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Review Article

Unraveling the Role of STAT3 in Various Diseases Your Pathway to a Healthier Life

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Abstract

This article aims to provide an overview of the role of Signal Transduction and Activator of Transcription 3 (STAT3) in major pathologies where it plays a crucial role. STAT3 is an intracellular protein and a critical regulator of gene expression that is considered the master regulator of vital functions in both health and disease. Initially, Stat3 is part of the acute inflammatory response, but if the initial injury is not controlled, it leads to chronic inflammation. When chronic inflammation sets in, STAT3 becomes abnormally activated, which, in conjunction with the complement system, maintains chronic inflammation and is responsible for many chronic diseases, a leading global cause of mortality. Many studies have shown that suppressing the overactive STAT3 is beneficial in controlling various diseases. Several types of Stat3 inhibitors have been created and are under development. While none of them have reached the market yet, we expect some to be approved soon.

What is a disease, and how can we prevent it?

Think of disease as a disruption in our body's tightrope act of balance and stability, known as homeostasis. Just like a circus acrobat walking on a tightrope while holding a pole to maintain equilibrium, our body strives to maintain balance and stability through a natural process called homeostasis. If this balance is upset, it's like the acrobat losing their grip on the pole-an accident waiting to happen. Similarly, if our body's balance and stability are disrupted, it can lead to a breakdown in homeostasis, resulting in a disease. A disease occurs when the acute inflammatory process, also known as the Acute Phase Response (APR) necessary for survival, fails to restore homeostasis. This failure is concealed in the chronic inflammatory process, a condition that demands our immediate attention and understanding. Although this topic has recently received attention, its urgency cannot be overstated. Among the risk factors associated with Chronic Inflammation (CI) are age, obesity, diet, smoking, low sex hormones and stress, and sleep disorders. Understanding these risk factors and their impact on chronic inflammation is paramount in our collective efforts to prevent diseases.

CI can stem from various sources, including infections, pollutants, autoimmune conditions, frequent episodes of acute inflammation, and biochemical inducers like oxidative stress and mitochondrial dysfunction. Collectively, these conditions are known as chronic inflammatory diseases, and they are a leading global cause of mortality.

Signal Transduction and Activator of Transcription 3 (STAT3)

In 1993, researchers discovered a crucial protein in the Acute Phase Response (APR). Initially named the Acute Phase Response Factor or APRF [1], this protein is now known as the Signal Transduction and Activator of Transcription 3 (STAT3). Over the years, scientists have conducted extensive research on the functions and diverse actions of the STAT3 protein in maintaining good health and preventing diseases. There are currently 36,714 publications available on PUBMED, an archive of the National Library of Medicine for Biomedical and Life Sciences literature, with the reports of these studies. STAT3 is located inside the cell, and its operating pathway communicates with many other pathways. All other signaling pathways are outside the cell. This STAT3 protein, a key player in maintaining homeostasis, is present in every mammalian cell. It regulates genes, cell signaling, and immune responses, thereby playing a crucial role in maintaining balance and stability in the body.

In healthy individuals, STAT3 is constantly activated but for just a few minutes, a process tightly controlled by activators and suppressors. However, in cases of Chronic Inflammation (CI), homeostasis has been altered. Now, STAT3 is phosphorylated and becomes constitutively activated, called p-STAT3, and has been extensively studied for its role in various chronic inflammatory diseases such as cancer, autoimmune disorders, infectious and degenerative diseases, vaccine responses, and metabolism. In this context, we will briefly discuss its important role in health and disease. STAT3 is activated by many players, including cytokines, growth factors, oncogenes, interferons, epidermal, fibroblast, granulocyte, and insulin-like growth factors [2,3]. It appears to be involved in contradictory cell responses, possibly due to the activation of different gene sets in different cells [3]. The role of STAT3 in mammalian development was recognized in 1997 [4]. Darnell published a seminal paper about STAT3 in 1997 that apparently stimulated research on this area [5].

Six other members (STATs 1,2,4,5A,5B, and 6) also play a role in cytokine-mediated activation of immune and non-immune cells, each with a variable function. This results in a high degree of redundancy [6]. It is now known that STAT3 is required for embryogenesis, activated and necessary for development [4], and indispensable during the first two years of life in humans, but it is dispensable for the function of normal cells and tissues in children (> two years) and adults. The dispensable intracellular protein STAT3 becomes constitutively activated (this abnormal, aberrant form is described as p-STAT3) in hyperproliferative conditions such as cancer, autoimmune and neurodegenerative diseases, and several other pathological conditions [7]. Here, we present a brief overview of conditions associated with alterations in STAT3. Some are caused by reduced or absent activation, while others result from excessive activation.

STAT3 gene alterations

Variations in the STAT3 gene are rare and can cause two distinct clinical syndromes - loss-of-function/dominant negative (LOF/DN) and Gain-Of-Function (GOF). Individuals with LOF/DN typically develop Autosomal-Dominant Hyper-IgE Syndrome (Job's syndrome), which is characterized by recurrent skin disease, impaired inflammatory responses, life-threatening infections, and high levels of IgE [8]. On the other hand, individuals with GOF develop a primary immune regulatory disorder that can cause lymphoproliferation, autoimmunity, immunodeficiency, and growth delay. This syndrome requires combination therapies due to its multisystemic clinical presentation [8,9].

Excessive STAT3 activation

Cancer

Cancer is a disease that has been extensively studied in relation to STAT3. About 70% of all cancers have p-STAT3, a key factor where multiple oncogenic signaling pathways converge within the cell [10]. STAT3 is the only pathway located inside the cell and is downstream of all others. It is constitutively activated in tumor and immune cells within the tumor microenvironment. This activation suppresses the expression of mediators essential for immune activation against the tumor cells. STAT3 facilitates communication between tumor cells and their immunological surroundings [11]. This interaction ultimately leads to harmful immunosuppression that significantly impairs the body's ability to fight cancer. p-STAT3 is involved in all aspects of cancer, including proliferation, metastasis, angiogenesis, metabolism reprogramming, and cancer stemness [12]. It's worth noting that are other STATs involved in cancer besides STAT3. One of the most important ones is STAT5, which plays a crucial role in the function and development of Tregs. If STAT5 is consistently activated, it can lead to a suppression in antitumor immunity, as well as an increase in proliferation, invasion, and survival of tumor cells [13].

Diagnostic tests have been developed to determine the presence of p-STAT3 and other STATs. They are very useful because these determinations have prognostic value and permit the selection of patients who can be treated with STAT3 inhibitors. Different techniques are available to isolate and quantify total and phosphorylated STAT3 in tissues from biopsies [14]. Technologies are now available to determine drug sensitivity in tissues taken from a patient, allowing the oncologist to select the effective drug for that patient [15]. Since several STATs are involved in cancer, a new pan-cancer test was developed utilizing high-throughput technologies. This data creates computational methods, like machine learning and deep learning, for predicting anti-cancer drug responses [16].

It is important to follow patients after the original tumor has been removed. However, after surgery, no more tissue is available to monitor the therapeutic effect. Fortunately, a diagnostic test denominated Liquid Biopsy (LB) has been developed. Some have already been approved by the FDA, while others are still in development. They can use blood, urine, cerebrospinal fluid, or saliva. LB detects circulating tumor DNA, small pieces of DNA from the tumor circulating in very small amounts and require very sensitive technologies. They are very useful to monitor the therapeutic response after the tumor has been surgically removed [17]. Another exciting area is the development of Multi-Cancer

Early Detection (MCED) tests that detect bits of DNA or RNA shed by tumor cells into the bloodstream. They are expected to allow for the detection of early-stage cancers before they give clinical symptoms and hopefully will allow the identification of persons at risk of developing cancer [17]

Many preclinical and clinical studies have been conducted to determine the mechanism of action, safety, and efficacy of STAT3 inhibitors. These compounds, in cancer studies, have been shown to inhibit proliferation, metastasis, and angiogenesis and have a beneficial effect on immunosuppression [12]. Anticancer treatment includes chemotherapies, targeted therapies, and radiotherapy. Unfortunately, after some initial response, the anticancer effect is lost, and in most cases, this is due to the development of Acquired Drug Resistance (ADR). It has been shown that this is usually due to the formation of p-STAT3 that reactivates the tumor. It is known that STAT3 inhibition reverses ADR [18]. The development of Stat3 inhibitors has been slow, partly due to the belief that STAT3 was an undruggable target. However, this idea has been proven incorrect, and we now have both direct and indirect STAT3 inhibitors in preclinical and clinical development. Recent research conducted by Yamei Hu and colleagues (reference 11) has provided a summary of numerous studies on anticancer treatments.

Autoimmune diseases

Diabetes

In 2015, 30 million people in the United States had diabetes. A human mutation in STAT3 was found to promote type 1 diabetes through a defect in CD8+ cell tolerance [19]. STAT3 plays a multifaceted role in diabetes, impacting β-cell function, insulin signaling, and overall glucose metabolism. Insulin resistance is a key characteristic of type 2 diabetes (T2D), a condition where peripheral tissues lose their sensitivity to insulin. STAT3 has been shown to negatively impact glycogen metabolism, contributing to insulin resistance in the liver [20]. In T2D, chronic high blood sugar levels stem from insulin resistance in peripheral tissues, as well as gradual defects in insulin secretion by pancreatic beta cells [21]. Other autoimmune diseases, like lupus [22], rheumatoid arthritis [23], psoriasis [24], and ankylosing spondylitis [25], involve the STAT3 pathway, and treatment with STAT3 inhibitors is being evaluated.

Chronic Kidney Disease.

The role of STAT3 in Chronic Kidney Disease (CKD) has only recently been recognized [26]. The effects of the IL-6R monoclonal antibodies tocilizumab and sarilumab and several direct inhibitors of p-STAT3 have been tested in several models of kidney disease and in some patients. JAK inhibitors that act by inhibiting STAT3 have been studied, tofacitinib in kidney transplant rejection and baricitinib in Diabetic Kidney Disease (DKD), but side effects have been found, and it appears that direct STAT3 inhibitors have a superior safety profile. Nifurozaxide, an antidiarrheal drug, is a potent STAT3 inhibitor and showed good effects in a model of CKD. SI3-201 and Static might be effective in DKD. SI3-201 is effective in animal models of Focal Segmental Glomerulosclerosis. SI3-201 and Static had positive effects on lupus nephritis. Pyrimethamine and SI3-201 showed good effects in polycystic kidney disease [27]. These are examples of the potential of STAT3 inhibition in several types of kidney disease, and more details are described in the publication by Pace et al. (reference [26]. Controlled clinical trials will have to be conducted to assess their safety and efficacy and hopefully to take the best to the clinic.

Neuro Degenerative Diseases (NDDs)

Chronic inflammation and viral infections are thought to contribute to neurodegenerative diseases [28]. The Inflammation-Pathogen Infection Hypothesis is gaining ground as an alternative to the Amyloid Hypothesis for Alzheimer's disease (AD) [29]. However, the virus presence itself doesn't cause NDDs; neuronal alterations are mediated by the infiltration of NK cell-like bystander-activated CD8+ T cells via NKG2D signaling. NKG2D is expressed by NK cells, γδ T cells, and CD8+ αβ T cells in humans, and its activation triggers cytotoxicity, leading to the formation of p-STAT3 [30]. All NDDs, including Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS), share chronic inflammation as a common factor. About 75% of dementia cases are due to AD. Since 2004, 2,700 AD clinical trials have been conducted, and 550 have been analyzed [31]. The success rate since 2003 was 2%; only aducanumab and oligomannate had positive data. Aducanumab was provisionally approved for AD under accelerated approval in 2021, but Biogen removed it from the market due to its limited efficacy and replaced it in 2023 with lecanemab, also approved under accelerated approval.

New and old drugs with different mechanisms of action are in clinical development. The National Institute on Aging is funding more than 450 active clinical trials. Among the old medications, we have the antidiabetic drug metformin, which has been in clinical use for more than 40 years. It is currently in phase 3 clinical development in patients with AD and is expected to be completed in 2026. The antiepileptic drug levetiracetam is also in phase 3 clinical development in patients with AD (Hope 4MCI trial).

STAT3 in Neurodegenerative Diseases

The extensive ongoing research around STAT3 inhibition is evidence of the significant role of CI and p-STAT3 in NDDs. Here are some recently reported studies on the various diseases of interest.

AD: A review of preclinical studies of AD indicates that inhibiting the STAT3 protein could be a potential therapeutic approach for treating Alzheimer's disease. For instance, when mice with Alzheimer's disease were treated with the STAT3 inhibitor LLL-12, they improved cognitive performance, better neural connectivity, and increased blood flow. Additionally, it was observed that LLL-12 reduced the formation of plaques, cerebral amyloid angiopathy, oxidative stress, and neuroinflammation in these mice [32].

PD: Brain-derived neurotrophic factor (BDNF), a protein that promotes the survival and growth of neurons, is widely distributed in the central nervous system (CNS). BDNF promotes STAT3 phosphorylation and regulates autophagy in neurons. In a mouse model of PD, BDNF enhanced the BDNF receptor, p-STAT3 PINK1,

and DJ-1 promoted autophagy, inhibited the level of p-α-syn (a protein associated with PD), and enhanced cell proliferation. The study suggests that BDNF alleviates PD pathology by promoting STAT3 phosphorylation and regulating neuronal autophagy [33].

ALS: JAK inhibitors correct several pathophysiological processes in ALS, such as mitochondrial dysfunction, autophagy, and neuroinflammation mediated by astrocytes, microglia, and NK T cells. They also reduce the risk of excitotoxicity, ER stress, and cytoplasmic calcium overload. JAK inhibitors correct several pathophysiological processes in ALS, such as mitochondrial dysfunction, autophagy, and neuroinflammation mediated by astrocytes, microglia, and NK T cells. They also reduce the risk of excitotoxicity, ER stress, and cytoplasmic calcium overload [34]. However, all JAK inhibitors approved have a warning box in the package insert due to safety concerns. It would be better to use a direct STAT3 inhibitor once approved [35].

Huntington Disease: Harigai et al. showed that the JAK2-STAT3 pathway controls a beneficial proteostasis response in reactive astrocytes in Huntington's disease. This process involves bi-directional signaling with neurons to reduce mutant Huntington aggregation, eventually improving disease outcomes. However, the safety of JAK inhibitors is a concern. It is hoped that a STAT3 inhibitor will reach the market soon [36].

Multiple Sclerosis (MS): The efficacy of STAT3 inhibition in MS has been demonstrated in a mouse model. The well-known S3I-201, a small molecule, ameliorated the clinical symptoms by regulating multiple intracellular signaling in Th1, Th17, and Treg cells [36,37].

AUTISM

Abnormalities in the immune system of individuals with Autism Spectrum Disorder (ASD) are characterized by increased immune cell activation, elevated proinflammatory cytokines, decreased anti-inflammatory cytokines, and evidence of neuroinflammation.S3I-201, a thoroughly studied STAT3 inhibitor, was tested in a model of autism. The treatment resulted in the suppression of Th17-related signaling and the enhancement of Treg-related signaling. These changes were accompanied by an improvement in autism-like behavior in BTBR mice. Therefore, the findings suggest that STAT3 inhibition could be potentially developed into a therapeutic approach for treating autism [38].

Epilepsy

Stat3 inhibition with a JAK inhibitor has been shown to inhibit primary epileptogenesis in an animal model of temporal lobe epilepsy [39]. In another animal model (nSTAT3KO mice), it was demonstrated that inhibiting neuronal STAT3 signaling prevented the progression of seizures and pathogenic changes associated with epileptogenesis [40].

Ophthalmology

Uveitis

CNS autoimmune diseases, such as uveitis and multiple sclerosis, occur when the immune system loses its ability to protect the brain, spinal cord, or neuroretina. A cell-penetrating STAT3 inhibitor nanobody, known as SBT-100, has been found to suppress uveitis in a model of autoimmune uveitis [41].

Cardiovascular

Cardiovascular disease is the top cause of death worldwide and has a significant economic burden. Immune dysregulation and inflammation play pivotal roles in many CVDs. Reducing inflammation may lower CV events. A major player in inflammation is the STAT3 pathway, which is now the topic of active research [42].

Arrhythmias

Left Atrial (LA) fibrosis plays a significant role in developing Atrial Fibrillation (AF). Recent research has studied the effects of STAT3 signaling on atrial fibrosis in mice with left ventricular dysfunction caused by myocardial infarction and in dogs with Heart Failure (HF) induced by Ventricular Tachypacing (VTP). The study found that HF dogs developed LA fibrosis, increased Platelet-Derived Growth Factor (PDGF), and increased susceptibility to AF after one week of VTP. The direct STAT3 inhibitor S3I-201 was administered to fibroblasts in vitro or mice in vivo. HF activated STAT3 in the LA and increased the Platelet-Derived Growth Factor (PDGF). S3I-201 was found to reduce the pro-fibrotic effects of PDGF stimulation, as well as LA-fibrosis and remodeling in post-MI mice. The JAK inhibitor AG-490, the PDGF inhibitor AG1296, and the STAT3 inhibitor S3I-201 effectively suppressed STAT3 and collagen upregulation. In vivo, treatment of MI mice with S3I-201 attenuated LA fibrosis, LA dilation, and P-wave duration. These findings suggest that STAT3 inhibition could potentially be used for preventing LA-fibrosis [43].

Ablation failure and recurrence after cardioversion are significant medical issues. Atrial fibrosis, which increases susceptibility to AF, is associated with the activation of STAT3. The role of the cell membrane protein CAV1 I in atrial fibrosis was studied in the human atrium evaluated by immunohistochemistry and in cultured rat atrial fibroblasts silenced using siRNAs. Atrial fibroblasts were treated with angiotensin II(AII). It was found that AII decreased CAV1 expression, upregulated atrial fibrosis, and overactivates STAT3 [44]. Postoperative atrial fibrillation is a common occurrence after cardiac surgery. Researchers Huang et al. hypothesized that a feedback loop exists between STAT3 and miR21, which could contribute to developing postoperative AF. They tested this hypothesis in a sterile pericarditis model and found that, indeed, such a reciprocal loop between STAT3 and miR-21 is activated after heart surgery and can contribute to the occurrence of AF [45].

Atherosclerosis

Chronic inflammation is responsible for atherosclerosis. Several studies have shown the major role of nuclear and mitochondrial STAT3 in endothelial cell dysfunction, macrophage polarization, inflammation, and immunity during atherosclerosis. STAT3 in mitochondria is also involved [46]. The dysfunction of the endothelium and the accumulation of oxidized low-density lipoproteins lead to plaque formation in the intima. This triggers

an immune and inflammatory response, promoting tissue damage, local inflammation, vascular dysfunction, and abnormal expression of adhesion molecules that adhere to the endothelium and activate the STAT3 pathway. Immune cells, including CD4+ cells, Th17 cells, Treg cells, and dendritic cells, all play important roles in the development of atherosclerosis. STAT3 inhibition should be a very effective therapy in atherosclerosis [47]. The publication by Makeover, et al. [48] highlights the urgent need for more targeted treatments. C3 complement is involved in the progression of Atherosclerosis [49]. Intracellular C3 initiates the activation of the JAK/STAT3 pathway during cancer studies and pretreatment with a JAK inhibitor prevents C3 from stimulating it [50]. It appears that there is a clear interplay among chronic inflammation, the STAT3 pathway and the complement system [49-51].

Pulmonary hypertension

Pulmonary Artery Hypertension (PAH) is a proliferative disease sustained by increased activity of STAT3 [52]. Chronic inflammation contributes to pulmonary artery remodeling and PAH, and many inflammatory mediators signal through the JAK/STAT pathway. There is substantial evidence that this pathway participates in the pathology of PAH, and Stat3 inhibition is expected to be beneficial [52]. MiRNA-based therapies are being investigated as diagnostic markers and therapeutic drugs for PAH treatment, and results are encouraging [53-57].

Safety of Stat3 Inhibitors

Although no STAT3 inhibitor has been approved yet, there are several clinical programs developing different types of molecules. Soon, breakthrough therapies will be available in the market. STAT3 is indispensable during gestation and the first 2 years of life. However, in children older than two years and adults, it is not essential for normal cell and tissue function. In these individuals, STAT3 is constantly activated but for brief periods (a few minutes) to transmit signals from cytokines and growth factors found on the cell membrane to the nucleus. The dispensable intracellular protein STAT3 becomes constitutively activated in hyperproliferative conditions such as cancer, neurodegenerative diseases (NDDs), and many other pathological conditions described earlier. This abnormal, aberrant form is referred to as p-STAT3.It is VERY important to mention that STAT3 inhibitors appear to be specific and selective and bind only abnormal STAT3 (p-STAT3). Research on this topic is ongoing. When a STAT3 inhibitor is given to a patient with a disease harboring p-STAT3, the drug binds only to it in an irreversible way and is degraded by ubiquitination followed by degradation by the proteasome [58]. There is an early reversible phase followed by an irreversible late phase. This irreversible phase explains the long-term biological effects. However, normal STAT3 is not affected by the STAT3 inhibitor. This appears to explain the tolerability and safety of STAT3 inhibition.

The dispensability of STAT3 was already known in the late 90s, and numerous reports have confirmed it [59]. A 2007 report stated that "its function is dispensable in most adult tissues" and that "it would seem to be a well-validated target for the development of rational cancer therapy" [60]. This 2007 statement has been corroborated by several years of studies with STAT3 inhibitors in animal models of several diseases and many patients studied during the clinical development of STAT3 inhibitors. STAT3 inhibitors have been used in long-term studies in rats and mice. Data from mouse studies are relevant in human research because almost 99% of mouse genes resemble the human genome. The NCI was looking for a new drug for chemoprevention studies in women genetically predisposed to developing breast cancer. A STAT3 inhibitor was selected, and long-term studies in mice and rats found it effective and safe to prevent mammary cancer. Mice were treated for up to 152 days, equivalent to 17 years in humans. This long-term data clearly indicates the safety of STAT3 inhibition [61]. Understanding the precise role of STAT3 in all these diseases has become increasingly important in recent years. Dissecting the complex functions of this protein can give us valuable insights into how these pathologies develop and progress, which can ultimately lead to the development of more effective treatments. Therefore, it is essential to continue investigating the function of STAT3 in all these diseases.

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