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# Insights of Interleukin-2 and Interleukin-6 in neurodegenerative Diseases

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**ABSTRACT**
*Neurodegeneration a condition with progressive loss of neurons that disrupts neuronal connectivity and signal transmission in brain. Extensive research has suggested a correlation of inflammation and neurodegeneration process. Inflammation a self defensive (biological) reaction which responds to tissue repairing, regeneration, elimination of injurious stimuli thus controlling progression of neurodegeneration. Brain infection or activation triggers innate or adaptive immunity causing activation of brain immune cells (B cells, T cells) and glial cells like astrocytes, microglia, macrophages releases inflammatory mediators mainly cytokines (TNF-α, IL-6, IL-1β) thus elevating progression of neuroinflammation. Cytokines are key hole causative agents that alter normal functioning of brain cells.As known, glial cells are the gate keeper cells of the CNS to prevent entry of foreign matter and infection in the brain. It has been widely studied and reported that the innate response exerted by the fighting cells is 'neuroprotective' while the chronic and prolonged immune response results in the toxicity to neurons leading to neurodegeneration and neuronal death. Therefore adequate response by the immune system of the brain is a strongly needed necessity. The pathways that are responsible for initiating the cascade of immune response is discussed in this review with a special emphasis on IL-2 and IL-6 as this could serve as a good target to antagonize neurodegeneration due to chronic neuroinflammation.*
***Keywords*** *- Interleukin-2, Interleukin-6, Neuroinflammation, Neurodegeneration, Immune response, SOCS, PTPs.*

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## INTRODUCTION

Brain is an immune privileged organ that controls functions of all organs in human body through neuronal connectivity and neuronal signal transmission [1].The neuronal circuits in CNS and its functions are disrupted in neurodegenerative diseases [2]. Inflammation, a self-defensive biological process [3] is thought to be a cause for progression of neurodegenerative disease, it functions to repair, regenerate, eliminate injurious stimuli and help in maintaining tissue integrity of the body [4]. According to Celsius observations [5] clinically four cardial signs that interpret inflammation are heat (color), redness (rumor), swelling (tumor), pain (dolor), loss of function (function laesa) at the site of injury [6].These cardial signs are innate immune responses seen in most of diseases but not in case of neurodegenerative diseases.

Neuroinflammation is nothing but host defensive mechanism which exhibit protective role and has restorative potential to retain normal structure and functional integrity against infection and injury [7]. Inflammation in brain is caused due to activation of microglia and astrocytes in response to pathogenic trigger that leads to release of various factors like cytokines, chemokines, or growth factors that results in the form of complex cascade between different brain cells (microglia, astrocytes, neurons, endothelial cells) (8). In neurodegenerative diseases, neuroinflammation initially clears the infection, thereby, controlling the severity and progression of disease thus acting as double-edged sword (9). On one side neuroinflammation may be protective recovering of injured neurons, but on the other hand, it may induce or aggravates the neuroinflammation by worsening the brain conditions [10]. Chronic inflammation induces certain cytotoxic effects that increase the severity of neurodegenerative diseases [11]. Thus, it has become a leading disastrous cause for progression of neurodegenerative diseases like Alzheimer disease (AD), Parkinson's disease (PD), Multiple sclerosis(MS) and Amyotrophic lateral sclerosis [12].It is also true that neuroinflammation is involved in neuropsychiatric diseases. In neurodegenerative disorders the glia cells are the first ones to initiates inflammatory response, characterized by loss of

neurons but this is not true for all neurodegenerative diseases [13].Some emerging evidence represented that inflammation is eminent pathological feature that is mainly characterized by activated microglia and T Lymphocytes infiltration at site of injury [4]. Though it was once believed that the Blood Brain Barrier (BBB) acts as preventive wall between immune cells and brain, the belief is not clearly proven. However, it is now clear that the permeability of BBB can be regulated in normal physiological state when compared to diseased state where it may be either repress or upregulated. The inflammatory reactions associated with brain are represented as either acute or chronic neurodegeneration. Thus, the term neuroinflammation is a coordinated response between microglia and other brain cells including astrocytes and peripheral immune cells infiltrating in central nervous system [14]. Neuroinflammation is an innate immune response which involves activation of glial cells present in brain and thatin turn increases the production of cytokines (i.e TNF-α, Interleukins) [15], chemokines, prostaglandins, complement cascade proteins and reactive oxygen species (ROS) that binds to the receptor based upon their pattern recognition receptor (PRR) depending on the pathogenic trigger [16].The occurrence of neuroinflammation is characterized by presence of reactive astrocytes and activated microglia in brain, but in certain neurodegenerative diseases it is due to damage of blood brain barrier infiltration of B and T cells and polymononuclear cells.

Neurodegeneration a condition where neuronal structure and functions are altered, due to progressive loss of neurons [17] and often by interneural and extracellular accumulation of fibrillary materials [14].While the causes associated with neuronal degeneration is not yet clearly understood but the occurrence of neuronal degeneration increases with age mainly mid to adult age population [18]. Thus, activation of immune system i.e innate or adaptive response [19] and the cellular response by microglia, astrocytes, neurons, endothelial cells [20] actively contribute to progression of neurodegenerative diseases.

**ROLE OF INNATE AND ADAPTIVE IMMUNE RESPONSE IN CNS:**

Though brain serves as 'immune privileged system' it is clear that both innate and adaptive responses are triggered due to pathogenic attack, infection, brain injury and so on [21]. Innate immune system, a decisive first line defence acts to oppose and clear apoptotic cells, misfolded or aggregated proteins (22). In CNS, the immune activation is due to participation of resident immune cells involving microglia, astrocytes [23] which play a pivotal role in homeostasis of brain during development, adulthood and aging [24]. Innate immune response is initiated by recognition of pathogen associated molecular patterns (PAMPS) conserved structures expressed by infectious agents [25] or due to endogenous signals that recognizes the danger associated molecular patterns (DAMPS) that includes a surplus of different molecules like nucleic acids, heat-shock proteins, ATP, high mobility group box chromosomal protein 1 (HMGB-1), fibrinogen and aggregated/misfolded proteinssuch as amyloid-beta (Ab), α-synuclein and microtubule associated protein-tau tend to appear due to stress or tissue damage [23].

Toll like receptors are upregulated in neurological disorders by altering the pattern of microglia, astrocytes, oligodendrocytes and neurons [26]. Activated TLRs promotes the production of proinflammatory cytokines stimulating environmental damage contributing to neuronal death [23]. For example, TLR2 and TLR4 in mice deficient model indicated that the reduced TLR levels promoted to progression of traumatic brain injury [22] whereas in AD microglia associated with neurons expressing Aβ plaques where TLR2 and TLR4 expression are involved in Aβ plaques [27,28].Thus TLR it seems to play beneficiary role in AD, where TLR aid to uptake aggregated proteins and clearing the debris in CNS but still it is unclear that cellular activation by whether to contribute to progression of Alzheimer Disease [29].

Microglial, astrocytes and endothelial cells act as antigen presenting cells, where as neurons themselves initiate immune activation process via secreting various complementary factors like chemokine's, MMPs and DAMP molecules. On the other hand, T cells show active entry by creating immunosuppressive environment in CNS. For example, CD4+ T cells are present in substantial nigra in PD, MS [30] and TBI patients [31]. In some cases CD8+ T cells show a close relation with neurons leading to neuronal damage mediated through cytotoxic CD8+ T cells (32). Both B cells and T cells (CD4+ and CD8+) play an important role in neurodegeneration (33) and this implicates close relation of T cells expressing TNF-related apoptosis-inducing ligand (TRAIL) with spinal motor neurons in MS [33]. Some T cells respond by producing neurotrophic factors like Brain derived neurotrophic factor (BDNF) [34]. In several cases autoimmune responses by T cells not always leads to destruction of neurons but rather they show crucial involvement in repair and regeneration process [35].Therefore, immune response can be both beneficial and destructive depending on the multiple conditions that prevail.

**Neuroinflammation leading to neurodegeneration:**

Neuroinflammation can be described as inflammation of the central nervous system (CNS), which is recognized as a prominent hallmark of many different pathological conditions [21]. CNS is distinguished as 'immune privileged organ' that forms a close relation between innate and adaptive immune response by controlling the responses of CNS with the peripheral cells. Some evidences suggests that a strong inflammatory response is exerted by systemic LPS [36] or viral infections [37] in the periphery result in the subsequent infiltration of leukocytes from the periphery to the CNS leading to neuroinflammation and neurodegeneration. An offensive response is first initiated by microglial activation that releases the proinflammatory mediators favoring the permeabilization through BBB. The infiltration of subsequent leukocytes including (T cells and B cells) into the CNS share same functional features with microglia [36] like Toll like receptors (TLR) activation by aggregated proteins or pathogen associated molecular pattern (PAMP) [38], the expression of major histocompatibility complex class II and the ability of T cells, CD4+ T cells to express antigen presenting site thus influencing functional phenotypic T cells [39], as well as microglial ability to distinguish the two phenotypic forms based on its functional capability as M1 inflammatory and M2 anti-inflammatory phenotypes which may get influenced by inflammatory T cells and lymphocytes regulatory T cells [40]. However subsequent permeability through BBB increases the possibility of peripheral macrophages acquiring a relevant role that may result in neuroinflammation. In neurodegenerative diseased patients, 'it is observed that the ratio of CD4+ and CD8+ T cells is altered suggesting that T cells undergo persistent antigenic challenge in neurodegenerative diseases. The altered ratio of CD4+/CD8+ T cells may contribute to harmful inflammatory reaction, recruitment of antibodies against harmful antigen present in brain, thus showing involvement of immune system in neurodegenerative diseases [23].Based on the consequences, acute neuroinflammation can be assumed as beneficiary to CNS that minimizes the injury by activating innate immune system [41,42]. Contradictorily on the other hand, Chronic inflammation is characterized by long lasting activation of microglia that releases inflammatory mediators leading to upregulate the oxidative and nitro stative stress thus prolonging the inflammatory process [43] resulting in long term inflammation [44,45] that may result to detrimental occurrence of several neurodegenerative diseases [46].

The fate of microglia is influenced by invasion of epithelial cells of BBB, infiltration of T cells through CNS, astrocytes and neurons [47]. The glial are seen in abundant population in CNS showing active participation as an innate immune response, triggering a cascade during inflammation or infection. Other than microglia the astrocytes found to function in similar way as that of microglia play a crucial role in HIV-1 (48) a virus mediated neurodegeneration [49]. The neurodegenerative disease is majorly caused due to prolonged chronic inflammation and activated microglia altering the environment of surrounding brain cells found to play a crucial role in the pathophysiology of neurodegenerative diseases. For example, IL-1-positive activated microglia restrain themselves with amyloid β plaques and neurofibrillary tangles in AD or present in degenerative motor neuron regions in ALS [50] patients leading to phosphorylation of tau proteins [51]. Neuroinflammation may either be consequence or cause of chronic oxidative stress, a characteristic feature of all neurodegenerative diseases that causes genetic structural alteration, lipid and protein dissolution resulting in neurodegeneration. Microglial cells are the prime source for reactive oxygen species, nitrogen species, tumour necrosis factor- α [52] and glutamate with detrimental neurotoxic effects when released at high dose after microglial activation [52,53] stimulating the TLRs (54) to induce signals through aggregated proteins in patients suffering with neurodegenerative diseases like AD [55], PD [56], MS [57], ALS [58].

**Cytokines involved in Brain injury**

Cytokines are diverse polypeptides(59)secreted by many cells, particularly those acting as mediators for inflammation, immune activation, regulation of cell proliferation and cell death (60)including interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), chemokines and growth factors(61).Various alternative names are given like lymphokines (lymphocytes), monokines (monocytes), chemokines (chemotactic activity), interleukins (Leucocytes). The "chemotactic cytokines" are involved in leukocyte chemoattraction and trafficking of immune cells to the injury site(62). Cytokines interact with nearby cells either in autocrine or paracrine way (63) where it controls the development and normal functioning of both immune and nonimmune cells.The cytokines are released in the cellular environment through the blood stream to induce local and remote responses (8).They mainly act on the membrane receptors, to initiate activation of intracellular signals that leads to certain changes in the pattern of gene transcription as a cellular response of milieu.

Inflammatory chemokines are predominantly synthesized by peripheral immune cells(Macrophages, Lymphocytes and Fibroblast) and also a diverse group of cells including Glial cells and neurons(64).The binding of chemokines to it's specific receptor initiates the cascade of signaling that results in activation of various cellular functions likecell adhesion, survival, cytokine secretion, phagocytosis, cell proliferation,

cell death, apoptosis [65], However subsequent exogenous or endogenous damage may takeover the offensive attack of peripheral immune cells(e. g. Neutrophils and macrophages) and may give rise to the progression of neurodegeneration or retrieval of neuronal function [66]. However it is known that variety of cytokines are present in Cerebrospinal fluid with very low concentration, but their expression is increased in case of disease pathogenesis or brain cell injury [64]. In CNS, a significant source of cytokines is peripheral blood cells that produces cytokines after injury or either due to infection or damage to Blood Brain Barrier (BBB) (67). Cytokines have been reported to influence numerous actions that mediate CNS and systemic control towards host defense and also they directly affect the neurons and glial cell development, growth function, damage and repair(60).They show a strong involvement in neurodegeneration and neurotoxicity by changing the expression and effects of cytokines that leads to modifications of endogenous cytokines [68].

**Interleukin-2**

Interleukin-2 (IL-2) has ability to stimulate the growth of T-cells (69) which was identified in 1976 in the supernatant culture of phyto-hemaglutinin .(PHA) stimulated human blood lymphocytes (Ly-CM) [70].Later on in 1983, it was cloned as cDNA a human T-cell leukemia cell line [71] and corresponding gene mapped on human chromosome 4 [72].The First data obtained through series of experiments performed on Lymphocyte conditioned medium suggested that IL-2 may exert a mitogenic effects on T cells or receptors and this helped in distinguishing the biological functions exerted by T cell from other immune cells (73, 74).It promotes the clonal expression of T-cells that is essential for proliferation and survival of T cells and also in generating effector and memory T cells [75]. It is predominantly secreted by activated T cells [59].Also known as growth factor or activator of T- cells they activate cytotoxic T lymphocyte (CTL), natural killer cells (NK) and stimulate development of lymphokine activated killer(LAK) cells (76) and downregulate B lymphocyte proliferation and immunoglobulin secretion.

IL-2, a pleiotropic glycoprotein structured as four α-helix bundle [77] entangled with approximately 15 kDa(78)consisting of 133 amino acids present on dendritic cells and extracellular matrix. It is synthesized in small amount by activated dendritic cells [79] and mast cells [80].IL-2 is involved in differentiation, immune response, homeostasis and maintaining regulatory T cells [81]. In addition, IL-2 also shows growth and effector functions on B and Natural Killer cells.It is mainly produced by CD4+ T helper (TH) cells in secondary lymphoid organs and, to some extent by CD8+T cells, natural killer (NK) cells and natural killer T (NKT) cells(77).

**IL-2 Receptor subtypes**

IL-2 that is predominately produced by antigen-activated T cell binds to the receptor depending on its binding affinity on the receptor, it mainly consists of 3 subunits, IL-2Ra (CD25), IL-2Rb (CD122), and gc (CD132)(82), that are readily present on Treg cells and antigen-activated T lymphocytes. The IL-2 have high affinity towards trimeric IL-2 R receptor, due to it's crystal structure that provides a molecular support model(83).The IL-2 is first captured by IL-2R due to its hydrophobic surface that is surrounded by polar periphery i.e. IL-2 – IL-2Rα. This binary binding shows certain conformational changes that promotes binding with IL-2β due to distinct polar interaction (IL-2-IL-2βR).Notably the extracellular domain of IL-2Rα does not interact with the binary complex but rather the binary complex appears in cis form. Further it forms ternary complex association IL-2Rα-IL-2-IL-2Rβ showing weak interaction with IL-2 and on the other, it strongly with quaternary complex showing high affinity towards IL-2 (84).

**IL-2 signaling pathway:**

**JAK/STAT pathway**

The IL-2 signaling is initiated through IL-2Rβ chain that composed of specific site on IL-2R. Like other cytokine family members [85], IL-R contains a reserved site for membrane proximal cytoplasmic tail known as Box 1 and Box 2, forming variable domain (V box). One of the cloning studies discovered that serine rich domain (S region) overlaps with Box 1 and Box 2 with high significant signaling [86]. Tyrosine kinase has been recognized [87] for its involvement in binding of JAK 1 and JAK 3 with Box 1 and Box 2 (88) present on IL-2 β that activates the IL-2 receptor [89]. JAK 1 binds to specific site on V domain and as well as Box 1 sand Box 2 whereas binding of JAK 3 overlaps on JAK 1 binding site [89]. In addition to JAK , Tyrosine Kinase associated with Syk is found to be associated in signaling [90]. Activation of JAK signals provides most of down streaming events. Mechanically JAK 1 and JAK 3 activation proceeds through phosphorylation of tyrosine residues present on kinase domain. Phosphorylated JAK increases certain catalytic activities that are necessary for JAK 1 and JAK 3 (91). The targets for JAK deactivation is the recruited molecules itself that are linked with receptor complex, leading to down stream of signals.

**Activation of STAT**: Activated JAK leads to phosphorylation of signal transducer and activation of transcription STAT-5A and STAT-5B associated closely with transcriptor factors that binds to phosphotyrosine and Shc domain [92]. Further phosphorylated STAT leads to recruitment of tyrosine on specific site of receptor through Shc domain. Thus phosphorylated STAT undergoes dimerization on

interaction with Shc-phosphotyrosine complex thus causing migration of dimer towards the nucleus of targeted gene [93]. In addition, STAT-5 recruits different Tyr 338, Tyr 392, Tyr 510 differing in the sequences of tyrosine residues. It has been postulated that Tyr 338 requires the adaptor protein for binding with Shc domain [94], thus Tyr 392, Tyr 510 lacks adaptor protein and fails to activate STAT-5. Alteration in C-terminal of Tyr 338 on IL-2Rβ distorts the structure thus interrupting the interaction with STAT-5. Alternatively, IL-2Rβ contains a negative regulatory domain, that inhibits the STAT-5 phosphorylation in context to mutation [95]. It is clear that STAT-5 is crucial for IL-2 signaling [96] that is required for the development of natural killer cells and intraepithelial lineages which is explored by some genetic model studies [97].

**PI3K pathway**

Activation of PI3K pathway occurs due to biochemical modifications of phospholipids. Particularly phosphatidylinositol 3-Kinase (PI3K), a lipid kinase catalyzes phosphorylation of phosphatidylinositol (PI) at D-3 OH- group, resulting in generation of intracellular messengers PI3-phosphate, PI 3,4-biphosphate and PI 3,4,5-triphosphate [98]. PI3-K, a 110kDa (catalytic unit) of which 85 kDa (regulatory unit) causes IL-2 signaling thereby inducing the phosphorylation of p85 tyrosine residue allowing recruitment of PI3K on cell membrane. Some evident studies explored that recruitment of PI3K occurs through adaptor protein Shc that binds to Tyr 338 [99]. The implication of the pathway results in proliferation and anti apoptosis of cells [100]. PI3K modulates E2F, a transcription factor that monitors genes involved in cell cycle progression [101]. Mutant of p85 subunit a inhibitor of E2F factor that inhibits PI3K pathway. Additionally PI3K signaling through IL-2 R increases p70s6 kinase that phosphorylates 40S ribosome of S6 subunit controlling translation of mRNA essential foe cell division [102].

Rafamycin an immunosuppressive drug majorly targets IL-2 dependent proliferation by forming inhibitory complex with FKBP (FK 506-binding protein) (103) regulator of mTOR is protein. mTOR a homologue of PI3K , but its function still remains unclear with PI3K signaling cascade [104]. Another pathway of cell survival through AKT, a protein kinase B that modulates phosphorylation of Bad (Bcl-2 family protein) [105,106] induces apoptosis promoting cell survival as shown in fig 1. Association of PI3K with adaptor protein promotes the down streaming pathways like IRS-1 (107), p120Cb1 and CrkL [108].

**MAPK pathway**

The MAPK Pathway controls cell differentiation, proliferation and cell death (109). Several reports have suggested that after Jak/Stat cascade phosphorylation leads to activation of MAPK complex wherein Tyr338 (110,111) serves as a docking site for adaptor protein Shc (112).Tyr 338 sequence pattern is recognized by phosphotyrosine domain that is present on Shc (113,114). Shc interacts with receptor that leads to recruitment of adaptor protein Grb 2 thus exchange of nucleotide SOS factor occurs that is involving in Ras-Raf-MAPK pathway which further stimulates the upregulation of several genes for example f-cos. Although MAPK pathway is associated with growth signaling that is neither necessary nor sufficient for IL-2 proliferation. In-vivo study on mutant IL-2Rβ evidences that mutant IL-2Rβ fail to activate MAPK pathway even though it increased the proliferation of cultured cells (95). Alone activation of MAPK pathway is not sufficient for prolong sustainability of IL-2 dependent cells, thus additional signaling pathways are required (115).

MAPK activation upregulates the apoptotic mediators Bcl-2 and Bcl-XLthat promotes cell survival (116,117,118). Thus induction of Bcl-2 gene through transcription factor Aiolos, that binds to bcl-2 promoter site inducing transcription process (119). The functional MAPK activation not only drives IL-2 dependent pathway but also controls Bcl-2 gene expression. Since in mutant IL-2R receptors in Tyr-338 is replaced by phenylalanine it induces bcl-2 mRNA in some cases acting as wild type receptor (94).Finally the Ras-Raf-MAPK complex regulates protein phosphatases 1α that inturn regulates proapoptotic mediator Bad (120). However Tyr 338 activates the MAPK but consequently it downregulates the other pathways related to proliferation and survival, but functional redundancy effects by these pathways are due to other signals generated by IL-2 R (98).

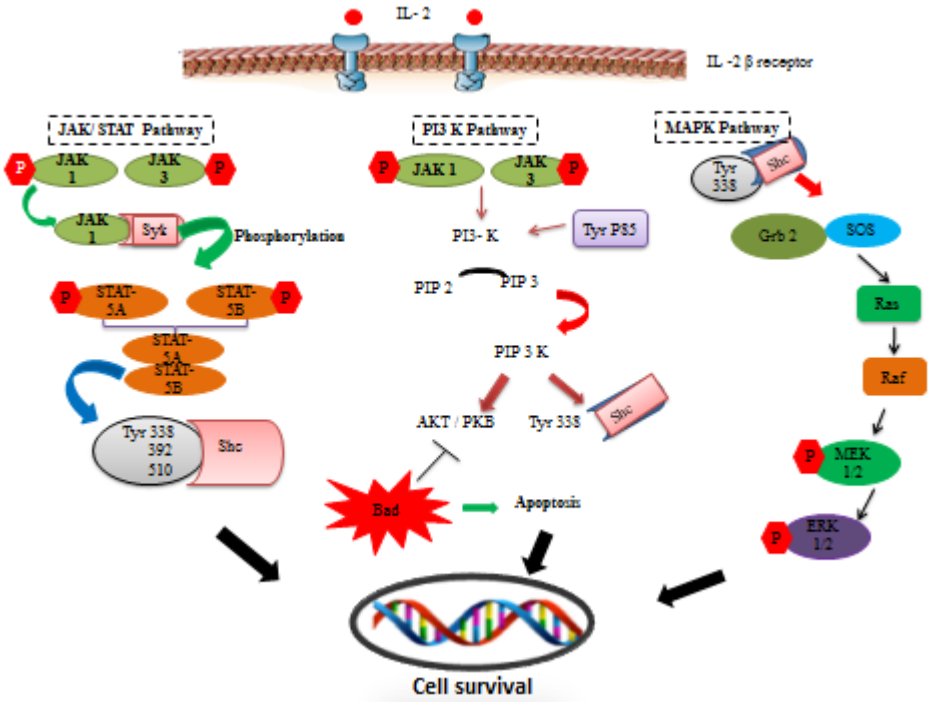


Fig 1 : IL-2 acting through different pathways thus promoting cell survival.

**INTERLEUKIN-6**

Interleukin-6,was identified as a factor produced by lymphocytes that act as stimulator for B cells to produce antibody(121). It is a soluble mediator with multifunctional biological effects on inflammation, immune response, and hematopoiesis[122]. Earlier it was known by distinct names like thename B- cell stimulatory factor 2 (BSF-2)due to its ability to produce differentiation of activated B cells into antibody (Abs) producing cells [123], Hepatocyte stimulating factor (HSF)due to its effects of acute phase protein synthesis on hepatocyte cells and was also known as Hybridoma growth factor(HGF) (124) due to its ability to cause growth of fusion cells between plasma cells and myeloma cells. In 1986, when BSF-2 was successfully cloned as cDNA [121] where it was found that molecules with different names were found to be identical, resulted in single name 'Interleukin-6'[125]. Along with B cell differentiation it also shows some effects on T cell growth and on many other cells it induces acute phase proteins release [126]. It was identified to be involved in tissue regeneration [127,128], inflammation [129] and pathogen defense (130). Human IL-6 is composed of 212 amino acids including 28 amino acid single peptide with gene located on chromosome 7p21.Although the size of IL-6 is 21- 26 kDa [122].

IL-6 modulates various functions like cell propagation, cell differentiation, apoptosis. Apart from it's inflammatory actions, it also show effects on different systems including neural and endocrine systems, bone metabolism and skeletal muscles [131] and hence forth known to be a pleiotropic cytokine [132].

**IL-6 and it's receptor**

IL-6, proinflammatory cytokine (133) is arranged in 4- α helical couple bundle in antiparallel helices [134]. Based on its length of IL-6 it is categorized under long chain cytokines that includes growth hormone (GH), erythropoietin and G-CSF factor [135]. According to mutagenesis studies, it has been recognized that IL-6 shows 3 active sites that binds with the receptor.

Binding of IL-6 occurs in two different types of glycoprotein receptor, together forming a common IL-6 receptor. The protein receptor only differ in their molecular weight i.e. IL-6Rα or CD126 (80kDa protein) and second gp130 or CD130 (130kDa protein) belonging to type I membrane protein consisting of transmembrane domain and extracellular N- terminal domain (130). Gp 130 protein is most commonly expressed in liver, kidney, cardiac, muscles and skeletal muscles etc. The population of IL-6 Rα is mainly restricted to certain targeted cells that mainly includes Hepatic cells, leukocytes (monocytes, neutrophils, B and T cells) and also neural, bone and skeletal tissue [131]. The small intracellular part of IL-6Rα shows a minor signal transmission that is initiated by intracellular domain of gp130 that contributes to IL-6 signals [136]. Like other receptors Gp 130 protein does not show any kinase activity rather it binds to intracellular part of JAK for signal transduction [137].

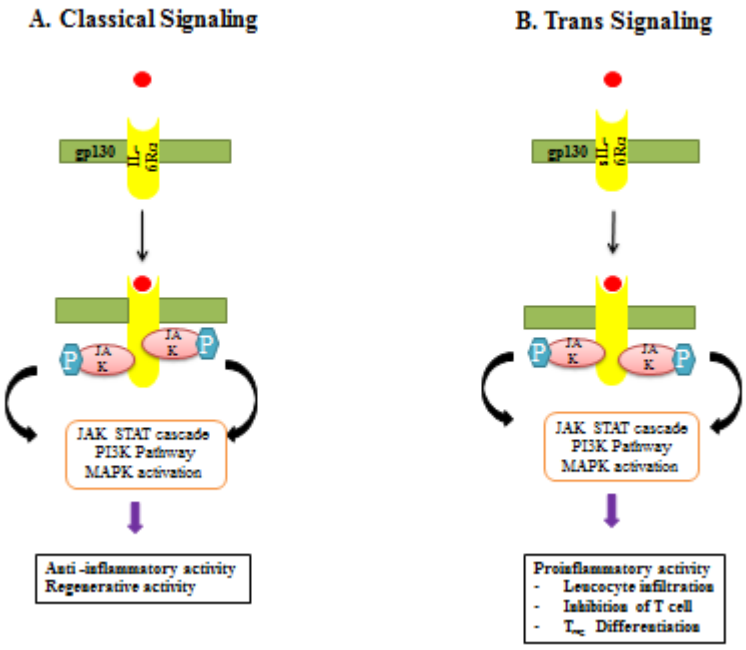


Fig 2 : IL-6 receptor signaling

**Intracellular Signal transduction by IL-6:**

**Jak Stat pathway**

Janus kinase/Signal transducer and activators of transcription (JAK/STAT) is a pathway involved in various pleiotropic complexes that induces multiple signals required for developmental regulation, growth control and homeostasis in humans (138). In mammals, JAK/STAT is the only signaling pathway that is activated by wide range of molecules (including cytokines and growth factors) [139]. Janus kinase, an intracellular tyrosine kinase with molecular mass of 120-140 kDa [140]. is composed of 4 (JAK1, JAK2, JAK3, Tyk2) members wherein JAK1, JAK2, Tyk2 are expressed mostly by all mammalian cells whereas Jak3 is expressed specifically by hematopoietic cells (141).STAT is comprised of seven different transcriptional factors i.e.STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, STAT6 (142). Although the JAK/STAT expression in CNS is weaker as compared to other systems as these proteins are present only in several brain areas like hippocampus, cerebral cortex, cerebellum, hypothalamus [143].

The gp130 receptor lacks kinase activity but forms active complex with Janus kinase a cytoplasmic (non receptor) kinase by forming homodimer loop (144). Thus the gp 130 receptor forms a close association with JAK followed by its auto-activation (131).The activated JAK shows its actions in two ways first, it will lead to phosphorylation of tyrosine residues present on intracellular domain of gp 130and second, binding of JAK molecules to STAT. STAT is the transcriptional factor that binds to phosphorylated tyrosine residues of gp 130 where the JAK induces phosphorylation of STAT followed by dimer formation that migrates towards the nucleus of target gene as shown in fig 3.

**Mitogen Activated Protein Kinase (MAPK)**

Homo dimerization of IL-6 receptor not only activates JAK/STAT pathway but also activates MAPK where SHP2 protein is involved (145). For MAPK activation, SHP2 a tyrosine phosphatase (65 kDa) is spontaneously expressed (140). SHP2 binds to gp 130 where phosphorylation occurs at Tyr759 residues by JAK1. When phosphorylated, SHP2 comes in contact with Grb2/SOS complex, binding of SOS to the receptor through Grp2 protein leads to Ras activation [146]. Activated Ras stimulates activation of Raf (Protein kinase). Phosphorylated Raf kinase activates MEK in MEK1 and MEK2 which on further phosphorylation leads to MAPK activation. The activated MAPK interacts with CREB leading to transcription, thereby controlling cell survival, cell proliferation as described in fig 3.

**PI3K PATHWAY**

IL-6 also activates PI3K cascade.The survival factors like BDNF (Brain Derived Neurotropic Factor) or IGF-1 (Insulin like Growth Factor- 1) binds to the tyrosine residue eliciting the PI3K activation to the vicinity of plasma membrane [147].PI3K modifies certain phospholipids leading to recruitment of AKT protein kinase to the plasma membrane [131]. The catalytic subunits of PI3K generates phosphoinositide

phosphatase PIP2 and PIP3 at the internal surface of the plasma membrane leading to phosphorylation at Thr308 and Ser478 which in turn activates AKT[148]. Activated AKT stimulates the phosphorylation of target proteins like Caspase-9 [149], forehead transcription factor (FKHR) [150], GSK-3b protein [151] promoting cell proliferation and cell survival as shown in fig 3.

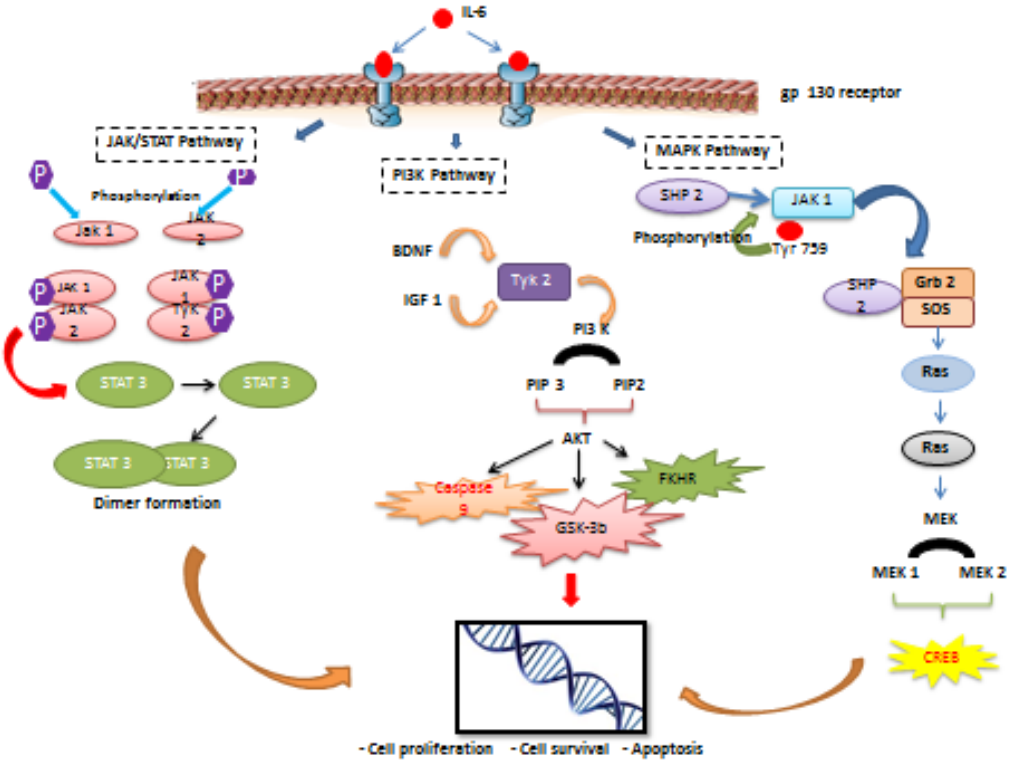


Fig 3 : IL-6 acting through different pathways thus promoting cell proliferation, cell survival and apoptosis.

**Terminators of IL-6 Signal transduction**

**Protein Tyrosine Phosphatases (PTPs)**

Once the IL-6 signal transmission is stimulated, it not only activates JAK/STAT but also causes the tyrosine phosphatase SHP2 activation through gp 130 receptor [140] and thus subsequent phosphorylation of every single molecule involved in signal transmission [131].The Protein tyrosine phosphatase SHP2 binds to tyrosine759 residue of gp130 intracellular domain as a signal of IL-6 signal transduction [152]. Tyrosine759 possess pleiotropic effects during transmission of IL-6 signals, substitution of tyrosine residue with phenylalanine reduces the binding of SHP2 on gp 130 receptor and subsequent phosphorylation [153] thereby stimulating IL-6 signals [154,155], thus SHP2 induces impairment of JAK/STAT cascade activation (156).On the other hand, mutation of tyrosine inhibits MAPK activation, though SHP2 act as adaptor protein for MAPK activation.

Thus every single phosphorylated tyrosine residues acts as a substrate for SHP2. Some reported evidences suggests that binding of SHP2 with Jak1, Jak2 and Tyk2 induces phosphorylation [15]) and thus absence of the STAT3-SHP2 cascade reveals that STAT3 is direct substrate for SHP2 activation [158].Thus SHP2 dephosphorylate STAT1 along with Tyr701 at Ser residue [159].

**Suppressor of Cytokine Signaling (SOCS)**

Though there are numerous terminating pathways recognized SOCS is also one of the mechanism involved in IL-6 signal transmission. SOCS are intracellular protein molecules [160] that can down regulate the JAK/STAT pathway by binding to catalytic site of JAK and further blocking the STAT protein activation (161). It is also known as cytokine inducible SH2 protein (CIS) or STAT induced STAT inhibitors (SSIs) including eight members (CIS, SOCS1-7).SOCS possess a common central SH2 domain, 40 amino acid C-terminal domain known as SOCS box [162]. The expression of SOCS (CIS, SOCS1-3) is rapidly induced by IL-6 [163] and other cytokines. Thus SOCS inhibits the JAK/STAT pathway via showing a classic negative feedback mechanism

The mechanism of action varies according to the SOCS subunits. SOCS1 and SOCS3 the two most widely studied members of family found to show involvement in inhibition of gp 130signalling [164]. SOCS1 and SOCS 3 mainly affect IL-6 cytokine signaling via exhibiting similar functional ability by acting on JAK and thus impairing the phosphorylation of gp 130 receptor, JAK and STAT (165). SOCS 1 terminates IL-6 signal transmission by binding to the active catalytic JH1 domain of JAK 2 inhibiting JH1 activity (166,167) on the other hand SOCS 3 not only binds to JAK 2 (168) but mainly binds to the phosphorylated tyrosine residue of activated gp 130 receptor [169] as described in fig 4.

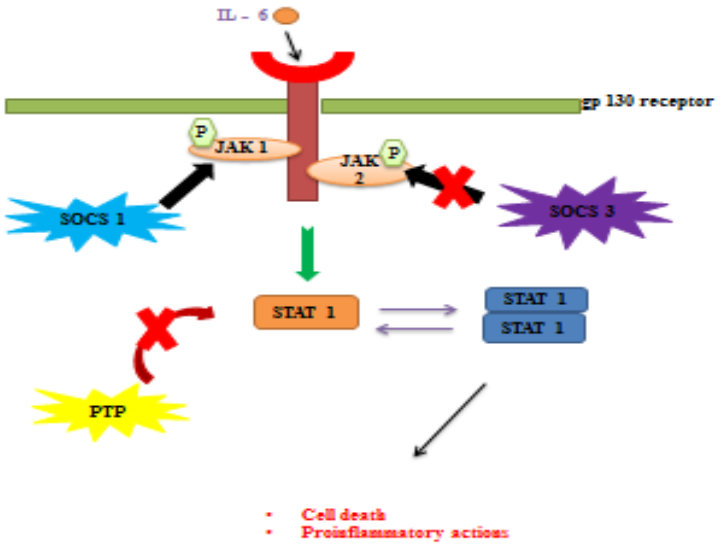


Fig 4 : IL-6 signal terminators inhibiting further signal transduction process.

## CONCLUSION

The molecular pathways leading to immune responses in the brain are very essential to understand in detail in order to control exaggerated and prolonged inflammatory response and thereby prevent neurotoxicity and degeneration.Interleukin-2 and Interleukin-6 are the two important players of immune system that exert an immune response after a cascade of signal transduction. Therefore, understanding the mechanisms responsible for the release and action of IL-2 and IL-6 right from their transcription until their degradation would be beneficial in controlling the exaggerated immune response leading to inflammation of neurons and hence would be helpful in neuronal disorders that occur due to neuroinflammation.

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