Review Article

JAK/STAT Signalling Overdrive in Immune Regulation: A Trigger for Autoimmunity

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ABSTRACT

The JAK/STAT signaling cascade is a comprehensively articulated intracellular signaling network and is well-known to be associated with multiple cellular events like apoptosis, cell proliferation and immune regulation. The pathway is necessary for inflammatory responses and its dysregulation leads to multiple diseases. Autoimmune disorders are a vast group of disorders illustrated by abnormal immune response in the host. The body, when subjected to harmful stimuli will trigger the innate immunity, which leads to inflammation and the activation of adaptive immunity. The stability amidst pro-inflammatory and anti-inflammatory cytokines has a fundamental function in autoimmune diseases. In general, autoimmune diseases result as a consequence of genetic susceptibility and various environmental factors. The cascade is primarily governed by the cytokines and instigates an innate and adaptive immune response, thus evoking immune and inflammatory responses. In the current investigation, we converse the involvement of JAK/STAT in immune mediated diseases like rheumatoid arthritis, Inflammatory bowel disease and their inhibitors currently in use for these diseases.

Keywords: JAK/STAT cascade, autoimmune diseases, cytokines, immune response, JAK inhibitors.

INTRODUCTION

The Janus Kinase/ Signal transducer and activators of Transcription (JAK/STAT) cascade is recognised as a crucial cascade involved in homeostasis and development in mammals[1,2]. The cascade influences the cellular mediated immune response to interferons, cytokines by influencing the molecular interactions to begin the gene expression[3]. More than 50 growth factors and cytokines like interferons (IFNs), hormones, interleukins (ILs) are recognised by JAK/STAT[4].

The cascade is noted to have a pivotal purpose in cell proliferation, apoptosis, differentiation, haematopoiesis tissue repair inflammation, and adipogenesis and is particularly a chief component in managing inflammation and immune response[5,6]. It is a signaling pathway in which cytokines need 3 components that is a receptor, kinase and transcription factor to give out feedback. Individual cytokines adhere to their particular receptors present on the target cell surface. These specific receptors have intracellular sectors which are closely related to the JAK family of tyrosine kinases[7].

Mutation or defective JAK/STAT cascade or its components is connected to multiple diseases in humans. Therefore, targeting the cascade has a promising effect in the treatment of multiple diseases[8,9]. The cascade, conveys the external signals via a transmembrane protein, called Janus-Kinase. This, then moves the signals to an intracellular abode by phosphorylation of the transcription factors, that then moves into the nucleus to synchronize its transcription[10]. Components of the cascade are presented in Figure 1.
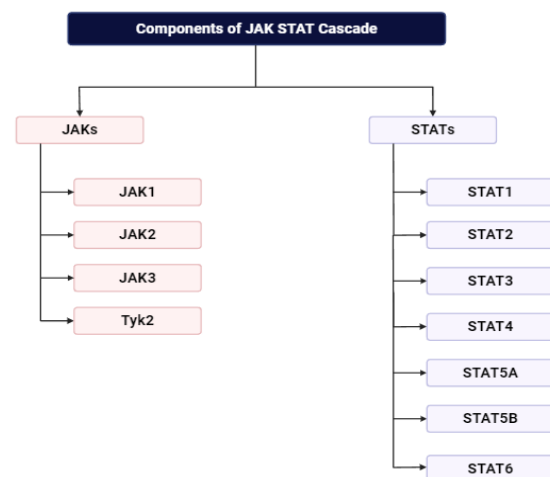

Figure 1: Components of JAK STAT cascade [11].

Regulation of JAK/STAT cascade

JAKs are inactive preceding the exposure to the cytokine, on adhesion of cytokine to its respective receptor induces their stimulation by transphosphorylation[12]. Once the JAKs are activated, they phosphorylate the receptors' intracellular tails on particular tyrosines, which successively acts as active sites for STAT transcription factors[13]. STATs that are receptor-confined are phosphorylated by JAK, that causes its detachment from the receptor and the movement into nucleus, which then directs the gene activation that respond to cytokines[14.] The phosphorylated STAT dimerizes with the other STAT family members with SH2 domains that are conserved. This dimer is then moved to the nucleus, where it adheres to its defined zone of the genetic material to stimulate or obstruct the transcription of target genes[15]. When the

ligand adheres to the receptor, 2 JAKs move closer and let the trans-phosphorylation of both the receptor and STATs with their reserved tyrosine residue which are present close to the C-terminal region occur. This phosphorylation is behind the dimerization of STATs, that stimulates the interactivity of the preserved sector known as the SH2 domain[16].

STAT is the transcription factor present in cell matrix. Phosphorylated STATs move into the nucleus via nuclear transport proteins called importin-α-5 and ran nuclear import. STAT dimers adhere to defined sequence for the initiation or suppression of target genes[17]. Abnormal initiation of this cascade leads to malignancies, genetically and metabolically altered cells[18]. Apart from regulating the biochemical processes, the cascade is involved in multiple malignancies and diseases. In case of solid malignancies, the abnormal initiation of the pathway results in the progression of benign tumours - hyperplasia to metastatic tumours – dysplasia[19]. STATs regulate the expression of multiple genes both positively and negatively[20]. The STATs and their target tissue regulate the genes they control, which then helps in the target gene identification[21]. Link amidst the adherence of specific cytokines with their respective receptor and thus following signal transduction is insisted by the receptor components. Namely, signaling in reply to adhering of IL-2,4,9,15 to type I receptor common γ chain (γc) is facilitated via JAK1 and 3 and brings about the phosphorylation and nuclear translocation of STAT5A and/or STAT5B - in response to IL-2, STAT6 - in response to IL-4[22,23].

And the signaling in reaction to adhering of IL-6,11, leukaemia inhibitory factor to the type I receptor common glycoprotein 130 chain occurs via JAK1, 2 and TYK2[24]. The IL10 and other components – IL-19,20, 22 and 26 adhere to type II cytokine receptors[25]. IL-12 and 23 common receptor chain (IL-12R) signals via JAK2 and TYK2[26]. The IL-12 acts via the initiation of STAT4 homodimers, and IL23, signals via STAT3 and STAT4[27]. Cytokine signaling through JAK/STAT is depicted in Figure 2.
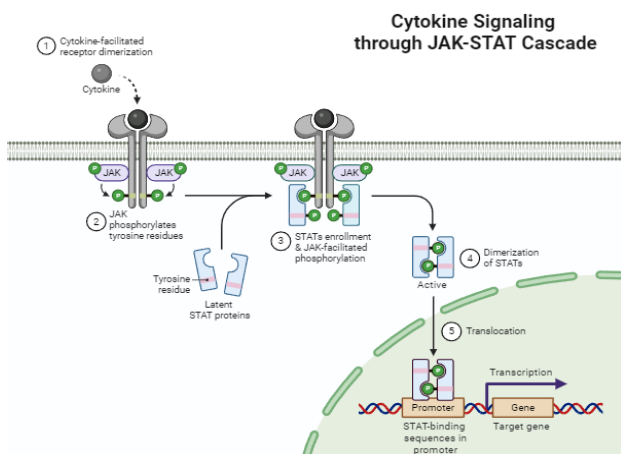

Figure 2: Regulation of JAK/STAT cascade: 1. Cytokines adhere to respective receptors, inducing receptor dimerization and activation of relevant JAKs. 2. JAK initiation results in tyrosine phosphorylation of the receptors. 3. STAT enrollment and JAK facilitated phosphorylation 4. Dimerization of STAT 5. Translocation occurs 6. STAT binds to promotor gene to bring about the response 7. This binding results in transcription of target gene

REPRESSION OF THE JAK/STAT CASCADE

SOCS Proteins

STATs drive transcription of target genes, specifically by inflammatory cytokines is harmful to both the organism and the cell. Hence it is firmly monitored by the SOCS family of proteins[28]. SOCS – Suppressor of Cytokine Signal is additionally called as STAT-induced STAT inhibitory proteins (SSI) whose activity is initiated by the activation of the pathway[29]. There are 8 components in the SOCS, namely - SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6, SOCS7 and cytokine-inducible SH2-containing protein (CIS). SOCS4-7 manages the growth factor receptor signaling, while SOCS1-3 and CIS carry out the negative feedback curve of cytokine signaling[30]. Each SOCS protein consists of 3 definite sectors – A distinct N-terminal adhering sector, a central preserved SH2 sector that is in charge of the specific target protein, and an extremely preserved C-terminal SOCS box sector that collaborates with the proteosome components[31]. SOCS manages the negative feedback mechanism of this network – the STAT dimers initiate the transcription of the SOCS genes, contrarily these SOCS genes adhere to the phosphorylated JAKs and the pathway shuts down[32]. The SOCS plays a detrimental role by adhering with the phosphating vehicle at the receptor – the SOCS cut the enrolment of signal transducer to the receptor or by adhering to the JAKs or by particularly hampering the tasks of JAKs[33].

Protein inhibitors of activated STAT (PIAS)

It is a member of c-IAPs (cellular inhibitor of apoptosis proteins) that monitor the regularity of cell death via out tissue repair, homeostasis and cell survival[34]. The PIAS includes: PIAS1, PIASxα, PIASxβ, PIAS3, and PIAS4 (PIASγ)[35]. Every component of the series includes - a serine/threonine rich realm situated at C-terminal, a preserved SAP domain, a Zn adhering finger-like section at the central position[36]. PIAS1 and 4 collaborate with STAT1 and PIAS3, PIASx collaborate with STAT3 and STAT4[37]. These proteins hamper STAT transcriptional activity via the following processes: Primarily, the PIAS inhibition is by PIAS initiated SUMOylation, or PIAS proteins first combine with STAT and dampen the STAT-DNA interactions, or by employing the transcriptional cofactors for STAT target genes[38].

CONNECTING THE DOTS: JAK/STAT PATHWAY IN AUTOIMMUNE DISEASES

Autoimmune Diseases

Immune tolerance is the insensitivity of the immune system to tissues in the body[39]. An Autoimmune disorder is a condition where the body's defence mechanism falters to identify between 'self' and 'foreign' molecules and

begins an attack on the self-molecules owing to decline of immunologic tolerance to autoimmunity[40]. These diseases can target basically any organ system and can affect individuals of any age group. Research has shown escalated prevalence of autoimmune disorders over the last few decades[41,42]. Common factors associated with the cause of autoimmune disorders are certain genetic factors like increased familial incidence, enhanced articulation of HLA Class II antigens on tissues involved in autoimmunity (especially can cause celiac disease), microbial factors like EBV infections and immunological aspects like polyclonal activation of B cells, generation of self-reacting B cell clones, failure of immune tolerance[43,44]. There are multiple autoimmune diseases that affect human beings, but they are mainly classified as systemic and organ-specific autoimmune diseases. Systemic (organic non-specific) autoimmune diseases mediated by antibodies and immune complex include systemic lupus erythematosus (SLE), Inflammatory myopathies, Wegner's granulomatosis and mediated by T cells include Rheumatoid arthritis (RA), systemic sclerosis. And organ specific autoimmune diseases mediated by antibodies and immune complex include Graves' disease, autoimmune haemolytic anaemia and those mediated by T cells include Type 1 diabetes mellitus and multiple sclerosis[45,46]. Types of autoimmune disorders are presented in Figure 3.
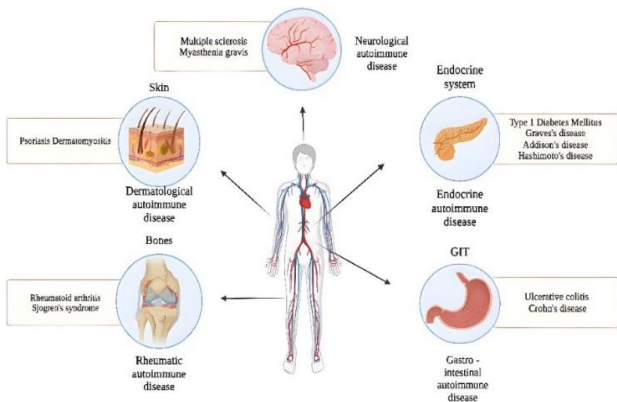

Figure 3: Types of Auto-Immune Diseases – Alteration in Immune Mediated response in the endocrine system, skin, Gastrointestinal Tract, Central Nervous System, and joints leads to Autoimmune Diseases.

The body when exposed to noxious extrinsic impulses, will activate the body's natural immune system and will provoke inflammation, after which adaptive immunity will kick in. Once the adaptive immunity is disoriented, it may contribute to autoimmune disorders. The stability between anti-inflammatory and pro-inflammatory cytokines is of high significance in AIDs, specifically IBD and RA which have constant inflammatory response in their advancement[47]. JAK/STAT signal transduction cascade is mostly monitored by cytokines and plays a pivotal role in activation of innate immunity, thus the acquired immune responses, and ultimately eliciting inflammatory and immune responses[48,49]. Alterations in JAK/STAT signaling cascade can result in multiple disorders, which are presented in Figure 4.
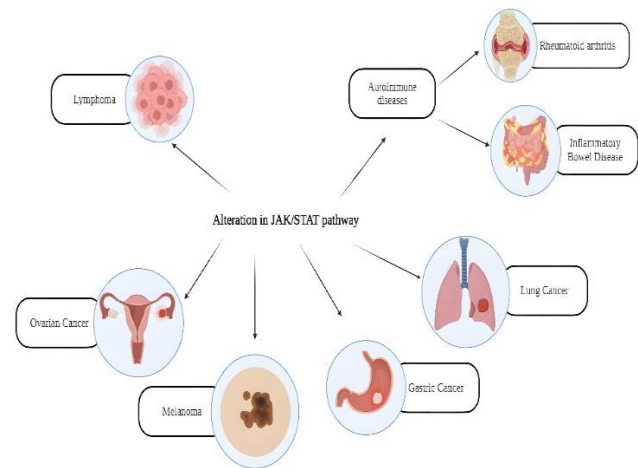

Figure 4: Alteration in JAK/STAT cascade results in Lymphoma, Ovarian Cancer, Melanoma, Gastric Cancer, Lung Malignancy and Immune mediated diseases.

THE JAK/STAT PATHWAY IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an immune mediated disease, that chiefly impacts the joints, depicted by systemic inflammation of the affected joints that is progressive in nature. This leads to cartilage loss, bone erosion and disability[50]. RA is illustrated as immune-mediated inflammatory disease, which involves abnormal humoral, innate and cellular immune responses[5,51]. Joint inflammation in RA is an outcome of immune instigation. The inflammation is marked from the movement of leucocytes to the synovial sac. The formation of synovitis is exhibited as agglomeration of natural and acquired immune cells. Natural immunity is activated by evoking dendritic cells (DCs) or by genetics. These cells then employ and trigger T cells which then activates B cells, synoviocytes, chondrocytes, osteoclasts, macrophages and produce pro-inflammatory and bone- destroying cytokines (IL-1β, IL-6, TNF -α)[52,53]. As a result, in the neighbouring bone marrow and synovial tissue, the amalgamation of both acquired and natural immune cascades encourages tissue injury[54].These flows of events promote chronic inflammation in the disease, and encourages the circulating leucocytes to move into the inflamed joint.

Multiple cytokines are involved in RA, like TNF- α, IL-1, and 6, have known to have a crucial function in the origin of RA and are associated with pain by autoimmunity initiation, and neighbouring tissue damage[55]. Granulocyte-macrophage colony–stimulating factor (GM-CSF) works via multiple signal transduction cascades, such as JAK2/STAT5 pathway, and then initiate the discharge of various other pro-inflammatory and chemokines[56]. IL-1b is a pro-inflammatory cytokine, which is elevated in RA. The elements of the IL- 1 clan are key promoters of pain and tenderness, leading to structural damage in arthritis[57]. IL-6 is the primary pro-inflammatory cytokine that mediates systemic inflammation in RA. Previous investigation reveals that IL-6 has a pivotal part in managing ache and soreness in the joints. IL-6 exerts its effects on pain by

adhering to the sIL-6R and signaling via gp130, that is indicated at multiple places in the nociceptive system, like dorsal root ganglion (DRG), neurons and glial cells[58]. Tumour Necrosis Factor alpha (TNF-α) is generated by the macrophages or the monocytes and are accountable for multiple events occurring within the cell, thus contributing to apoptosis or necrosis[59].TNF- α is structurally a homotrimer, comprised of 157 amino acids, chiefly induced by triggered T-lymphocytes, and macrophages[60]. TNF- α mainly adheres to its TNFR1 and TNFR2 receptors, which then send chemical signals for cellular events like apoptosis and inflammation[61]. The pathogenesis of RA through JAK/STAT cascade is as depicted in Figure 5.
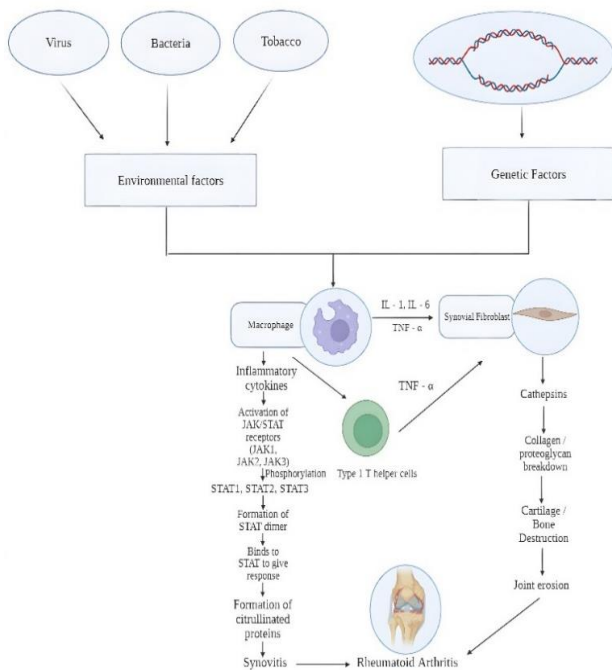

Figure 5: Pathogenesis of Rheumatoid arthritis- RA results as an outcome of Genetic predisposition and Environmental triggers which leads to production of inflammatory cytokines, that activates JAK/STAT receptors which adheres to STAT dimers, which leads to Synovitis and ultimately Rheumatoid arthritis. Also, TNF-α stimulation prompts synovial fibroblasts into action, leading to excessive production of cathepsins, which leads to cartilage breakdown, thus resulting in bone destruction and joint erosion.

JAK INHIBITORS FOR RA

Over the years, JAK inhibitors have exhibited themselves as one of the assuring methods for management of RA and other inflammation and immune mediated disorders. Currently, tofacitinib and baricitinib are available.

Tofacitinib

Tofacitinib was the principal JAK inhibitor that was accepted in the therapy of immune mediated diseases in humans[62]. It is an artificially engineered drug with the chemical formula $C_{16}H_{20}N_6O \cdot C_6H_8O_7$[63]. It is an active suppressor of JAK1 and JAK3 and exhibits mild suppression on JAK2 and Tyk2[64]. It adheres to the ATP-adhering cleft

and serves as an adaptable contender of ATP in the adhering sector of the JAKs, thereby regulating their inactivation and prohibiting the downstream initiation of STATs [65,66]. It is currently being used in the treatment of RA in adults as well as in case of unacceptability to methotrexate (MTX) or disease-modifying antirheumatic drugs (DMARDs). It is usually administered individually or in combination with MTX or other DMARDs[67]. The most commonly observed undesirable effects during clinical trials are upper respiratory tract infection, bladder infection, nasopharyngitis and gastrointestinal disturbances[68,69].

Baricitinib

It is an oral, reversible ATP kinase inhibitor of JAK1 and 2 [69,70]. The molecular weight is 371.42 Da with chemical formula C16H17N7O2S. It adheres to the adenosine 5'-triphosphate-adhereing cleft to bring about the action and in regard to the adverse events the most commonly occurring infections are UTIs and bronchitis[70,71].

THE JAK/STAT PATHWAY IN INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease (IBD) is a persistent recurring idiopathic auto immune ailment that affects the gastrointestinal tract. It primarily involves 2 manifestations, Crohn's Disease/ Regional Enteritis and Ulcerative Colitis[48,73]. Both are linked to a disoriented immune response, atypical intestinal microbiota and a weak epithelial tissue barrier permeability in genetically prone individuals[71,74]. Crohn's disease usually affects any part of the alimentary canal whilst Ulcerative Colitis mainly affects the colon[75]. Even though the exact etiology of IBD is unknown, various factors such as environmental factors, alteration in intestinal microbiota, genetic susceptibility, dietary alterations, and a dysregulated immune system[76,77]. Multiple cytokines have known to be involved in IBD like IL- family, TGF-β, IFN-γ, and TNF-α via their anti-inflammatory and pro-inflammatory effects[78].
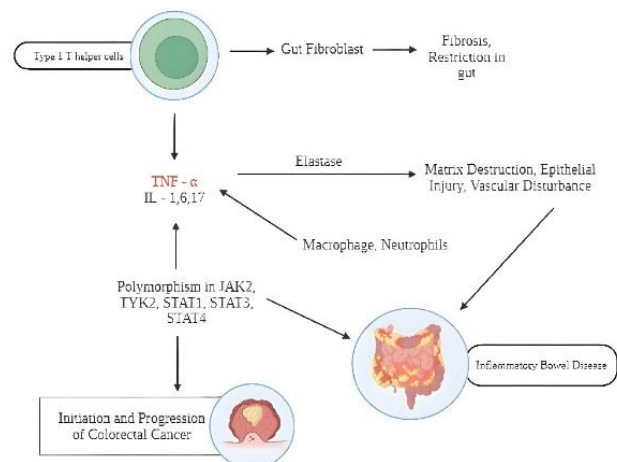

Figure 6: Pathogenesis of Inflammatory Bowel Disease – TNF- α is released by Th1 cells, alongside various cytokines, released cytokines induce gathering of immune cells, such as intestinal fibroblasts, neutrophils, and macrophages,

within the alimentary canal. This results in Epithelial injury and thus leading Inflammatory Bowel Disease. Also, polymorphism in JAK/STAT cascade can lead to colorectal cancer.

These cytokines are effective in assembling the neutrophils, intestinal fibroblasts and macrophages in the GIT. These piled up fibroblasts lead to intestinal fibrosis, then further leads to a restriction in the gut. The accumulated neutrophils in the gut release elastin, which causes matrix destruction. Ultimately, the piled-up macrophages in the gut release IL-1, TNF-α and IL-6, which promotes gut lining destruction, epithelial injury, endothelial initiation and vascular disturbance[79,80]. Polymorphisms in JAK, STAT, and TYK2 in the cascade elevates the risk of IBD and also can lead to the initiation and progression of colorectal cancer[81]. The pathogenesis of IBD through JAK/STAT cascade is presented in Figure 6.

JAK INHIBITORS FOR IBD

Tofacitinib is at present being considered for the management of IBD, primarily Ulcerative Colitis. Tofacitinib has produced promising outcomes after the phase II trials. The reports show that tofacitinib can be used in the management of UC, the long-term open OCTAVE trials will bring about more information concerning the effectiveness of JAK inhibition in UC. Tofacitinib did not show any vital effect among individuals diagnosed with Crohn's disease. Implications from the clinical trials of tofacitinib in CD indicate that it can be used in maintenance therapy of CD[81,82].

CONCLUSION

The JAK/STAT signaling cascade is a signaling cascade associated with cell differentiation, immune regulation, apoptosis, and cell proliferation. It is widely acknowledged that the cascade regulates multiple signals to maintain homeostasis in inflammatory conditions. Dysregulation of the JAK/STAT, alters regulation of apoptosis, cell proliferation and immune response leading to autoimmune diseases. In the last few years, the participation of JAK/STAT cascade in cancer as well as tumours has been immensely scrutinized.

ACKNOWLEDGEMENT

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