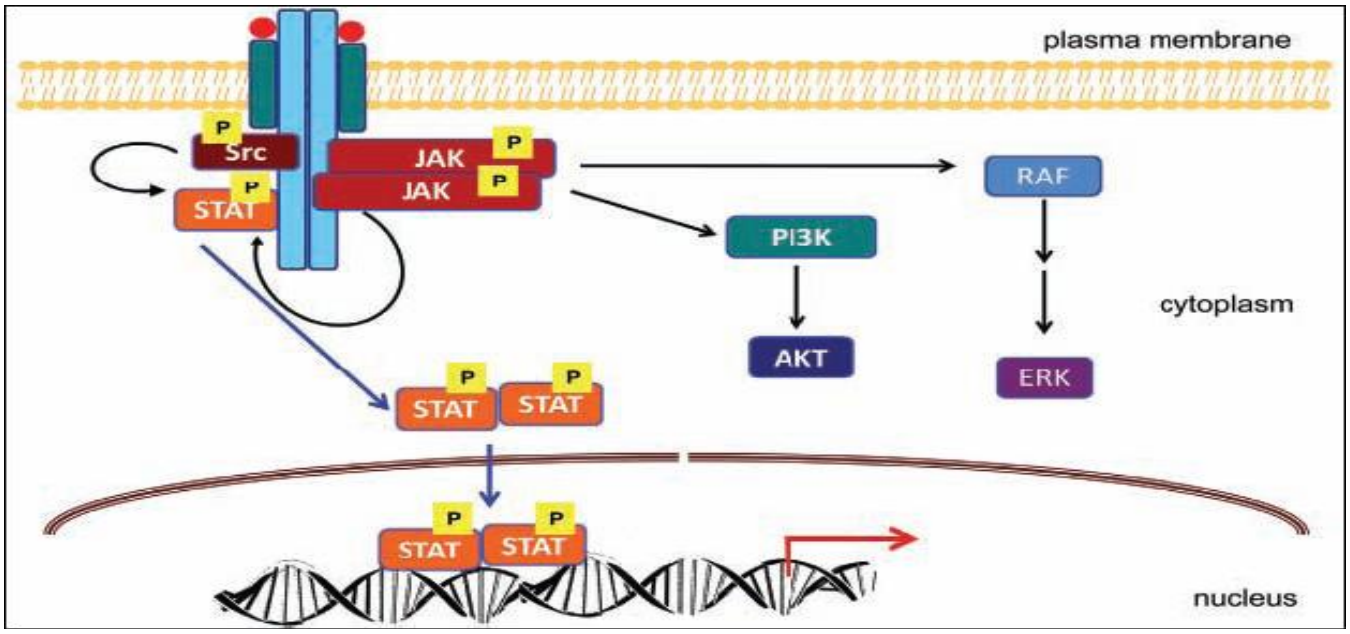

Fig. 1: *Jak-STAT Signaling pathways facilitated by JAKs. Ligand binding to cytokine receptor induces receptor dimerization. JAKs, subjected to transphosphorylation and eventually phosphorylate STAT proteins. The activated STATs dimer enterinto the nucleus, where they trigger the promotergene. As a result, translation of specific sequence leads to the formation or activation of specific proteins. Adapted from Jatiani et al.*[4]

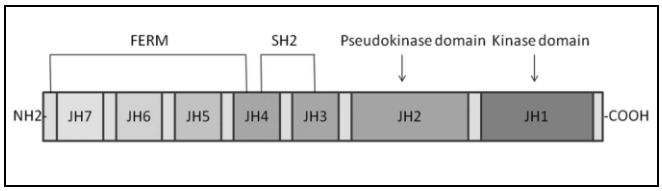

Fig. 2: *Structure of Janus kinases (JAKs). JAKs contain 4 functional domains i.ea FERM, an SH2, a pseudo-tyrosine kinase and a catalytically active tyrosine kinase domain. Adopted from Wang et al.*[9]

STAT proteins

STATs are cytoplasmic transcriptional factors that play a part in gene expression. There are seven different types of STAT (STAT 1, 2, 3, 4, 5a, 5b and 6) proteins. They are primarily activated via membrane receptor complex that are linked with Jak tyrosine kinases. Once STAT protein reaches to the nucleus, it binds with DNA recognition motif (GAS) in the promoter region and starts to activate translation of a specified sequence that helps in regulation of the gene expression.[1,3,6]

STAT proteins can be dephosphorylated by a number of negative regulators such as nuclear phosphatases. Subsequently, these inactivated STAT proteins transported out of the nucleus by anexporter (Ran GTP complex). To control the Jak-STAT pathway activation, three main negative feedback mechanisms have been proposed. These include suppressor of cytokine signaling (SOCS), protein tyrosine phosphatases (PTPs) and protein inhibitors of activated STATs (PIAS).[1] Simplest of all these mechanisms is tyrosine phosphatases. These proteins can attch to phosphorylated receptors, Jaks or STAT proteins to deactivate signaling molecules. SOCS proteins directly adhere to Jak or receptor complex to suppress the Jak kinase activity. PIAS proteins attach to phosphorylated STAT dimers and blocks the DNA binding as shown in figure 3. There are some other mechanisms which inclued in the regulation of Jak-STAT pathway like endosomal degradation of Jak-receptor complex etc[1,2,6,10]

METHODS

Literature related to Jak-Stat pathway is available on Pubmed and Google scholar.

We included those studies that focus on regulation and mutations of Jak-Stat pathway especially Jak 2 mutation in hematological neoplasms, all the studies focusing at Jak 2 mutation related to non hematological malignancies were excluded.

RESULTS

A huge number of research data related to Jak-Stat pathway regulation and mutations found since 2000 to uptill now. After title and abstract screening, we found that a certain number of literature is present on Jak 2 mutation in hematological neoplasms it present.

DISCUSSION

Role of Jak and STAT proteins with hematological neoplasms, alteration in Jak-Stat pathway confers the hematological as well as non hematological malignan-

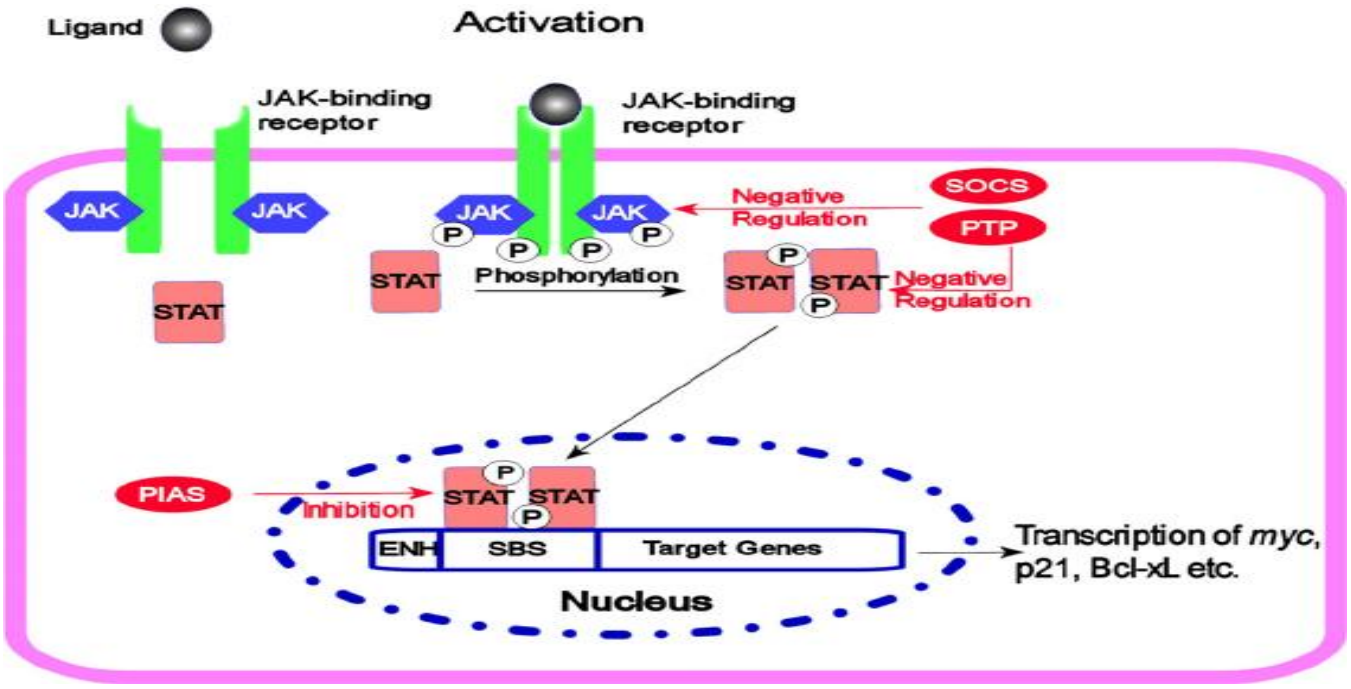

Fig. 3: *In Jak-STAT signaling pathway negative regulation is carried out by PTP, SOCS and PIAS proteins. Adopted from Furqan et al.*[1]

cies.[3] The most common hematological malignancies include the myeloproliferative neoplasms (i.e. chronic myeloid leukemia, polycythemia vera, essential thrombocythemia and primary myelofibrosis) in which abnormal activation of Jak-Stat pathway is seen. These hematological diseases are clonal defect of multipotent hemopoietic stem cell. Until 2005, genetic cause of these hematological diseases was not clear.In the year 2005, a single point mutation (JAK2V617F) in the cytoplasmic tyrosine kinase JAK2 gene was proposed by several researchers in most of patients with PV, ET and PMF.[4,6,10] Jak 2 gene is situated on chromosome 9p.[24] This gene has 25 exons that produce a protein of about 1132 amino acids.[10,11] Jak 2 V617F is a somatic point mutation (G to T) at position 1849 in exon 14 of Jak 2 locus. This mutation causes the substitution of a valineto phenylalanine at position 617 in pseudokinase JH 2 domain. As a result, it directly activates Jak-STAT pathway and causes cytokine independent proliferation of multipotent hemopoietic progenitor uncontrolled cell growth.[4,10]

All triggering factors such as point mutations, deletions and/or insertions in Jak2 gene result in myeloproliferative neoplasms that can further progress into leukemias and myelodysplastic syndromes. V617F mutation arises in 95% of polycythemia vera, 50-60% of essential thrombocythemia and 30-50% of primary myelofibrosis patients.[4,10,12] Majority of PV patients (95%) show V617F mutation while the remaining cases (5%) of PV exhibits Jak2 gene exon 12 mutation.[10] Other mutations in the Jak2 gene such as exon 13 and 15 also exhibits the same disease symptoms.[4,12]

Mutation in Jak2 gene showed frame shift, missense and point mutations. Jak2 exon 14 has H606Q, H608Y, V617I, and C618R. Jak2 exon 12 lesions comprises K539L, F537-K539 delinsL, N542-E543del, I540-E543delinsKK, V536-F547 dup, T514M, N533Y, H538Q, F547L and L545V.[4,10,12]

Mutations in Jak2 exon 13 contain F557L, R564L, R564Q, V567A, G571S, G571R, L579F, H587N and S591L. Jak2 exon 15 mutation includes I645V and L624P.[4,12]

Jak2 mutation is commonly seen in Philadelphia negative myeloproliferative neoplasms. For many years, it was presumed that Jak2 mutation and BCR-ABL translocation were mutually not present. Though, recently few cases of CML (Philadelphia positive) patients have been reported in which concomitant Jak2 V617F mutation is seen.[13,14] Carranza C *et al.*, Nadali F *et al.*, Hassan A *et al.*, Krämer A et *al.* and few other studies described the co-exsitance of both BCR-ABL translocation and Jak2 mutation in the same patient. In these studies, patients were initially diagnosed as BCR-ABL positive with chronic myeloid leukemia. Later on, Jak2 mutation developed after treatment with tyrosine kinase inhibitor (Imatinib).[13-16] Literature is still debating on the possibility of both mutations on a single clone.

Mechanism of co-existance of two diseases in same patients is still unclear. Researchers are unanswerable to this question that how the same mutation can cause 3 different phenotypical diseases?[10] They have propo-

sed the hypothesis to explain the process of the disease in myeloproliferative neoplasms. One of the most common hypothesized models is the dose response gene theory. The basic concept of the theory is based on allelic load. Many researchers have explained it with the mutant allele levels. High mutant allele level is seen in PV while low level in ET and PMF. Its mean that mutant allele load in hemopoietic stem cells leads to the patients homozygous or heterozygous state. Patients with ET and PMF show disease heterozygosity while PV shows homozygosity.[10,17]

CONFLICT OF INTEREST

The author declares no conflict of interest. She was fully responsible for all content and editorial decisions related to the development of the paper.

ACKNOWLEDGEMENT

We fully acknowledge the HEC, help to access the online data basis to extract paper and made us possible to write this review article.

Author's Contribution

KQ: Manuscript idea and writing. MS: Provided critical review and final approval.

Grant support & financial disclosures

None.

REFERENCES

1. Furqan M, Mukhi N, Lee B, Liu D. Dysregulation of JAK-STAT pathway in hematological malignancies and JAK inhibitors for clinical application. Biomark Res. 2013; 1 (1): 5. Doi: 10.1186/2050-7771-1-5.
2. Rawlings JS, Rosler KM, Harrison DA. The JAK/STAT signaling pathway. J Cell Sci. 2004; 117 (Pt8): 1281-3. Doi:10.1242/jcs.00963.
3. Thomas SJ, Snowden JA, Zeidler MP, Danson SJ. The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. BrJ Cancer, 2015; 113 (3): 365-71. Doi: 10.1038/bjc.2015.233.
4. Jatiani SS, Baker SJ, Silverman LR, Reddy EP. JAK/STAT pathways in cytokine signaling and myeloproliferative disorders approaches for targeted therapies. Genes cancer, 2010; 1 (10): 979-93. Doi: 10.1177/1947601910397187.
5. Quintás-Cardama A, Verstovsek S. Molecular pathways: Jak/STAT pathway: mutations, inhibitors, and resistance. Clin Cancer Res. 2013; 19 (8): 1933-40. Doi: 10.1158/1078-0432.CCR-12-0284.
6. Springuel L, Renauld JC, Knoops L. JAK kinase targeting in hematologic malignancies: a sinuous pathway from identification of genetic alterations towards clinical indications. Haematologica. 2015; 100 (10): 1240-53. Doi: 10.3324/haematol.2015.132142.
7. Silvennoinen O, Ungureanu D, Niranjan Y, Hammaren H, Bandaranayake R, Hubbard SR. New insights into the structure and function of the pseudokinase domain in JAK2. Biochem Soc Trans. 2013; 41 (4): 1002-7. Doi: 10.1042/BST20130005.
8. Salmoiraghi S, Guinea Montalvo ML, D'Agostini E, Amicarelli G, Minnucci G, Spinelli O, Rambaldi A. Mutations and chromosomal rearrangements of JAK2: not only a myeloid issue. Expert Rev Hematol. 2013; 6 (4):4 29-39. Doi: 10.1586/17474086.2013.826910.
9. Wang SW, Sun YM. The IL-6/JAK/STAT3 pathway: potential therapeutic strategies in treating colorectal cancer. Int J Oncol. 2014; 44 (4): 1032-40. Doi: 10.3892/ijo.2014.2259. Epub 2014 Jan15.
10. deFreitas RM, da Costa Maranduba CM. Myeloproliferative neoplasms and the JAK/STAT signaling pathway: an overview. Rev Bras Hemoter. 2015; 37 (5): 348-53. Doi: 10.1016/j.bjhh.2014.10.001.
11. Tefferi A, Pardanani A. Myeloproliferative neoplasms: a contemporary review. JAMA Oncol. 2015; 1 (1): 97-105. Doi: 10.1001/jamaoncol.2015.89.
12. Ma W, Kantarjian H, Zhang X, Yeh CH, Zhang ZJ, Verstovsek S, Albitar M. Mutation profile of JAK2 transcripts in patients with chronic myeloproliferativeneoplasias. J Mol Diagn. 2009; 11 (1): 49-53. Doi: 10.2353/jmoldx.2009.080114.
13. Carranza C, Tinti D, Herrera M, Rosales L, Villegas M, Silva G. Detection of JAK2 V617F mutation, secondary to the presence of BCR-ABL1 translocation in a patient with chronic myeloid leukemia: report of a case and review of the literature. Int J Genomic Med. 2014; 2 (1): 1-4. http://dx.doi.org/10.4172/2332-0672.1000116.
14. Nadali F, Ferdowsi S, Karimzadeh P, Chahardouli B, Einollahi N, Mousavi SA, Bahar B, Dargahi H, *et al.* JAK2-V617F Mutation and Philadelphia positive chronic myeloid leukemia. IJHOSCR. 2009; 3 (4): 43-5.
15. Hassan A, Dogara LG, Babadoko AA, Awwalu S, Mamman AI. Coexistence of JAK2 and BCR-ABL mutation in patient with myeloproliferative neoplasm. Niger Med J. 2015; 56 (1): 74-6. Doi: 10.4103/0300-1652.149177.
16. Hummel JM., Kletecka MCF, Sanks JK, Chiselite MD, Roulston D, Smith LB, et al. Concomitant BCR-ABL1 Translocation and JAK2V617F Mutation in Three Patients with Myeloproliferative Neoplasms. Diagn Mol Pathol. 2012; 21 (3): 176-83. Doi: 10.1097/PDM.0b013e318246975e.
17. Krämer A, Reiter A, Kruth J, Erben P, Hochhaus A, Müller M, Cross NC, Jones AV, *et al.* JAK2-V617F mutation in a patient with Philadelphia-chromosome-positive chronic myeloid leukaemia. Lancet Oncol. 2007; 8 (7): 658-60. PMID: 17613428. Doi: 10.1016/S1470-2045(07)70206-1.