

# STAT signaling pathways in immune cells and their associated mechanisms in cancer pathogenesis

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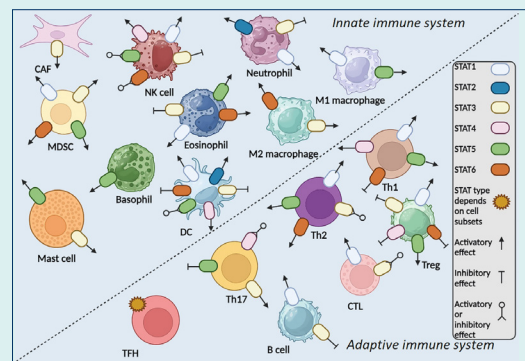
## Abstract

**Introduction:** Signal transducer and activator of transcriptions (STATs) factors as critical proteins in cell signaling regulate diverse biological processes such as differentiation and proliferation of cells. STATs have been shown to play distinct roles in modulating immune responses mediated by innate and adaptive immune cell subsets due to their significant roles in cytokine signaling.

**Methods:** In the current study, we review recent studies on the contribution of individual STAT proteins to cytokine signaling, development, and activity of diverse immune cells that constitute the whole immune system and help its performance against endogenous or exogenous agents with a particular focus on meaningful STAT factor in each of innate and adaptive immune cells' subsets to clarify their function in favor of the tumor or against it.

**Results:** Dysregulation of signaling pathways in the immune cells is associated with various immune disorders, such as the inability of immune system cells in the effective destruction of cancerous cells. Increase of knowledge about these pathways' functions is essential to understand how they can be effectively targeted to eliminate tumors.

**Conclusion:** The majority of immune cells use the Jak/STAT signaling pathway, which is one of the most important signaling pathways with a role in induction of proper immune responses. Since each of the STAT factors has a specific role in diverse immune cells' subsets, appropriate targeting of them can be a promising strategy for patients who suffer from immune system disorders; specifically it can be beneficial as an approach for cancer immunotherapy.



## Introduction

The immune system is basically divided into innate and adaptive immune systems, comprising cells that are known to act against endogenous or exogenous pathogens.<sup>1</sup> The innate immune system can be considered the fastest and frontline of immune defense against environmental agents. The innate immune system is known chiefly for neutrophils and macrophages (MQs) as phagocytes.<sup>2</sup> Natural killer (NK) cells are innate cytotoxic cells. These cells recognize infected cells by natural cytotoxicity receptors (NCRs).<sup>3</sup> Other cells such as cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), eosinophils, basophils, mast cells, and dendritic cells (DCs) are included in this category. The

distinguishing superiority of the adaptive immune system over the innate immune system is the existence of memory cells and advanced recognition systems. The adaptive immune system consists of the humoral (B cell) and cellular immune (helper T cells (Ths), regulatory T (Treg) cells, and cytotoxic T lymphocytes (CTLs)) systems. The humoral immune system consists of B cells, which get activated by the B cell receptor (BCR) that is necessary for their activation, differentiation, and immunoglobulin (Ig) production.<sup>4</sup> Two fates of B cells would be developing into plasma cells or memory B cells. Igs stimulate the complement system to trigger the destruction of bacterial cells. Moreover, antibodies ease the opsonization of foreign particles. The cellular immune system is mainly



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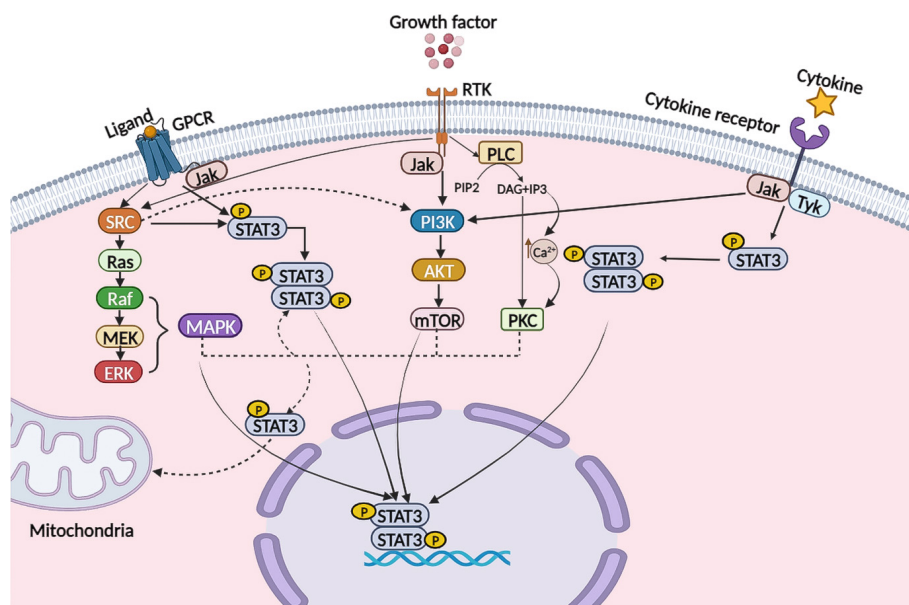
composed of T cells. T cells interact with antigen-presenting cells (APCs) through major histocompatibility complex (MHC) molecules and receive signals by T cell receptor (TCR) to counteract the pathogen directly (CD8<sup>+</sup> T cells kill infected cells) or by other immune cells such as B cells and make them produce antibodies (especially CD4<sup>+</sup> T cells).<sup>5</sup> T lymphocytes also have regulatory effects on the immune system, which is discussed in more detail below. Immune system components are associated with each other by divergent signaling pathways, which make this complicated plexus to do their function. Immune cells express numerous types of signaling molecules for different goals such as differentiation, recognition, antigen presentation, immunogenic function, nourishment, apoptosis, and interaction with immune or non-immune cells. Learning about these pathways can be a promising way to understand immune cells' cross-talking and ,subsequently help us use the information to direct some parts of the immune system for particular therapeutic goals such as treatment of autoimmune disease, cancer, and rejection of transplanted organs, and disease progression/regression foresight.<sup>6-8</sup> One of the most significant signaling pathways employed in the majority of immune cells is the Janus kinase (Jak)/signal transducer and activator of transcription (STAT) signaling pathway.

STAT proteins are known as regulators of various biological processes like cellular maintenance, proliferation, immunity, and differentiation that occur after exposure to various agents consisting of growth factors, cytokines, and other stimuli.<sup>9,10</sup> Gene ablation investigations of the various STATs discovered their crucial functions, notably in the formation and maintenance of blood and immune cells.<sup>11</sup> Every STAT comprises between 750 and 900 residues of amino acids.<sup>12</sup> Seven members of this protein exist: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Although the mentioned STATs have some similarities, each of them is located in a special chromosomal location and responds to specific extracellular stimuli, thus regulating different cellular processes.<sup>13,14</sup> Six domains organize STAT proteins, i.e., the N-terminal domain (NTD), coiled-coil domain (CCD), deoxyribonucleic acid (DNA) binding domain (DBD), linker domain (LD), Src-homology 2 (SH2) domain, and transcription activation domain (TAD).<sup>15</sup> Entering the nucleus and STAT-constant dimerization are done through the NTD.<sup>16</sup> The DBD is used for attaching to particular palindromic sequences in the promoters of objective genes.<sup>17</sup> The CCD domain mediates cooperation among several proteins related to nuclear import and export.<sup>18</sup> The SH2 domain is needed to recognize tyrosine phosphorylation on receptor subunits.<sup>19</sup> Finally, the TAD, located in the C-terminal region and encompassing tyrosine and serine phosphorylation sites, is required for the highest STAT-regulated gene transcriptional activation.<sup>20</sup> Mechanistically, cytokine receptors are

phosphorylated through the Jak. This process can activate cytokine receptor-associated kinases that phosphorylate the STAT molecules in the tyrosine site. The SH2 domain exerts the function of homo- or hetero-dimerization of two STAT molecules and lets them transmit to the nucleus for attaching to special DNA elements for mediating specific gene expression.<sup>21</sup> Targeting the Jak/STAT pathway during type I and type II cytokine signal transduction has been found to exert positive therapeutic benefits in the area of numerous autoimmune disorders, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis (PsO), and inflammatory bowel disease (IBD) and various cancers.<sup>22</sup> There are specific Jak inhibitors for each autoimmune disorder. For instance, Tofacitinib, baricitinib, upadacitinib, and peficitinib are the four oral inhibitors of Jak and subsequent downstream STAT proteins that have been authorized for the treatment of RA. Tofacitinib was the first JAK1/JAK2/JAK3 inhibitor with a greater preference for JAK1 and JAK3 to be authorized by the European Medicines Agency (EMA; March 2017) and US Food and Drug Administration (FDA; November 2012) to treat moderate-to-severe active RA.<sup>23</sup> In summary, the interactions between the Jak/STAT pathway and pathways mediated by other immune receptors possess the capability to regulate cytokine signaling in various immune cells. Therefore, considering cytokine signaling and their related Jak/STAT signaling pathway is crucial in immune cells and treating different related disorders.<sup>24</sup> A comprehensive search was conducted throughout the Web of Science, PubMed, and Scopus databases to retrieve scholarly papers in the categories of original research, literature reviews, systematic reviews, and meta-analyses. The search was limited to articles published before to the year 2023. In this review, we review new findings about the function of STAT proteins in the battle against cancer, specifically how these proteins influence cytokine signaling, development, and activity in innate and adaptive immune cell subsets.

### Overview of the JAK/STAT-3 pathway

STAT3 is located in chromosomal region 17 and exists in eukaryotes with conservation.<sup>25</sup> Phosphorylation of the linked Jak's intracellular domain is instantly triggered when cytokines attach to the tyrosine kinase-associated receptor on the cell membrane. The phosphorylated tyrosine site on Jak serves as a binding point to attract STAT3 with the SH2 domain for phosphorylation alteration. Moreover, the phosphorylated STAT3 is transported to the nucleus to interact with the genes and control specific transcriptional activity (Fig. 1).<sup>26</sup> It has been revealed that the expression of the STAT3 target gene can be stimulated in the case of recruiting nuclear factor- $\kappa$ B (NF- $\kappa$ B) and Lys-685 acetylation without requiring STAT3 phosphorylation.<sup>27</sup> Histone



**Fig. 1.** STAT3 signaling pathway. After induction of GPCR, RTK, and cytokine receptors by their associated ligands, STAT3 undergoes Y705 phosphorylation, forms homodimers or heterodimers, and moves to the nucleus where it transcriptionally affects several biological activities. These receptors work via engaging adaptor kinases (like Jaks and SRC) to spread downstream signals since, except for receptor tyrosine kinases, they lack intrinsic kinase activity. Furthermore, serine/threonine kinases (such as MAPK, mTOR, and PKC) can phosphorylate STAT3 at S727, enhancing STAT3 transcriptional function in the cell's nucleus or guiding STAT3 to the mitochondria. Abbreviations: AKT: protein kinase B;  $Ca^{2+}$ : calcium ion; DAG: diacylglycerol; ERK: extracellular signal-regulated kinase; GPCR: G-protein coupled receptor; IP3: inositol triphosphate; Jak: Janus kinase; MAPK: mitogen-activated protein kinase; MEK: mitogen-activated protein kinase; mTOR: mechanistic target of rapamycin; P: phosphorylation; PI3K: phosphatidylinositol 3-kinase; PIP2: phosphatidylinositol 4,5-bisphosphate; PKC: protein kinase C; PLC: phospholipase C; RAF: rapidly accelerated fibrosarcoma; RAS: rat sarcoma virus; RTK: receptor tyrosine kinase; S727: serine 727; SRC: proto-oncogene tyrosine-protein kinase; STAT: signal transducer and activator of transcription; Tyk: Non-receptor tyrosine-protein kinase; Y705: tyrosine 705.

acetyltransferases (like CREB-binding protein (CBP)/ histone acetyltransferase p300 (p300)) acetylate lysine 685 (K685) and histone methyltransferases (like histone-lysine N-methyltransferase SET9 (SET9)) methylate lysine 140 (K140), favoring or impairing STAT3 transcriptional function, respectively.<sup>28</sup> Two isoforms with diverse functions, including STAT3 $\alpha$  and STAT3 $\beta$ , organize STAT3. Phosphorylation of tyrosine 705 (Y705) or serine 727 (S727) results in STAT3 activation.<sup>29</sup> However, S727 deficiency in STAT3 $\beta$  causes this isoform activation just in the condition of Y705 phosphorylation. STAT3 $\alpha$  can exert transcription activity better than STAT3 $\beta$ . On the other hand, STAT3 $\beta$  is more potent for binding to specific DNA sites in contrast to STAT3 $\alpha$ . Some stimulus consisting of interferon (IFN)-Is, interleukin (IL)-21, IL-27, granulocyte colony-stimulating factor (G-CSF), and leptin, the members of IL-10 family (IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26), and the participants of IL-6 family (ciliary neurotrophic factor) CNTF(, leukemia inhibitory factor (LIF), oncostatin M) OSM(, cardiotrophin-1 (CT-1), IL-6, IL-11, IL-31, etc.) possess the capability to induce STAT3.<sup>10,30,31</sup> STAT3 plays different roles including controlling Th17 cells' differentiation, improving tumor progression activity of tumor-associated macrophages (TAMs) and MDSCs, hampering cell apoptosis in multiple myeloma patients, resistant to chemotherapy in high-grade breast cancers, and modulating cancer stem cells (CSCs).<sup>32-35</sup>

Hypoxia-inducible factor-1 $\alpha$ -Jak1-STAT3, retinol-binding protein 4-Jak2-STAT3, IL-6-Jak2-STAT3, and IL-6-Jak1-STAT3 have been considered the pathways by which CSCs' survival increases during breast or colon cancer.<sup>35</sup>

### The role of STATs in the innate immune system *Cancer-associated fibroblasts*

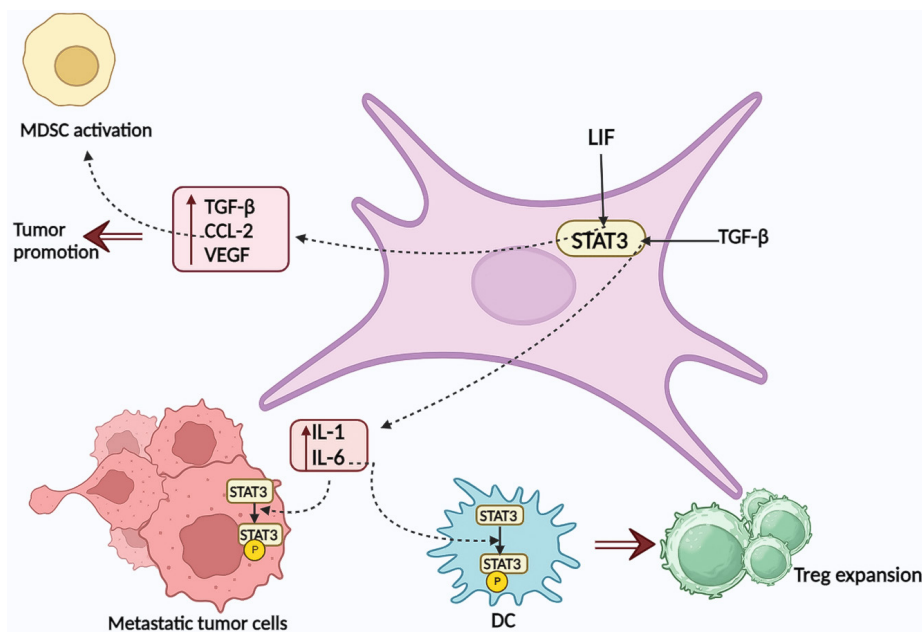
CAFs, as the resident cells in the tumor's mass milieu, mostly originate from mesoderm, similar to the other fibroblasts. They have interlinking functions between tumor cells and the immune system, so these cells have been studied to see if they can be utilized in cancer immunotherapy. It is shown that CAFs use various signaling pathways, such as STATs, to produce the mentioned effects.<sup>36</sup> Accumulating evidence suggests that a reduction in longevity in patients with colorectal cancer can be associated with STAT3 phosphorylation in CAFs.<sup>37</sup> Multiple cytokines, such as leukemia inhibitory factor (LIF), can intensify activation of STAT3 in CAFs, resulting in the production of immunosuppressive factors, including transforming growth factor beta (TGF- $\beta$ ), chemokine (C-C motif) ligand 2 (CCL-2), and vascular endothelial growth factor (VEGF) for the tumor-promoting function of these fibroblasts.<sup>38,39</sup> Moreover, IL-1 and IL-6 are secreted from TGF- $\beta$ -stimulated CAFs, leading to glycoprotein 130 (GP130)/STAT3 signaling in

tumor cells and establishing further metastasis.<sup>40,41</sup> Elevated STAT3 activity in CAFs also affects other immune cells. For example, secreted CCL-2 through CAFs with STAT3 hyperactivation may trigger MDSC immunosuppressive activation in hepatocellular carcinoma.<sup>39</sup> CAFs-secreted IL-6 increases STAT3 activation in DCs, which enables them to expand Treg cells and inhibit effector T-cell proliferation (Fig. 2).<sup>42</sup>

### Myeloid-derived suppressor cells

MDSCs are the activated forms of monocytes and neutrophils, capable of immunosuppressive effects. MDSCs are classified into two subgroups, named monocytic MDSCs (M-MDSCs) and granulocytic/polymorphonuclear MDSCs (PMN-MDSCs), based on the monocytic or granulocytic myeloid cell lineages. They get activated to restrict chronic infection and autoimmune disease, although they deteriorate malignancy-caused conditions in the body. MDSCs, like many other immune cells, use the plexus of interlinking signal pathways such as STAT pathways for their survival and action.<sup>43,44</sup> Some studies displayed that STAT1 can play a role in IFN- $\gamma$  and IL-1 $\beta$  activation, and this protein loss in MDSCs inhibits their suppressive effects on T cells due to lack of nitric oxide synthase (iNOS) and arginase activation.<sup>45</sup> The MDSC population can be decreased due to IFN regulatory factor-8 (IRF-8) overexpression. It has been revealed that induction of G-CSF/granulocyte-MQ colony-stimulating factor (GM-CSF) diminishes IRF-8 expression after recruiting STAT3 and STAT5 pathways in these cells.<sup>46</sup>

Although several mechanisms could regulate the production of reactive oxygen species (ROS) in different cells, in MDSCs, it has been indicated that STAT3, by increasing activation of NADPH oxidase (NOS) 2, has a vital role in the production of augmented ROS. Moreover, STAT3 activation mediates MDSC generation and migration by regulating the S100 calcium-binding protein A8 (S100A8) and S100A9 expression.<sup>47,48</sup> Moreover,  $\beta$ 2 adrenergic receptors on MDSCs can be mediated through STAT3,<sup>49</sup> and the IL-6/STAT3 axis regulates MDSC differentiation in tumor microenvironment (TME).<sup>50</sup> Peng Qu et al. and colleagues, in their study about lung bronchioalveolar adenocarcinoma, have demonstrated that increased expression of STAT3 in lung alveolar cells induced production of IL-6 and IL-1 $\beta$ , resulting in MDSC enhancement in the lung. All of the above indicated that STAT3 led to inflammation and tumor progression via augmenting MDSC involvement.<sup>51</sup> Another study revealed that enhancement of suppressors of cytokine signaling (SOCS) 1 as STAT3 inhibitor occurs after stimulator of IFN genes (STING) induction leading to tumor suppression via regulating MDSC differentiation.<sup>52</sup> Furthermore, in the mice model of breast cancer, utilizing both direct suppressor of STAT3 (HJC0152) and STING agonist c-diAM (PS)2 is associated with enhancement of CD8<sup>+</sup> T cells and also reduction of Treg cells and MDSCs in the TME.<sup>53</sup> Another inhibitory function of STAT in MDSCs can be defined by the STAT6 subtype, which can be activated after IL-4 and IL-13 attachment to CD124 receptors in mentioned cells, leading to overexpression of



**Fig. 2.** Different roles of STAT3 in CAFs. LIF can accelerate STAT3 activation in CAFs, leading to the synthesis of immunosuppressive substances, including TGF- $\beta$ , CCL-2, and VEGF, for the tumor-promoting activity of these fibroblasts. TGF-stimulated CAFs release IL-1 and IL-6, which activate STAT3 signaling in tumor cells and promote further metastasis. MDSC immunosuppressive response may be brought on by secreted CCL-2 through CAFs with hyperactivated STAT3. Furthermore, CAFs-secreted IL-6 increases STAT3 activation in DCs, which enables them to expand Treg cells. Abbreviations: CAF: cancer-associated fibroblast; CCL: chemokine (C-C motif) ligand; DC: dendritic cell; IL: interleukin; LIF: leukemia inhibitory factor; STAT: signal transducer and activator of transcription; TGF- $\beta$ : transforming growth factor beta; Treg: regulatory T; VEGF: vascular endothelial growth factor.

TGF- $\beta$  and arginase and further diminishing of T cell and M1 MQ recruitment.<sup>45,54</sup>

### Neutrophils

Neutrophils, also called PMN leukocytes, are the most affluent circulating granulocytes. They are known as the frontline of immune defense cells and play the role of phagocytes. PMNs are derived from bone marrow in a naïve form, which means they need to be differentiated and activated, and the Jak/STAT signaling pathways can play an essential role in this procedure.<sup>55</sup> As mentioned before, survival, activation, and differentiation of neutrophils can be controlled by the involvement of type II cytokine receptors and following the Jak/STAT signaling pathway.<sup>56,57</sup> Moreover, Jak/STAT, besides phosphoinositide 3-kinases (PI3K) signaling, has the potential of controlling the anti-apoptotic B cell lymphoma-2 (Bcl-2) family protein A1/Bcl-2 related gene expressed in fetal liver (BFL-1) expression by which neutrophils mediate their maintenance and hemostasis.<sup>58</sup> Some investigations demonstrate that all-trans retinoic acid (atRA) increases SOCS1 expression for suppressing STAT1, which leads to lower neutrophil gathering, enhances N2 neutrophil phenotype polarization, and declines neutrophil extracellular traps (NET) organization.<sup>59</sup> STAT2 besides extracellular signal-regulated kinases (ERK), protein tyrosine kinase 2 (PTK2), rat sarcoma virus (RAS), rapidly accelerated fibrosarcoma (Raf)-1, I $\kappa$ B, and GBY involves in N1 phenotype signaling.<sup>60</sup> It is better to note that Oncostatin M (OSM) (neutrophil-derived granule cargo) involves Jak/STAT, PI3K, and mitogen-activated protein kinase (MAPK) signaling pathways by which tumor angiogenesis and neovascularization occur, mainly in skin squamous cell carcinoma.<sup>61,62</sup> Additionally, in acute inflammation, infiltration of inflammatory neutrophils is restricted after IL-6-induced STAT3 activation. Thus, the activation of STAT3 after IL-6 induction is essential for ending the innate immune response in such inflammations.<sup>58</sup> Another study has displayed that the outcome of cross-talk between tumor-associated neutrophils (TANs) and neoplastic cells is GM-CSF secretion from tumor cells, which in turn induces neutrophil synthesis and IL-6 generation. IL-6 can also boost VEGF-A production via the Jak/STAT signaling pathway to tumor progression.<sup>63</sup>

### Eosinophils

Eosinophils are bone marrow-derived granulocytes. An activated eosinophil gets degranulated and releases variant proinflammatory molecules. It is known that these cells are also capable of immunomodulatory effects. Eosinophils are a part of IgE-mediated hypersensitivity reactions. STAT signaling pathways are necessary for the eosinophil's function and survival.<sup>64</sup> Based on investigations, IL-31 attachment to the IL-13 receptor

of eosinophil activates Jak/STAT, leading to the postponement of eosinophil apoptosis and provoking the release of proinflammatory cytokines and chemokines.<sup>65,66</sup> In nasal polyps, phosphorylated-STAT3 (pSTAT3) and VEGF expression and eosinophil infiltration were elevated displaying that VEGF and eosinophil infiltration can be controlled via STAT3.<sup>67</sup> In another study, it has been indicated that the majority of malignant T cell patients who had positive staining for phosphor-Y705 of STAT3 (pY-STAT3), contained positive stains for eosinophils, too.<sup>68</sup> Surprisingly, IL-5 (which mainly plays a role in the proliferation and differentiation of B cells) activates Jak2-STAT1/STAT5 and MAPK pathways for controlling genes correlated with the survival, proliferation, and effector function of eosinophils.<sup>69-71</sup> Studies also demonstrated that in atopic dermatitis (AD), eosinophil skin infiltration needed the activation of STAT6.<sup>72</sup>

### Basophil and Mast cells

Basophils, as a member of granulocytes, can release the granules and produce inflammatory cytokines like IL-4 and IL-13 while activated by endogen or exogenous stimuli such as IgE-mediated pathways.<sup>73</sup> Mast cells, which are also called mastocytes, take part in both innate and adaptive immune systems. They are found in tissues such as skin, mucosal surfaces, and many other sites of the body. Mast cells have antibacterial and anti-parasitic functions and contribute to inflammatory disorders as they are a part of immune system cells in tissues under chronic inflammation. STAT proteins are the crucial signal transducers to activate these two types of innate immune cells.<sup>74</sup> In associated disease with allergy, mast cell mitochondrial STAT3 is a vital factor in their degranulation. Some experimental evidence indicated that utilizing the mast cell mitochondrial STAT3 inhibitors can alleviate exocytosis and cytokine secretion due to phosphorylation of STAT3 in serine 727 and reduction of oxidative phosphorylation (OXPHOS) function. A diminish in the level of blood histamine exemplifies the importance of such inhibitors.<sup>75</sup> It has been indicated that the STAT5 transcription factor (TF) connects to the promoter and an intronic region of the GATA-binding factor 2 (*Gata*)2 gene, which is essential for maintaining the Fc receptor-chain (*Fcer*)1a messenger ribonucleic acid (mRNA) and expression of high-affinity Fc receptor for immunoglobulin E (Fc $\epsilon$ R) I $\alpha$  protein in mast cells and basophils. In mast cells, GATA2 also has the ability to maintain the expression of KIT proto-oncogene (*Kit*) mRNA and c-Kit protein. Furthermore, the synthesis of histamine and expression of *Il4* mRNA depends on GATA2. Generally, differentiation (from pre-bone morphogenetic proteins (BMPs)) and maintenance of mast cells and basophils require the STAT5-GATA2 pathway.<sup>76</sup> Based on relevant studies, IL-3, which is a crucial factor in mast cell and basophil biology besides

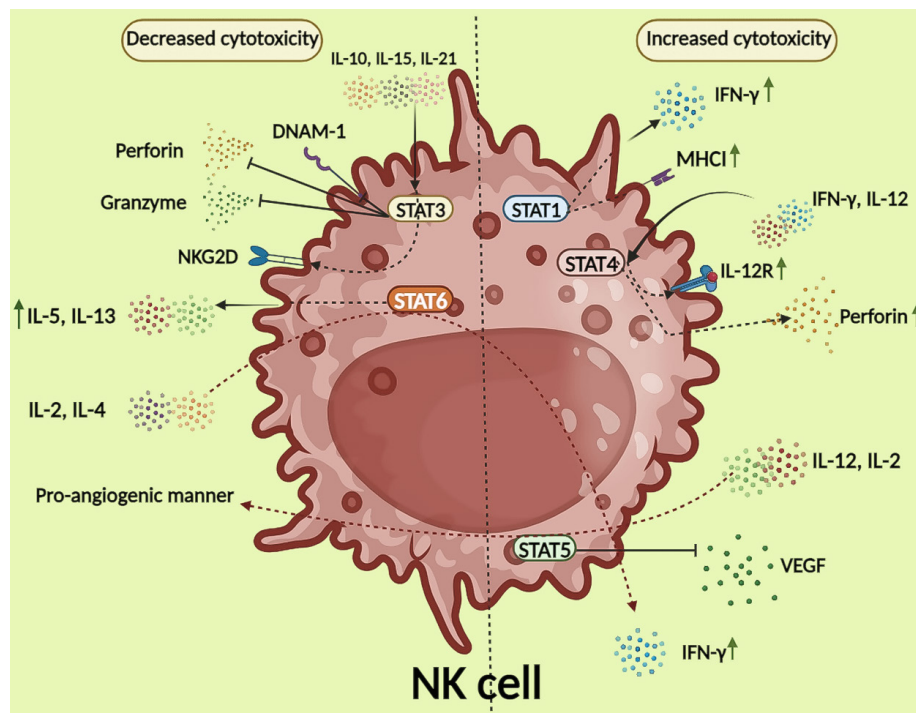
the Fc $\epsilon$ RI signaling pathway, activates phosphorylated STAT5. Furthermore, IgE-mediated mast cell activation resulting in degranulation and production of cytokines requires STAT5 activation, too.<sup>77,78</sup>

### **Natural killer cells**

NK cells are granular lymphocytes found in most body tissues and are a part of the innate immune system. They are specified to kill microorganisms and infected cells and are capable of tumor-destructive effects. These cells perform their cytotoxic actions through the Jak/STAT pathway.<sup>79</sup> Various cytokines including IFNs, IL-2, IL-7, IL-12, IL-15, IL-21, and IL-27 are needed for NK cell maturation and activation. These cytokines exert their functions through the downstream Jak/STAT pathway.<sup>80</sup> STAT family members have different functions in NK cells in a way that STAT1, STAT4, and STAT5 positively influence NK cells and promote their cytotoxicity, while STAT3 and STAT6 hamper NK cell activation. IFN- $\gamma$  production and NK cell cytotoxicity are controlled by STAT1.<sup>81</sup> Here, we will discuss the main role of each STAT in NK cells. It has been revealed that MHC1 expression is lowered in a STAT1-deficient manner, which affects the responsive potential of NK cells.<sup>82</sup> STAT1 exists in immunological synapses between NK cells and target cells, including tumor cells. In this position, STAT1 can bind to different proteins and guide various processes.<sup>83</sup> Loss of STAT3 raises CD226 (as an activating receptor), perforin, and granzyme B expression. Moreover, STAT3 is involved in stimulating the expression of NK receptor group 2, member D (NKG2D) after induction of IL-10 and IL-21.<sup>84</sup> IL-15-activated STAT3 prohibits IL-15-induced STAT5, which is thought to mediate NK cell cytotoxicity.<sup>84</sup> IL-12 and IFN- $\gamma$  stimulate STAT4-mediated cytotoxicity in NK cells.<sup>85</sup> STAT4 can also bind to the perforin promoter of NK cells and up-regulates IL-12 receptor (IL-12R) expression.<sup>86,87</sup> STAT5 is the main regulator of NK cells due to its capability of controlling survival and cell growth as well as cell maturation and activation. Furthermore, STAT5 suppresses VEGF-A produced by NK cells, resulting in the inhibition of tumor progression.<sup>88</sup> It is attractive to speculate that the STAT5B defect (despite STAT5A) is paralleled by the reduction of NK cell numbers and weakens its cytolytic responses.<sup>89</sup> STAT5B possesses the potential of down-regulating VEGF-A expression as the promising tumor-promoting factor.<sup>90</sup> Interestingly, activated STAT5 following IL-2 and IL-12 induction has a pro-angiogenic manner besides NK cell cytotoxicity.<sup>91,92</sup> In NK cells, STAT6 provokes the production of IL-5 and IL-13 and restricts their associated cytotoxicity.<sup>93</sup> Nevertheless, besides its tumor-promoting effect, STAT6 can exert a tumor-suppressive effect by elevating IFN- $\gamma$  expression after IL-2 and IL-4 co-stimulation with NK cells (Fig. 3).<sup>94</sup>

### **Macrophages**

MQs are the famous phagocytes of the immune system. They are found at extravascular sites and react to exogenous pathogens, injured cells, and cellular debris, so they play a role in tissue injury repair. MQs receive signals from the periphery through STAT signaling pathways, which make them mature and activated.<sup>95</sup> STAT1 activation is triggered through IFN- $\gamma$  leading to boost proinflammatory cytokine production. Thus, polarization to M1 MQs is induced. Moreover, iNOS and IL-12 transcription in M1 MQ is promoted by IFN- $\gamma$ -induced STAT1.<sup>96</sup> In MQs, IRF5, activated by proinflammatory cytokines, affects IFN- $\gamma$ /Jak/STAT1 positively. However, IRF4, activated by anti-inflammatory cytokines, inhibits the IRF5 effect on these cells.<sup>97,98</sup> Conversely, reprogramming of the M2 MQ phenotype occurs after IL-4, IL-13, and IL-10 stimulation and following Jak/STAT-signaling activation. After IL-4 stimulation, STAT3 and STAT6 play a role in polarization to M2 phenotype. The expression of cellular Myelocytomatosis (c-Myc) is induced to up-regulate the expression of the M2 phenotype genes, including scavenger receptor class B type 1 (Scarb1), MQ mannose receptor (Mrc1), STAT6, and peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ).<sup>99,100</sup> IL-13 has the potential to activate STAT1, STAT3, and STAT6. The expression of resistin-like molecule alpha 1 (Fizz1), chitinase-like protein (Ym1), mannose receptor, and anti-inflammatory cytokines as M2 phenotype genes is enhanced through STAT3 and STAT6. In contrast, STAT1 is involved in the activation of proinflammatory cytokines. Thus, the prevalence of STAT3 and STAT6 over STAT1 activation possesses the capability to justify the anti-inflammatory response of IL-13.<sup>101</sup> It has been revealed that the expression of the M2 phenotype genes including TGF- $\beta$  and IL-10 is stimulated. Also the genes implicated in the production of M1 cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are suppressed through IL-10 attachment to its specific receptor and subsequent Jak1 and STAT3 activation.<sup>102</sup> SOCS1 and SOCS3 are two significant regulators of the Jak/STAT signaling pathway in M1/M2 MQs.<sup>103</sup> M1 phenotype development is suppressed when SOCS1-induced IL-4 hampers STAT1. SOCS3 blocks STAT3 via IFN- $\gamma$  and toll-like receptor (TLR) 4 ligands, leading to the inhibition of M2 phenotype formation.<sup>104</sup> Simultaneously, STAT6 (the M2 phenotype transcription factor) and STAT1 (necessary for M1 phenotype formation) are activated by SOCS1 and SOCS3, respectively.<sup>101</sup> Other studies indicate that STAT5 signaling in MQs is activated through tumor-derived GM-CSF. STAT5 deficiency in MQs enhances expression of tumor-promoting factors and increases tumor cell migration and metastasis.<sup>105</sup> A previous study revealed that aging leads to diminished MQ response to some signals such as IFN- $\gamma$  and lipopolysaccharides (LPS). Reduced tyrosine phosphorylation of STAT1  $\alpha$



**Fig. 3.** Different functions of STAT family members in NK cells. STAT1 can increase IFN- $\gamma$  and MHCII production. STAT3 diminishes DNAM-1, perforin, and granzyme B expression. Moreover, STAT3 stimulates the expression of NKG2D after induction of IL-10 and IL-21. STAT4 can also bind to the perforin promoter of NK cells and up-regulate IL-12R expression. IL-12 and IFN- $\gamma$  stimulate STAT4-mediated cytotoxicity in NK cells via increasing the expression of perforin IL-12R. Furthermore, STAT5 suppresses VEGF-A produced by NK cells, resulting in the inhibition of tumor progression. On the other hand, activated STAT5 following IL-2 and IL-12 induction has a pro-angiogenic manner besides NK cell cytotoxicity. In NK cells, STAT6 provokes the production of IL-5 and IL-13 and restricts their associated cytotoxicity. STAT6 can exert a tumor-suppressive effect by elevating IFN- $\gamma$  expression after IL-2 and IL-4 co-stimulation with NK cells. Abbreviations: DNAM-1; DNAX accessory molecule-1; IFN- $\gamma$ ; interferon gamma; IL: interleukin; IL-12R: interleukin 12 receptor; MHCII: major histocompatibility complex class II; NK: natural killer cell; NKG2D; STAT: signal transducer and activator of transcription; VEGF: vascular endothelial growth factor.

and  $\beta$  explains the reason for this phenomenon, which in turn restricts STAT1 gene expression. The mentioned mechanism explained why tumor-killing potential and nitrogen and oxygen species generation are lower in the MQ of aged people in contrast to young ones.<sup>106</sup>

### Dendritic cells

DCs are the most potent cells for antigen capture and presentation and are also called APCs. DCs are divided into two major subgroups named plasmacytoid DCs (pDCs) and conventional DCs (cDCs), which have two types: cDC1 and cDC2. cDC1 is specified to activate Th1, and cDC2 activates follicular helper T (Tfh) cells. cDCs interaction with T cells is basically under the control of STAT signaling pathways.<sup>107,108</sup> The different roles of each STAT will be further defined. IFN-I-induced STAT1 augments the activation and maturation of DCs via upregulating the expression of MHC and co-stimulatory molecules for presenting antigens to T cells effectively.<sup>109</sup> It has been revealed that the cDC activation and their related potential for cross-presenting antigens to CD8<sup>+</sup> T cells are enhanced after induction of TLR3, -4, -7, and -9 and subsequent STAT2 activation.<sup>110,111</sup> About the STAT3 protein roles in DCs, it should be declared that FMS-like tyrosine kinase three ligand (FLT3L) despite

IL-32 enables STAT3 to up-regulate the expression of Pu.1 which is required for the differentiation of DCs.<sup>112</sup> Previous studies demonstrated that STAT3 can regulate the development of pDC but not CD103<sup>+</sup> DCs and GM-CSF/IL-4-derived monocyte-derived DC (moDCs) from bone marrow.<sup>113,114</sup> Furthermore, the decreased expression of MHC and co-stimulatory molecules and the following inhibited T-cell induction can occur after IL-10-mediated STAT3 stimulation.<sup>115</sup> Additionally, IL-6/IL-10-induced STAT3 results in enhanced activation of Treg and the generation of tolerogenic DCs.<sup>116,117</sup> Fukao et al, in their study for inducible expression of STAT4 in DCs and MQs, have demonstrated that STAT4 expression can be augmented in the presence of TNF- $\alpha$  and IL-1 $\beta$  leading to moDC maturation.<sup>118</sup> It has been suggested that GM-CSF-mediated STAT5 activation is related to enhanced differentiation of cDCs (CD103<sup>+</sup> DCs), as well as suppression of FLT3L-dependent pDCs and CD8<sup>+</sup> cDCs formation. In addition to suppressing the transcription factors IRF7, IRF8, and Spi-B, as well as certain receptors, including TLR9 and FLT3, necessary for the growth of pDCs, GM-CSF/STAT5 also stimulates IRF4, which is necessary for cDC development.<sup>119-121</sup> Due to the induction of cytokine-induced SH2-containing protein (SHP2) and SOCS1, SOCS2, and SOCS3 during DC maturation, it has

been shown that the STAT6 signaling pathway remains less active in mature DCs (mDCs) as opposed to immature DCs (iDCs), suggesting that DC maturation depends on STAT6 signaling pathway suppression.<sup>109</sup> The main roles of STAT protein in each innate immune cell are indicated in Table 1.

### The role of STATs in the adaptive immune system cells Helper T cells

T cells are a major part of the adaptive immune system. CD4<sup>+</sup> T cells, which are commonly known as Th cells, are the lymphocytes divided into many types like Th1, Th2, Th17, and follicular Th cells.<sup>122</sup> The vital role of Jak and STAT in the polarization of different Th cells has been proven so that irregularities in these pathways are correlated with multiple immunological disorders.<sup>123</sup> Not only are Jak and STAT involved in Th cell function, but we can also see other signaling molecules such as PI3K, MAPK, and ERK.<sup>124</sup>

#### Th1 cells

Th1 activation is intended to create a defense against intracellular infections. T-box transcription factor TBX21 (bet) is the primary TF. However, other important TFs for Th1 polarization include STAT1, which is essential for IFN- $\gamma$  signaling, and STAT4, which is required for IL-12 signaling, are involved.<sup>125</sup> In Th1 cells, IL-12 and TCR trigger Map3K8, which STAT4 binds to directly. This Map3K8 then activates downstream ERK, leading to an increase in the production of cytokines.<sup>126</sup> Interestingly, STAT5A and STAT5B play roles in Th1 and Treg through the expression of T-bet and forkhead box P3 (FOXP3), respectively.<sup>127</sup> Th1-particular pathways are blocked via STAT6, too. It has been recommended that Th1 can be silenced through the attachment of STAT6 to the particular site of the *IL4* promoter.<sup>128</sup>

#### Th2 cells

Th2 cells stand against parasites and develop allergic responses. IL-4, IL-5, and IL-13 are the main products of these cells. GATA3 is known as a specific TF for Th2 cells.<sup>129</sup> STAT6 is a factor for Th2 polarization and also inhibits Th1 polarization. Although some studies have indicated that Th2 polarization can happen even with the loss of STAT6.<sup>130</sup> Phosphorylation of STAT6 in CD4<sup>+</sup>CD161<sup>+</sup> T cells is enhanced in asthmatic patients, resulting in IL-4 and IgE level augmentation, and STAT3 and STAT6 are in turn activated through IL-4 and IL-13, while in monocytes, IL-13 can affect just the activation of STAT1.<sup>131</sup> I-Cheng Ho and coworkers in their study about essential functions before and after Th2 differentiation have displayed that differentiation of Th2 cells and B cell class switching leading to IgE production occurred after the effect of the IL-4/STAT6 axis in asthma.<sup>132</sup> T cells with impaired STAT6 activity are incapable of decreasing the expression of the cell cycle-dependent kinase inhibitor p27KIP after IL-4 provocation, leading

**Table 1.** The total function of STATs in the innate immune cells

Cell type	Main triggered STAT(s)	Total role of triggered STAT(s) in related cell	References
CAFs	STAT3	Activatory	38, 39
	STAT1	Activatory	45
MDSCs	STAT3	Activatory	47
	STAT5	Activatory	46
	STAT6	Activatory	54
Neutrophils	STAT1	Activatory	59
	STAT2	Activatory	60
Eosinophils	STAT3	Inhibitory	58
	STAT1	Activatory	71
	STAT3	Inhibitory	72
	STAT5	Activatory	71
Basophils	STAT6	Activatory	72
	STAT5	Activatory	76
Mast cells	STAT3	Activatory	75
	STAT5	Activatory	76
NK cells	STAT1	Activatory	82
	STAT3	Inhibitory	84
	STAT4	Activatory	85
	STAT5	Activatory or inhibitory (based on conditions)	88, 91, 92
	STAT6	Activatory or inhibitory (based on conditions)	93, 94
M1 MQs	STAT1	Activatory	96
	STAT5	Activatory	105
M2 MQs	STAT3	Activatory	101
	STAT6	Activatory	101
DCs	STAT1	Activatory	109
	STAT2	Activatory	110
	STAT3	Inhibitory	112
	STAT4	Activatory	118
	STAT5	Activatory or inhibitory (based on condition)	119, 120

Abbreviations: CAFs: cancer-associated fibroblasts; DCs: dendritic cell; MDSCs: myeloid-derived suppressor cells; MQs: macrophages; NKs: natural killer cells; STAT: signal transducer and activator of transcription.

to hampered progression from the G1 to the S phase of the cell cycle.<sup>133</sup> It is interesting to clarify that STAT3 can raise Th2 cytokines and survival and extend their inflammatory effects.<sup>134</sup> However, Camille A Knosp and colleagues revealed that a lack of STAT3 activation was paralleled with increased Th2 cell responses.<sup>135</sup> Other studies have shown that in Th2 cells, expression of T1ST2 (a member of the IL-1R family), as IL-33R, is controlled by GATA3 and STAT5. Furthermore, STAT5 activators, including IL-2, IL-7, and TSLP, stimulate the expression of GATA3. Relative findings have also demonstrated that T1ST2, expressed on Th2 cells, triggers IL-13 generation in a NF- $\kappa$ B and p38-dependent manner.<sup>136</sup> Thereby, two factors are required for Th2 cell differentiation. The first



is STAT3, which is required to attachment STAT6 to its target gene. Another factor is STAT5A/B, which increases the expression of GATA3 and IL-4Ra.<sup>72</sup> Another finding revealed that STAT1 can be activated through histamine recruitment, which affects the Th2 response, and subsequent AD is observed.<sup>137</sup>

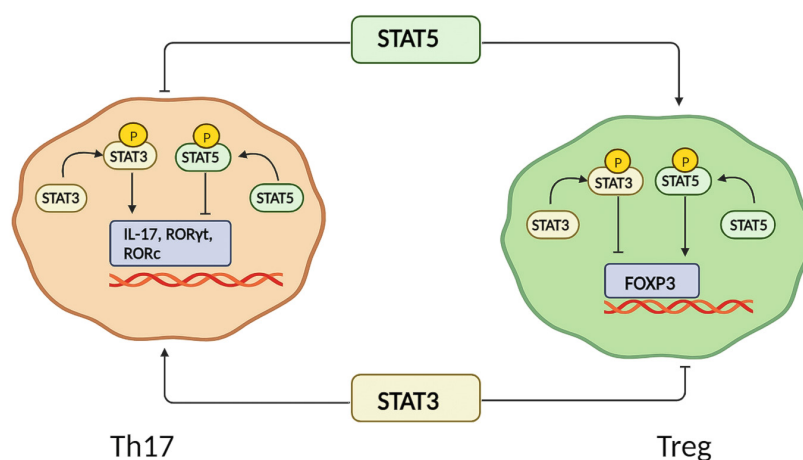
#### Th17 cells

Th17 cells will be activated against extracellular bacteria. RAR-related orphan receptor gamma (ROR $\gamma$ t), as the main TF of these cells, is induced via STAT3, and both of these factors up-regulate the expression of IL-17 (Fig. 4).<sup>138</sup> Although Th17 can play a role in inducing inflammatory conditions, it can have a suppressive effect on the immune system during cancer. Chalmin and colleagues have indicated that during Th17 cell differentiation, IL-6/ STAT3 axis and growth factor independence-1 (Gfi-1) transcription, which is down-regulated as a result of TGF- $\beta$ , increased the expression of CD39 and CD73 ectonucleotidases. CD39 and CD73 ectonucleotidases, via inducing adenosine release, contribute to inhibiting the effector functions of CD4<sup>+</sup> and CD8<sup>+</sup> T cells *in vitro*, leading to the inhibitory fate of Th17 cells in the immune system.<sup>139</sup> Some findings revealed that suppression of SOCS3 results in improved phosphorylation of STAT3 and following enhancement in IL-17 generation.<sup>140</sup> IL-17 expression is limited through STAT5 A/B which may inhibit ROR $\gamma$ t in Th17 cells (Fig. 4).<sup>141</sup> Furthermore, for Th17 cell lineage differentiation, there is competition between STAT3 and STAT5 for attaching to binding sites on *Il17* loci. After STAT5 attachment to the *Il17* gene locus, the nuclear receptor co-repressor 2 (NCOR2) is recruited to interact with STAT5.<sup>142</sup> In T-bet-deficient cells, the potential of hampering Th17 response via IFN- $\gamma$  and IL-27 decreases while even in STAT1-deficient T cells, T-bet possesses the capability to down-regulate IL-22, ROR $\gamma$ t, IL-17F, and IL-17A expression.<sup>143</sup> Two studies displayed that loss of STAT4 causes diminished production of IL-17 in Th17 cells although other investigations indicated

that STAT4 might not regulate the expression of IL-17, positively.<sup>144, 145</sup>

#### Follicular helper T cells

Tfh cells are a subset of Th cells. They adjust and coordinate B cells maturation and activity and, subsequently, the humoral immune responses. They are resident in germinal centers (GCs) of secondary lymphoid tissues. There are different subsets of Tfh consisting of Tfh1, Tfh2, Tfh3, and T follicular regulatory (Tfr). Activation of STAT signaling pathways induces Tfh cell differentiation and activation that are further defined with more details in each subset.<sup>146,147</sup> In acute viral infections, IFNs and IL-6-activated STAT1 cause induction of the Bcl-6 expression and trigger Tfh1 cell differentiation at an early stage.<sup>148</sup> T-bet is also a critical factor in Tfh1 expansion and maintenance.<sup>149</sup> STAT4 activated by IL-12 may contribute to the differentiation of Tfh1 cells, so a lack of STAT4 can lead to diminished production of IL-21 and IFN- $\gamma$  from Tfh1 cells.<sup>150</sup> Generally, some extra signals besides STAT1/4 are required for Tfh1 differentiation.<sup>146</sup> Further investigations demonstrate that IL-2-STAT5 and IL-2R expression is hampered by IL-4 in Tfh2 differentiation unlike the Th2 differentiation process.<sup>151</sup> Furthermore, Tfh2 differentiation is improved by IL-4-STAT6. Other findings revealed that in Tfh2 cells, cooperation of basic leucine zipper ATF-like transcription factor (BATF), STAT3, and STAT6 results in enhanced production of IL-4.<sup>152</sup> Whereas, STAT3 can play a suppressive role at the early stage of differentiation of Tfh2 cells.<sup>153</sup> It has been indicated that in the process of TFH formation, STAT3 might not be effective alone. TGF- $\beta$  besides cytokines that activate STAT3/STAT4 (IL23/IL12), can affect Tfh17 differentiation positively through increasing the expression of IL-21, C-X-C chemokine receptor type 5 (CXCR5), and Bcl-6.<sup>154</sup> Bcl-6 expression is suppressed through the IL-2/STAT5 axis which can impair Tfh differentiation.<sup>155</sup> Based on investigations, the concentration-dependent



**Fig. 4.** Opposed roles of STAT3 and STAT5 in Th17 and Treg cells. STAT5 induces FOXP3 expression in Treg cells while down-regulate the expression of IL-17, RORc, and ROR $\gamma$ t in Th17 cells. STAT3 acts totally in an opposed manner in contrast to STAT5 in the mentioned cells. Abbreviations: FOXP3: forkhead box P3; IL: interleukin; STAT: signal transducer and activator of transcription; Th: T helper; ROR: RAR-related orphan receptor.

manner of IL-2 is considered to guide Tfh, Treg, and Tfr differentiation. Tfh cells can be converted to Tfr-like cells during exposure to IL-2. Furthermore, IL-2-induced STAT3 develops the expression of FOXP3 and maintains the expression of Bcl-6 as well.<sup>155,156</sup> Thus, rather than being entirely distinct inhibitory agents, IL-2-STAT5 should be viewed as a controller of Tfr differentiation.<sup>156</sup>

### Regulatory T (Treg) cells

Another subset of T lymphocytes consists of the regulatory T cells called Treg cells. Treg has immunomodulatory function and tolerance to self-antigens by their special cytokine production and signaling, which results in the suppressive impact of these cells on autoimmunity. There are complicated signaling pathways, such as STATs for Treg cell differentiation and activation.<sup>157</sup> FOXP3 is the main TF in Treg cells.<sup>129</sup> The maintenance of *Foxp3* expression relies on the conserved non-coding sequence 2 (CNS2) region which contains binding sites for STAT5. Demethylation of this region occurs via STAT5, leading to the conversion of naïve CD4<sup>+</sup>FOXP3<sup>-</sup> T cells into CD4<sup>+</sup>FOXP3<sup>+</sup> induced Treg (iTreg)s (Fig. 4).<sup>158</sup> The promoter of the FOXP3 gene is a location to which STAT5 can bind. Thus, this STAT5 can help Treg differentiation by regulating FOXP3 expression.<sup>159</sup> STAT5 probably inhibits RORc thus STAT5A and STAT5B are known as factors by which Th17 differentiation is regulated, negatively (Fig. 4).<sup>141</sup> Any impairment in members of the IL-2/CD122/Jak3/STAT-5 signaling pathway causes thymic and peripheral Treg reduction.<sup>141</sup> Moreover, on iTregs, the expression of the IL-6 receptor is diminished by IL-2 to inhibit iTregs from differentiating to Th17 cells.<sup>160</sup> It has been indicated that for controlling iTreg development, STAT5 and STAT3 signaling should be balanced manner.<sup>142</sup> IL-4-dependent STAT6 and IL-12-dependent STAT4 block Treg development through decreasing STAT5 attachment to the promoter and/or CNS2 region of the *Foxp3* gene.<sup>161</sup> Furthermore, IL-6/STAT3 suppresses the expression of FOXP3.<sup>162</sup> Based on investigations, homeostasis and inhibitory function of Tregs are controlled by the IFN- $\alpha$  signaling pathway, and further phosphorylation of STAT5 and STAT1.<sup>163</sup>

### Cytotoxic T lymphocytes

CTLs are the differentiated form of CD8<sup>+</sup> T cells and capable of recognizing virus-infected cells and cancer cells to induce cytotoxicity against them by releasing the contents of the granules, which encompass lytic agents, also called lytic granules (LG).<sup>164</sup> It has been shown that induction of CTL is restricted after STAT1 deficiency, and this event has been decreased more in the case of mutation in the S727 phospho-receptor site.<sup>165</sup> Furthermore, multiple findings explained that S727-phosphorylated STAT1 is an indispensable factor in DC activation. This information illustrates that S727-

phosphorylated-STAT1 is required for DC maturation, which in turn stimulates CTL activation and is also used for direct control of T cells.<sup>166</sup> Yu et al have demonstrated that loss of STAT3 in CD8<sup>+</sup> T cells can increase their cell division.<sup>167</sup> Improved proliferation in CD8<sup>+</sup> T cells with STAT3 deficiency manner results from p21waf1 (cyclin-dependent kinase (CDK) inhibitor), p27KIP1 (cyclin-dependent kinase (CDK) inhibitor), forkhead box protein O1 (FoxO1), and FoxO3A downregulation. In contrast to CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells are more impressible to STAT3 growth repressive effects. Interestingly, some studies indicated that IFN- $\gamma$  production is improved through STAT3 pathways, but exact triggered mechanisms have not been considered yet. Regulatory CD8<sup>+</sup> T cells, which produce IL-10, are hampered by STAT3, too.<sup>167,168</sup> An investigation revealed that STAT3 induced by IL-10 and IL-21 can lead to memory CD8<sup>+</sup> T cell differentiation and do not let them convert to effector ones. Activated CD8<sup>+</sup> T cell initial expansion can be trigger by STAT3 recruitment.<sup>168</sup> According to J Z Quin and coworkers' findings, for maintaining effector CD8<sup>+</sup> T cells, the expression of Bcl-2 is stimulated via STAT5 after IL-7 and IL-15 induction.<sup>169</sup> Although some other reports have demonstrated that STAT5 is not required for induction of Bcl-2 expression.<sup>170,171</sup>

### B cells

B cells are the bone marrow-derived lymphocytes and the arm of the humoral immune system with the ability of Ig production, which can release proinflammatory cytokines and present antigens to T cells. Overall, they have a key role in the activation of T cells and substantially, initiation of inflammation in the immune system. B and T lymphocytes are interlinked in various aspects.<sup>172</sup> These complex functions by B cells need to be worked out by unique signaling pathways, and STATs are the important ones. It has been shown that Src family kinases such as Lyn start BCR engagement, and multiple following signaling cascades are begun for proliferation, differentiation, and even restriction of B cell growth.<sup>173</sup> Correlation between CD19 and BCR could enhance STAT1 tyrosine phosphorylation compared to BCR lonely cross-linking. Preceding events help us to consider CD19 as a positive modulator for STAT activation after BCR engagement.<sup>174</sup> Signaling guided by STAT1 and IFN- $\gamma$  receptor (IFN- $\gamma$ R) is a pivotal factor in spontaneously developed germinal centers (GCs [Spt-GCs]) and the formation of Tfh cells. Moreover, IFN- $\gamma$ -R and STAT1 signaling regulate Spt-GC and Tfh cell development by inducing B cells to express T-bet and produce IFN- $\gamma$ .<sup>175</sup> Some findings have recommended that gain of function mutation in STAT1 leads to deficiency in B-cell differentiation.<sup>176</sup> Moreover, in the bone marrow and marginal zone, STAT1 can improve B-cell differentiation in mice.<sup>177,178</sup> For regulation of B-cell response and differentiation, STAT3 is activated

through IL-21.<sup>179</sup> Moreover, the number of antigen-specific memory B cells is decreased and the formation of plasma cells from naive B cells is inhibited after IL-21 induction due to STAT3 mutations. A defect in the molecular mechanism, which is needed for plasma cell (PC) production, is what led to the previous incident. Whereas IL-21-stimulated Ig secretion and memory B cell formation are unaffected by STAT1 impairment.<sup>180</sup> Differently from mutated-STAT3, mutated-STAT1 after IL-21 induction decreases the expression of the paired box (*PAX5*) and enhances the expression of PR domain zinc finger protein 1 (*PRDM1*) and X-box binding protein 1 (*XB1*) in contrast to normal naive B cells, indicating the unessential role of STAT1 for this process. IL-6-induced STAT3 can mediate the function of B cells by improving antibody secretion from human PCs through augmenting IL-6R expression.<sup>181,182</sup> Uri Rozovskii and colleagues in their study revealed that in chronic lymphocytic leukemia cells, B-cell receptor stimulation has the potential of activating the Jak2/STAT3 signaling pathway.<sup>183</sup> The prominent roles of STAT protein in each adaptive immune cell are summarized in Table 2.

The inhibitory and activatory roles of main triggered STATs in different innate and adaptive immune cells have been demonstrated (Fig. 5).

#### **A perspective on the different roles of STATs in cancer STAT role in the innate immune system in cancer**

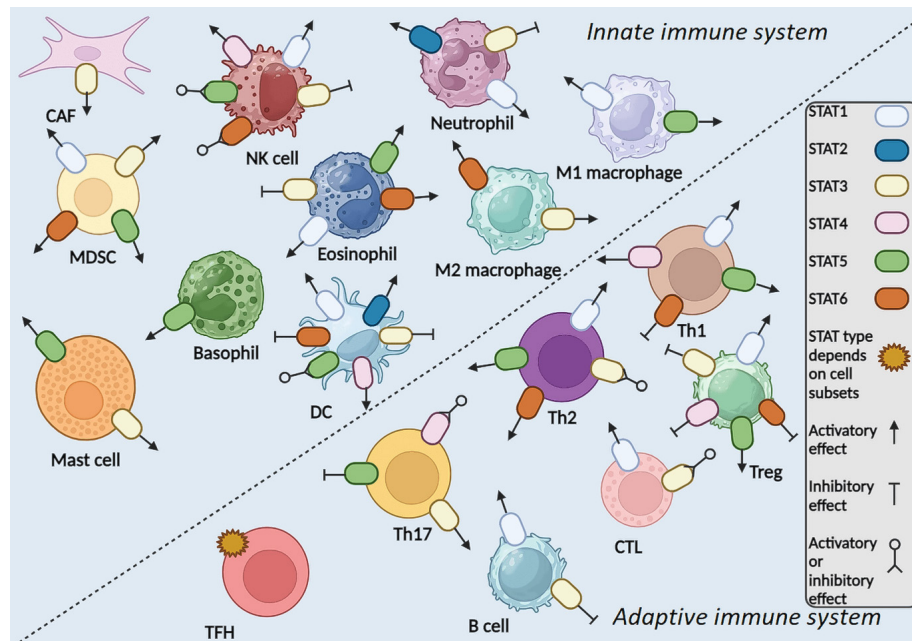
CAFs and MDSCs, as members of the TME, provide a place for tumor proliferation and metastasis. As discussed before, CAF and MDSCs have a main signaling pathway as the regulator of the cells' function, which is called STAT3. Targeting this TF may cause the favorite results for cancer immunotherapy by adjustment of the mentioned cells' function.<sup>172,184</sup> According to investigations, IL-6 binds to its receptor IL-6Ra on the cell surface of neutrophils, hepatocytes, monocytes, and B and T cells, activating Jak1, which stimulates the STAT3.<sup>185</sup> This signaling promotes growth and prevents apoptosis, including the activation of genes encoding Bcl-xl and Bcl-2.<sup>186</sup> STAT3 is thought to be a negative modulator of inflammatory reactions. Moreover, mice lacking the STAT3 gene in neutrophils show increased inflammatory activity.<sup>187</sup> It is shown that eosinophils may have double-edged effects on cancer. Some studies resulted in the association of eosinophils with good prognosis in breast cancer cases.<sup>188</sup> However, some studies pointed out that Jak3/STAT3 and eosinophils had cooperative attitudes in T cell-induced malignancies. These data show that this signaling pathway can be considered the appropriate target for immunotherapy planning.<sup>188</sup> Treg-produced IL-13 has been proven to induce basophil activation through STAT5, which in turn contributes to Th2 response. Previous events cause tumor promotion, thereby either hampering the basophil activation or the IL-3/IL-3R axis, resulting in induced

**Table 2.** The total roles of main STATs in the adaptive immune cells

Cell type	Main triggered STAT(s)	Total roles of triggered STAT(s) in related cell	References
Th1	STAT1	Activatory	125
	STAT4	Activatory	125
	STAT5	Activatory	127
	STAT6	Inhibitory	128
Th2	STAT1	Activatory	137
	STAT3	Activatory or inhibitory (based on condition)	134, 135
	STAT5	Activatory	136
Th17	STAT6	Activatory	130
	STAT3	Activatory	138
	STAT4	Activatory or inhibitory (based on condition)	144, 145
Tfh1	STAT5	Inhibitory	141
	STAT1	Activatory	146
TFHs	STAT4	Activatory	146
	STAT3	Activatory	152
	STAT5	Inhibitory	151
	STAT6	Activatory	152
Tfh17	STAT3	Activatory	154
	STAT4	Activatory	154
Tfr	STAT5	Activatory	156
Tregs	STAT1	Activatory	163
	STAT3	Inhibitory	162
	STAT4	Inhibitory	161
	STAT5	Activatory	159
	STAT6	Inhibitory	161
CTLs	STAT1	Activatory	165
	STAT3	Activatory or inhibitory (based on condition)	167
B cells	STAT5	Not clear	169-171
	STAT1	Activatory	175
	STAT3	Inhibitory	183

Abbreviations: CTL: cytotoxic T lymphocytes; Th: helper T cells; STAT: signal transducer and activator of transcription; TFH: follicular helper T; Tfr: T follicular regulatory cells; Treg: regulatory T.

anti-tumor effects.<sup>189,190</sup> The tumor microenvironment's cytokines influence NK-cell development and function. Many cytokines communicate through the Jak/STAT pathway, which is constitutively active in a wide range of tumor cells.<sup>191</sup> STAT1 plays a vital role in IFN- $\gamma$  expression and NK-cell cytotoxicity.<sup>192</sup> Conversely, STAT3 activity is thought to impede tumor immune surveillance, allowing the cancer to evade the immune system.<sup>193</sup> Even STAT3 activation in NK cells decreases cytotoxicity, according to animal studies. So, STAT3 deletion in NK cells increased cytotoxicity in leukemia and melanoma models and resulted in longer survival.<sup>194</sup> STAT5 inhibits NK-cell tumor-promoting activity. NK cells, like myeloid cells, have the ability to promote tumor growth by secreting



**Fig. 5.** Inhibitory or activatory roles of different STATs in innate and adaptive immune cells. Abbreviations: CAF: cancer-associated fibroblast; CTL: cytotoxic T lymphocyte; DC: dendritic cell; MDSC: myeloid-derived suppressor cells; NK: natural killer cell; STAT: signal transducer and activator of transcription; TFH: follicular helper T cell; Th: helper T cell; Treg: regulatory T.

VEGF-A. STAT5 inhibits VEGF-A expression and tumor promotion, with STAT5B being the critical isoform.<sup>195</sup> It has been demonstrated that the tumor-inducing factor cyclooxygenase-2 (COX-2) is expressed more often in MQs following STAT3 ablation and Jak/STAT suppression and that blocking COX-2 improves tumors' sensitivity to ruxolitinib.<sup>196</sup> Another study has revealed that arachidonate 5-lipoxygenase (ALOX5), which encodes 5-lipoxygenase stimulates, metastases and invasion in pancreatic cancer via controlling TAM polarization via the Jak/STAT pathway. Zileuton blocks ALOX5 to prevent these outcomes.<sup>197</sup> Studies have demonstrated that the accumulation of STAT3 precludes the differentiation of immature DCs to mature ones and increases the impacts of tumor-derived factors on the differentiation of myeloid cells in cancer. Moreover, being able to recognize CD28 receptors on T cells, the level of expression of intracellular IFN- $\gamma$ , and the suppression of the generation of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) in breast cancer lymph nodes are all improved as a result of enhanced CD86 expression on DCs after STAT3 blocking.<sup>198</sup>

#### **STAT role in the adaptive immune system in cancer**

Th cells are capable of the anti-cancer immune response, as seen in CD8<sup>+</sup> T cells. It is observed that Th1 has the potential to limit angiogenesis and metastasis and to activate the apoptotic processes in cancer cells by IFN- $\gamma$  production, which is induced by the expression of T-bet TF, which in turn becomes activated through STAT1 and STAT4 activatory signaling pathways.<sup>199</sup> Chimeric antigen receptor (CAR) T cells can get Th1 phenotype

and function. Subsequently, they can be used in T cell therapy for several types of malignancies.<sup>200</sup> Th2 cell action through STAT5 and STAT6 is more related to malignant cells' progression in comparison to anti-cancer function. Thus, the application of Th2 in T cell therapy has some limitations, whereas Th2 anti-tumor roles through innate immune cells are seen in pancreatic and colon cancer.<sup>201,202</sup> Recent research mentioned STAT3's role in stem cells and cancer stem cell control. One study intended to determine the position of activated STAT3 in gastric cancer stem cells (GCSCs) and the Th17/Treg cell paradigm. The results show that gastro-spheroids, as a model of GCSCs, had higher levels of STAT3 activity, increased levels of VEGF, TGF- $\beta$ , and lower levels of IL-6. Treatment with static small molecules prevents STAT3 activation in cancer cells, which lowers stemness properties. For instance, stemness gene expression, in vivo tumorigenicity potential, and TGF- $\beta$  expression are all down-regulated in the cancer cells. Additionally, co-culture of STAT3-inhibited cancer cells with normal peripheral blood mononuclear cells (PBMCs) results in a decrease in the proportion of Treg cells and an increase in Th17 cells.<sup>203</sup> It is well-recognized that IL-17 is an angiogenic agent and may enhance metastasis and tumor growth via STAT-3 signaling and other mechanisms.<sup>204</sup> Research about the STAT role in Tfh in cancer has displayed that the contribution of STAT3, STAT6, and BATF results in augmented production of IL-4 that can exert a tumor-suppressing effect. Furthermore, in Tfh2 cells, it has been reported that the anti-tumor effect of IL-21 resulting from STAT4 induction can be increased in combination with anti-CTLA-4 or anti-programmed death-1 (PD-1)

immunotherapy.<sup>205</sup> STAT is a crucial signaling pathway that Tregs activate to support angiogenesis, metastasis, immunosuppression, and apoptosis resistance in cancer cells. The TME's immunosuppression is facilitated by STAT3 and STAT5.<sup>206</sup> Tregs interact with a variety of cells, including M2 cells, through STAT signaling. For example, the development of monocytes into M2 cells is mediated by Tregs through STAT3 activation, secretion of IL-10, and VEGF generation. In turn, M2 cells release IL-6<sup>207</sup> and IL-10<sup>208</sup> for increasing Treg activity within the TME.<sup>209</sup> It has been revealed that Ruxolitinib, a Jak/STAT inhibitor, promotes CTL infiltration in the tumor microenvironment in the pancreatic cancer mice model by selectively inhibiting STAT1 and STAT3 activation. The suppression of STAT3 increases T cell activation and effector function by decreasing the generation of immune suppressive cytokines by tumor cells. Ruxolitinib afterward dramatically enhances the effectiveness of anti-PD-1 immunotherapy to circumvent pancreatic cancer resistance.<sup>210</sup> According to Viganò and colleagues' investigations about primary mediastinal large B-cell lymphoma (PMBCL), the gain of function mutation in IL-4R results in constitutive activation of the Jak/STAT pathway and further increase in the expression of downstream cytokine and B cell-specific antigens, leading to the development of lymphomagenesis. STAT6-induced IL-4 and IL-13 lead to differentiation and activation of B cells, resulting in establishing tumor suppression.<sup>211</sup>

### STAT3 therapeutic potentials

As previously stated, STAT3 is a transcription factor in the cell cytoplasm that regulates multiple signaling pathways in the immune system, especially those related to malignancies.<sup>26</sup> This member of the STAT protein family causes a reduction in anti-tumor responses, which are usually made by NK cells, Treg cells, CD8<sup>+</sup> T cells, and DCs.<sup>212</sup> STAT3 is known to suppress MHCII and expression of CD86, IL-12, CXC motif chemokine ligand (CXCL)10, and CCL5, which overall causes the impedance of maturation and antigen-presentation in DCs that is followed by the debilitation of Th1 and CTL aggregation and anti-cancer immune responses.<sup>213,214</sup> STAT3 activation in MQs has a similar effect to DC activation and its further impacts on T cells.<sup>215</sup> In addition, STAT3 activators in bone marrow progenitor cells lead to neutrophil inhibition. The immunosuppression that happens through STAT3 has a notable impact on protecting tumor cells by providing a perfect TME and promoting their growth.<sup>214</sup> In parallel, STAT3 induces the direct expression of cancer-promoting genes. Recent research has indicated that STAT3 activation is associated with a poor prognosis in patients with solid tumors.<sup>216</sup> These results suggest that targeting the STAT3 signaling pathway in different directions can be a promising therapeutic option for various malignancies. STAT3 is found to play

a role in the growth, invasion, promotion, and metastasis of cancerous cells, such as breast cancer, hepatocellular carcinoma (HCC), non-small cell lung cancer (NSCLC), glioblastoma, and colorectal cancers.<sup>217,218</sup> Hampering STAT3 by the special agents is utilized in the control of diseases in the context of inflammation or infection, diabetes, osteoporosis, and even psychotic disorders next to malignancies.<sup>26,219,220</sup> Some drugs are STAT3 inhibitors with completed clinical trials and benefits in terms of safety, tolerability, and sufficient anti-tumor effects. STAT3 inhibitor agents can have a negative influence on tumor growth, suppress angiogenesis, and reduce the probability of tumor metastasis.<sup>221,222</sup> Small molecules, peptides, oligonucleotides (with direct impact), phytochemical agents, and Chimeric antigen receptor redirected T cells (CART-cells) are examples of a class of drugs able to inhibit STAT3 activation.<sup>220</sup> AZD9150 works as an inhibitor of the STAT3-related gene and has been shown to impact numerous solid malignancies, such as HCC. BIOMOL, as a small-molecule inhibitor, works directly on STAT3.<sup>223</sup> Napabucasin is an example with the small molecule and possesses the capability to suppress the STAT3 mRNA formation from the related gene, which has been involved in clinical trials for treating malignancies such as pancreatic adenocarcinoma, colorectal carcinoma, and malignant pleural mesothelioma.<sup>224</sup> Curcumin and even some antibiotics such as nifuroxazide and atovaquone are drugs with the purpose of preventing STAT3 from becoming phosphorylated.<sup>225,226</sup> Furthermore, it is shown that restriction of STAT3 function elevates the sensitivity of tumor cells to radiotherapy and chemotherapy.<sup>227,228</sup>

### Concluding remarks

Undoubtedly, STAT transcription factors influence diverse immune cell subsets' differentiation, proliferation, and function. Even numerous studies have demonstrated the therapeutic potential of their targeting in immune system disorders. Controlled and balanced activation of these cells requires correlation between various signaling pathways, and one of the most significant pathways employed in the majority of immune cells is the Jak/STAT signaling pathway. As we reviewed, different STAT factors play meaningful roles in diverse innate and adaptive immune cell subsets, and subsequently, they show their impacts to overcome immune-related disorders or act in favor of disease progress like tumor growth. For instance, a reduction in longevity in patients with colorectal cancer can be associated with STAT3 phosphorylation in CAFs, and even STAT3 can lead to tumor progression via augmenting MDSC involvement. Also, in allergy, STAT signaling pathways are necessary for the eosinophil's function and survival because Jak/STAT leads to the postponement of eosinophil apoptosis. About mast cells, mitochondrial STAT3 is a vital factor in their degranulation. NK cells that perform cytotoxic

actions, act through Jak/ STAT: STAT1, STAT4, and STAT5 positively influence NK cells and promote their cytotoxicity, while STAT3 and STAT6 hamper NK cell activation. About MQs, STAT1 activation is triggered through IFN- $\gamma$ , leading to boost proinflammatory cytokine production. Thus, polarization to M1 MQs occurs, but on the other hand, after IL-4 stimulation, STAT3 and STAT6 play a role in polarization to M2 phenotype. DCs that are very important for antigen presentation require STAT1 to up-regulate the expression of MHC and co-stimulatory molecules for their effective performance, but STAT3 decreases the expression of these mentioned molecules. Irregularities in Jak/STAT pathways in T cells are correlated with multiple immunological disorders. For example, Th1 activation, which is needed to create a defense against intracellular infections, requires STAT1 for IFN- $\gamma$  signaling and STAT4 for IL-12 signaling. For protection against parasites, Th2 cells are required, so STAT6 should perform Th2 polarization. Against extracellular bacteria, Th17 cells will be activated, and these cells are induced via STAT3, which even up-regulates the expression of IL-17. For immunomodulatory function and tolerance to self-antigens, Tregs' appropriate functions are required, but any impairment in the STAT-5 signaling pathway causes a reduction in these Treg numbers. Finally, for regulation of B-cell response and differentiation, STAT3 is activated through IL-21. In conclusion, targeting each of these STAT factors with paying precise attention to its specific role in each immune cell subset may cause the favorite results for immune system disorders such as cancer immunotherapy by adjusting the mentioned cells' function.

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#### Competing Interests

The authors declare that there is no conflict of interest.

#### Ethical Statement

Not applicable.

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### Review Highlights

#### What is the current knowledge?

- One of the significant mechanisms involved in the immune cells' activation is the Jack/STAT signaling pathway.
- Jack/STAT signaling pathway alteration causes various illnesses, including cancer.

#### What is new here?

- Determining the inhibitory, activatory, or both roles of STATs in modulating innate and adaptive immune cells.
- Investigation of alteration of specific STAT in immune cells leading to tumor progression or inhibition.

- models of cellular signaling, cytokine crosstalk, and cell-cell communication in immunology. *Front Immunol* **2019**; 10: 2268.
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