STAT3, a Master Regulator of Anti-Tumor Immune Response

Cédric Rébé * and François Ghiringhelli *

Platform of Transfer in Cancer Biology, Centre Georges François Leclerc, INSERM LNC UMR1231, University of Bourgogne Franche-Comté, F-21000 Dijon, France

* Correspondence: crebe@cgfl.fr (C.R.); fghiringhelli@cgfl.fr (F.G.); Tel.: +33-3-8073-7790 (C.R. & F.G.)

Received: 18 July 2019; Accepted: 29 August 2019; Published: 30 August 2019

Abstract: Immune cells in the tumor microenvironment regulate cancer growth. Thus cancer progression is dependent on the activation or repression of transcription programs involved in the proliferation/activation of lymphoid and myeloid cells. One of the main transcription factors involved in many of these pathways is the signal transducer and activator of transcription 3 (STAT3). In this review we will focus on the role of STAT3 and its regulation, e.g., by phosphorylation or acetylation in immune cells and how it might impact immune cell function and tumor progression. Moreover, we will review the ability of STAT3 to regulate checkpoint inhibitors.

Keywords: STAT3; cancer; CD4⁺ T cells; CD8⁺ T cells; myeloid cells; immune check point

1. Introduction

STAT3 is part of the Signal Transducer and Activator of Transcription (STAT) family which includes seven members encoded by distinct genes. STAT3 has evolutionary conserved amino acid sequences between *H. sapiens* and *S. harrisii* (99.09%) [1]. In resting cells, STAT3 remains in an inactive form in the cytoplasm. Once activated, mainly through phosphorylation, STAT3 translocates to the nucleus to play its transcription activity for specific target genes [2]. STAT3 phosphorylation on tyrosine (Y705) is mainly regulated by members of Janus-activated kinases (JAK), whereas its phosphorylation on serine (S727) is commonly regulated by mitogen-activated protein kinases, CDK5 and protein kinase C [3]. Finally, histone acetyltransferase-mediated reversible acetylation of STAT3 on a single lysine residue (K685) is a third mechanism of STAT3 activation through STAT3 dimer stabilization [4]. However, the phosphorylation on S727 is responsible for a mitochondrial relocalization of STAT3 where it exerts non-transcriptional roles. This mitochondrial localization enables STAT3 to increase cell respiration (through electron transport chain complex activation) and Ras transformation [5]. Non-nuclear STAT3 can also regulate glycolysis, thus enhancing lactate production leading to the protection of cells from apoptosis and senescence and can also regulate calcium homeostasis, energy production and apoptosis at the endoplasmic reticulum level [6].

Regulation of STAT protein activation is controlled by negative regulators, e.g., PIAS (protein inhibitor of activated STAT) and SOCS (suppressors of cytokine signaling) proteins as well as protein tyrosine phosphatases. PIAS are nuclear factors that negatively regulate STAT transcriptional activity through many mechanisms, especially by interacting and thus blocking the DNA binding activity [7]. SOCS proteins directly or indirectly interact with tyrosine kinase SH2 domains to prevent JAK from activating STAT3 [8]. Protein tyrosine phosphatases (such as CD45, SHP-1 and SHP-2) remove phosphates from activated STATs, which represent a third level of STAT modulation [9–11]. Lastly, STAT3 has also been shown to go through ubiquitination-dependent proteosomal degradation [12]. Moreover, because of their homologies, STATs can form homodimer and heterodimers. Specificity
depends on the activator signal and leads to the transcription of different target genes. For example, STAT3 can heterodimerized with STAT1, under IL-6 treatment [13].

It is now well-established that STAT3 signaling is a major intrinsic pathway driving apoptosis, inflammation, cellular transformation, survival, proliferation, invasion, angiogenesis and metastasis in cancer [14–17]. Moreover, STAT3 in cancer cells affects stromal cells function, establishing crosstalk between cancer cells and its microenvironment. For example STAT3 can dampen STAT1-mediated upregulation of MHC class I, allowing immune escape [1]. The other way for STAT3 to drive tumor immune escape is to regulate the function of stromal cells and more particularly immune cells.

In general, all seven STAT family members have prominent roles in T-cell function or T-cell differentiation, survival or expansion. STAT4 is essential for Th1 and STAT6 is important for Th2 differentiation. Similarly, all STAT proteins have all seven prominent roles in myeloid cells and they all influence each other’s expression and activity status on complex and not understood chromatin regulation. All that makes the interpretation of complex immune cell scenarios triggered by multiple action of cytokines, growth factors, hormones and chemokines a tricky business to correctly relate functions to this or that STAT family member. Importantly, T-cell expansion by common γ-chain cytokines and many T-cell effector functions such as CD8+ T-cell, γδ T-cell generations and cytokine release function and mounting a killing or efficient cytokine signaling response against foreign or mutated antigen is a STAT5-mediated affair together with proper recognition and signaling through the T-cell receptor (TCR), where again interplays are not carefully understood or worked out [18,19]. Furthermore, STAT5 is also essential to generate Treg cells, where both Foxp3 and Cd25 are direct STAT5 target genes [20]. STAT5 has also essential functions in erythropoiesis or macrophage or dendritic cell (DC) polarization, but due to space constrains and focus on fine-tuning and twisting immune responses in health or disease we will here illuminate STAT3 function in immune cells. We illuminate many important immune modulatory interplays of STAT3 signaling in distinct T-cell and myeloid cell compartments. We describe current knowledge on the impact of STAT3 activation in immune cells on the balance between immunosurveillance and immunoecape. We will describe how STAT3 affects both myeloid and lymphoid cells usually in a way to inhibit anti-tumor immune response and to promote tumor growth.

2. STAT3 and T-Cells

T lymphocytes or T-cells play a central role in host adaptive immune response to cancer [21]. Tumor-infiltrating CD4+ and CD8+ T-cells are associated with varying clinical outcomes and survival in many types of cancer such as colorectal, [22] breast [23] and lung cancers [24]. Cytokines can shape T-cells immune response and tune CD4+ T-cells differentiation and CD8+ T-cells activation [25]. Among T-cells, different subsets have been described (regulatory T-cells, cytotoxic T-cells, T helper cells) with distinct functions that could be regulated by STAT3 (Table 1).

2.1. Th1/Th2

CD4+ T helper (Th) cells assist other hematopoietic cells in immune processes, including activation of cytotoxic T lymphocytes (CTLs), natural killer (NK) cells and macrophages. Th cells are activated when stimulated with a peptidic sequence of the antigen they specifically recognize. These peptides are presented to Th cells by antigen presenting cells (APCs), such as DCs through MHC class II molecules. Once activated, they rapidly proliferate and secrete cytokines that will inhibit or assist the active immune response [26].
Table 1. Impact of STAT3 in T-cell subsets.

| Immune Cell Family | STAT3 Role in | STAT3 Modulators | Effects | Reference |
|--------------------|---------------|------------------|---------|-----------|
|                    | Th1           | IL-21            | IL-10 secretion | [28]      |
|                    | Th2           | IL-21            | IL-10 secretion | [28]      |
|                    | Th17          | KO STAT3         | Inhibition of Differentiation | [29,30]  |
|                    |               | IL-6, IL-21, IL-23 | ROY1-2 and ROR-RORα → Differentiation (↗ IL-17) | [31-35]  |
|                    |               | PPARγ ligand, Platelet factor 4 | SOCS3 → Inhibition of Differentiation | [36]      |
|                    |               | SHP1             | pSTAT3 → Inhibition of Differentiation | [37]      |
|                    |               | LOXL3            | STAT3 deacetylation → Differentiation | [38]      |
|                    |               | Metformin, Resveratrol | SIRT1 activation → STAT3 acetylation → Th17 Differentiation | [39]      |
|                    |               | IL-6 (+ TGF-β)   | STAT3 activation and ↘ Gft-1 → ↗ CD39 and CD73 expression | [40]      |
|                    |               | miR29a-3p, miR-21-5p | STAT3 deacetylation → Th17 Differentiation | [41]      |
|                    | Treg          | KO STAT3         | ↘ number of Treg | [42-44]  |
|                    |               | IL-2             | STAT3 + STAT5 → ↗ FOXP3 → → inhibitory functions | [45]      |
|                    |               | SIPK1            | STAT3 → Treg migration in the tumor | [46]      |
|                    |               | IL-6, IL-27      | → STAT3 → ↘ FOXP3 → ↘ Treg differentiation | [34,46]  |
|                    |               | CDK5             | pSTAT3(S727) → ↗ FOXP3 | [47]      |
|                    |               | GATA-3           | miR125a-5 → ↘ IL-6R + STAT3 → ↘ Treg conversion | [48]      |
|                    |               | Wogonin          | pSTAT3(Y705) → pSTAT3(S727) → ↘ Treg differentiation | [49]      |
|                    |               | WP1066           | pSTAT3 → ↘ FOXP3* Treg | [50]      |
|                    |               | compound# (fluorinated β-amino-ketone) | ↘ FOXP3* Treg | [51]      |
|                    |               | anti-sense oligos + radiations | ↘ FOXP3* Treg | [52]      |
|                    | Thh           | KO STAT3 or STAT3 siRNA | GATA-3, IL-4 (Th2) | [53]      |
|                    |               | STAT DNA Binding domain mutation | STAT3 activity → ↘ IL-21 | [54]      |
|                    |               | TGF-β            | pSTAT3 → ↘ GATA-3, IL-4 (Th2) | [55]      |
|                    |               | Intratumoral Thh-like cells | → ↘ IL-21, IFN-γ → ↗ M2b | [56]      |
|                    | Th9           | KO STAT3         | pSTAT5 → ↘ IL-9 | [57]      |
|                    |               | Murine IL-10     | pSTAT3 → ↘ IL-9 | [58]      |
|                    |               | Human IL-21      | pSTAT3 → ↘ T-BET → ↗ IL-9 | [59]      |
|                    | CD8+ T-cells  | KO STAT3         | IFN-γ → ↗ CXCL10 production by myeloid cells | [60]      |
|                    |               | CD28 stimulation | ↗ CD8+ proliferation and tumor invasion | [61]      |

Expression levels of Th1 cell genes coding for Interferon-γ (IFNG), TAP1, Granzym B (GZMB) are significantly higher in colorectal tumors than in normal tissue. A high expression of Th1 cytotoxic genes was associated with significantly improved disease-free survival whereas a low expression of those genes lead to disease recurrence [63]. T-BET, the master transcriptional regulator for Th1 differentiation is induced by TCRs and IL-12 stimulation [64]. In contrast, GATA-3 is the master assessor for Th2 differentiation, after stimulation with IL-4 [65]. IL-27, a member of the IL-6/IL-12 family produced by macrophages and DCs, favors Th1 differentiation by up-regulating T-BET, down-regulating GATA-3 and suppressing proinflammatory cytokine production such as IL-2, IL-4, and IL-13 [27,66]. In this context, only the IL-27-dependent Th1 proliferation was mediated by STAT3 [27]. In contrast, in a different cytokine context, in patients harboring STAT3 dominant negative mutations or STAT1 or IL-21R loss of function mutations, it was shown that IL-21/IL-21R, STAT3 and STAT1 signaling are required for in vitro differentiation of IL-10-secreting cells, related to Th2 [28].

2.2. Th17

Th17 cells are CD4+ T-cells induced by TCR triggering together with IL-6, transforming growth factor (TGF)-β, and IL-23, an IL-12 family member, stimulation [67]. Th17 cells have emerged as key drivers of a wide range of autoimmune disorders, including inflammatory bowel disease, psoriasis, and ankylosing spondylitis [68]. Th17 cell expansion was observed in human cancers such as ovarian, melanoma, breast or colon cancers [69]. In colorectal cancer, patients with low expression of Th17 genes seem to have a prolonged disease-free survival [63]. However, a positive role of Th17 was proposed in melanoma and ovarian cancer. Therefore, the role of Th17 cells in cancer immunity remains controversial [70].

Th17 are characterized by the expression of the transcription factors RORγt and RORα and the production of IL-17A [71]. In addition, STAT3 is also essential for Th17 cell differentiation, since STAT3 ablation in mice CD4+ T-cells, abrogates Th17 differentiation [29,30]. Moreover, in patients harboring STAT3 dominant negative mutations, IL-21R loss of function mutations or STAT1 gain of function mutations, it was shown that IL-21/IL-21R/STAT3 signaling is required for in vitro production of IL-17A/F by Th17 cells whereas STAT1 overexpression inhibits it [28]. STAT3 can associate with Trim28 and RORγt to drive the transcription of target cytokines such as IL-17A/F [72]. Moreover, many in vitro studies have shown that STAT3 can be activated by several pro-inflammatory cytokines including IL-6, IL-21 and IL-23 leading to the regulation of RORγt and RORα expression, along with the development and the stabilization of Th17 cells [31–35]. We found that the n-3 fatty acid docosahexaenoic acid (DHA) was able to induce the expression of SOCS3 in a PPARγ-dependent manner. SOCS3 then inhibits pSTAT3 and Th17 differentiation [36]. Another regulator of STAT3 activation in Th17 is the tyrosine phosphatase SHP1, which dampens IL-6- and IL-21-driven Th17 development and limits colitis in mice [37]. Similarly, the Platelet Factor 4 (PF4) can also up-regulate SOCS3 expression leading to the inhibition of STAT3, Th17 differentiation and tumor growth [73].

The STAT3 acetylation profile is also involved in Th17 polarization. First, lysyl oxidase-like 3 (LOXL3) is able to deacetylate STAT3 and to inhibit its transcriptional activity. Loxl3 deficiency leads to constitutive STAT3 K685 acetylation causing reduced Th17 differentiation associated with resistance to DSS-induced colitis in mice [38]. Second, we showed that metformin and resveratrol, two SIRT1 activators, entail STAT3 acetylation leading to Th17 differentiation impairment and limit tumor growth in mice. The capacity of metformin to promote acetylation of STAT3 and to decrease Th17 differentiation was also shown in patients [39].

We have shown that in vitro Th17 cells differentiated with IL-6 and TGF-β and in vivo tumor-infiltrating Th17 cells express CD39 and CD73 ectonucleotidases. This ectonucleotidase catalytic machinery entails the degradation of extracellular ATP into adenosine, an immunosuppressive molecule which suppresses effector T-cells. The expression of ectonucleotidases is dependent on IL-6-driven STAT3 activation and TGF-β-mediated downregulation of the zinc finger protein Growth Factor Independent-1 (Gfi-1), both required for the transcriptional regulation of ectonucleotidase expression during Th17 cell
differentiation. CD39 expression at the surface of Th17 cells fosters tumor growth, suggesting that the immunosuppressive functions of Th17 cells in cancer are dictated by ectonucleotidase expression [40]. It has been reported that naïve T-cells can be differentiated into Th17 cells with IL-1β, IL-6, IL-23 and without TGF-β. Unlike Th17 cells generated with TGF-β and IL-6, these Th17 cells were highly pathogenic in vivo [74] and didn’t express ectonucleotidases [40]. These observations propose STAT3 and Gfi-1 as key determinants in the immunoregulatory function of Th17 cells, at least in part through the regulation of ectonucleotidase expression [40].

The mechanistic role of STAT3 in Th17 positive effects on anti-tumoral response is less documented. TAM-derived exosomes can deliver miR-29a-3p and miR-21-5p to CD4+ T-cells leading to the inhibition of STAT3 and consequently to Th17 polarization in favor to Treg, which is beneficial for epithelial ovarian cancer progression [41].

2.3. Treg

Suppressor regulatory T-cells (Treg) maintain peripheral immune tolerance [75,76]. Co-stimulation of naïve CD4+ T-cells with TCR and TGF-β, triggers the generation of CD4+CD25+ Treg cells. This leads to the expression of FOXP3, Tregs master transcription factor [77]. These T-cells accumulate in tumors and in cancer patients peripheral blood [78]. An increase in Treg frequency is generally considered as a marker of poor prognosis in cancer, probably because Treg mediate suppression of anti-tumor immunity [79–81].

The role of STAT3 in Foxp3 expression regulation in Tregs appears to be context-dependent. In vitro, IL-2 induces the binding of STAT3 and STAT5 to a highly conserved STAT-binding site located within the first intron of the Foxp3 gene, leading to FOXP3 expression up-regulation in purified CD4+CD25+ T-cells but not in CD4+CD25− cells [42].

In tumor-infiltrating Tregs, both STAT3 and STAT5 bind to a STAT consensus site in the Foxp3 promoter to enhance FOXP3 expression which seems to be important in maintaining Tregs inhibitory functions [42–44]. S1PR1 (Sphingosine-1 Phosphate Receptor 1) signaling has been shown to restrain Treg number and functions. An increase in S1PR1 in CD4+ T-cells promotes STAT3 activation and JAK/STAT3-dependent Treg tumor migration, whereas STAT3 ablation in T-cells diminishes tumor-associated Treg accumulation and tumor growth [45]. Treatment of metastatic cancer or chronic myelogenous leukemia after allogeneic hematopoietic stem cell transplantation in patients with low-dose IL-2, leads to an increase of peripheral blood CD4+CD25+ cells and to FOXP3 expression in CD3+ T-cells [42]. STAT3 and FOXP3 co-operatively control a subset of genes, responsible for Treg cell ability to suppress Th17 cell-mediated inflammation [82]. In contrast, IL-21 which activates STAT3 but not STAT5 has no effect on Treg viability, activation or function, suggesting that in this context IL-21-mediated STAT3 activation is not sufficient [83]. The regulation of Foxp3 expression by STAT3 was strengthened by other studies. CDK5 increases Foxp3 gene expression through phosphorylation of STAT3 at serine 727 [47]. GATA-3 controls the expression of miR-125a-5p, which in turn inhibits the expression of IL-6R and STAT3 and dampens Treg conversion [48]. In contrast, differentiation of naïve T-cells into Tregs in vitro, is impaired when STAT3 is activated (by IL-6 or IL-27) [34,46]. In a different context, STAT3 binds to a silencer element within the Foxp3 locus [84] and could also inhibit STAT5 interacting with the Foxp3 promoter [85], to prevent FOXP3 expression.

One possible explanation for these ambivalent actions of STAT3 on Treg differentiation could be the phosphorylation site. Indeed, wogonin, a natural flavonoid from Scutellaria baicalensis, inhibits Treg induction by down-regulating ERK and STAT3-Y705 phosphorylation and promoting NF-κB and STAT3-S727 activation [49]. The modulation of STAT3 activity by molecular compounds could lead to inhibition of Tregs activity. Thus, WP1066 (an inhibitor of STAT3 signaling) enhances T-cell cytotoxicity against melanoma through inhibition of FOXP3+ Tregs [50]. Compound#9, a fluorinated β-amino-ketone molecule, also inhibits Treg induction both in vitro and in vivo, via blockage of JAK2 signaling [51]. Finally, STAT3 inhibition with anti-sense oligonucleotides in association with radiation is a potent therapeutic target against Tregs [52]. All these studies suggest that STAT3 is required for immunosuppressive functions of Tregs.
2.4. T Follicular Helper Cells

Tfh differentiation is complex because it requires interaction with other cells such as B cells or DC. In mice, IL-6, IL-21 and IL-27 are essential for Tfh formation while in humans, Tfh generation relies on TGF-β, IL-12, IL-23. In both mammalian species of rodents or humans, Tfh cells express BCL6, ASCL2, IL-21, PD-1, and ICOS and produce IL-21 and CXCL13 \[86,87\]. While the role of Tfh is ambiguous in lymphoid tumors, many studies report that accumulation of Tfh in tertiary structures within the tumor is of good prognosis for breast, colon and non-small cell lung cancer patients \[88,89\]. Even if the protective effects of Tfh cells seem to be dependent on IL-21 and CXCL13-mediated recruitment of leucocytes, little is known about the accurate mechanism of Tfh anti-tumoral effects.

Generation of Tfh cells in patients with impaired STAT3 DNA-binding function is compromised due to the inability of IL-12 to induce IL-21 production without affecting its capacity to induce ICOS, BCL6 or CXCR5 expression \[54\]. When siRNA specific for STAT3 was used, TGF-β, IL-12, IL-23 failed to induce BCL6 expression in vitro \[53\]. However, the requirement of STAT3 seems to depend on the differentiation status of Tfh cells: It is required for Tfh generation but once these cells are generated it is no longer required \[90\]. In the same context, murine STAT3-deficient CD4$^+$ T-cells, Tfh cells expressed less or more BCL6 and IL-21 according to the immune environment \[91,92\]. Moreover, in conditions where STAT3 is necessary for Tfh differentiation, two studies showed that it cooperates with the IkZF transcription factors Aiolos and Ikaros. Moreover, the kinase activity of ROCK2 (Rho-associated coiled-coil kinase 2, an actin cytoskeleton assembly regulator) is required to induce STAT3 phosphorylation, nuclear relocalization and DNA binding to regulate Bcl6 expression \[93,94\]. Finally, the importance of STAT3 in Tfh differentiation was strengthened by its capacity to block the expression of the Th2-associated genes Gata3 and Il4 \[53,55\].

A new protumorigenic IL-21$^+$ Tfh-like cell subset with a CXCR5$^-$PD-1$^-$BTLA$^-$CD69hi phenotype was identified in hepatocellular carcinoma (HCC). STAT1 and STAT3 activation are critical for these Tfh-like cell induction which operate via IL-21-IFN-γ pathways to induce plasma cells and create conditions for M2b macrophage polarization and tumor growth \[56\].

The importance of STAT3 in Tfh differentiation and its pro- or anti-tumoral role is not clear and could be dependent on differentiation stage, localization and environment.

2.5. Th9

Th9 cells have been characterized as a proinflammatory CD4 T-cell subset that can be generated through TGF-β and IL-4 stimulation. These cells are characterized by IL-9 secretion. Th9 harbor potent IL-9-dependent anti-cancer properties in most solid tumors and especially in melanoma while they can promote the development of many hematological human tumors, including Hodgkin’s lymphoma and other B cell lymphoma. Th9 cells activate both innate and adaptive immune responses, thereby favoring anti-cancer immunity and tumor elimination \[95\].

In this CD4 T-cell subset, STAT3 was shown to dampen IL-9 production through STAT5 inhibition in Th9 cells \[57\]. In vitro, Th9 long term ability to secrete IL-9 is inhibited by pSTAT3 through an IL-10 receptor signaling \[58\]. In contrast, in humans Th9, pSTAT3 (mainly driven by IL-21 self-induction) inhibits pSTAT1-mediated T-BET induction, through SOCS3 induction. Since T-BET is an inhibitor of IL-9 transcription, this sustains IL-9 production. Patient-derived Th9 cells with dysfunctional STAT3, lose their capacity to produce IL-9, because of SOCS3 expression down-regulation, which leads to an increase pSTAT1 and T-BET expression. In the same study, the loss of function mutations observed in patients were recapitulated with deletion studies in mice, revealing that absence of STAT3 culminates into increased IL-9 production \[59\].

2.6. CD8$^+$

CD8$^+$ T lymphocytes are central players in cancer immune response, through their capacity to kill malignant cells. Upon recognition by the TCR of specific antigenic peptides presented on the surface
of target cells by human leukocyte antigen class I (HLA-I)/beta-2-microglobulin (β2m) complexes, the CTL effector functions are activated. These functions are mediated either directly, through exocytosis of cytotoxic granules containing perforin and granzym into the target cells, resulting in cancer cell destruction, or indirectly, through secretion of cytokines, including IFN-γ and TNF [96].

The stimulation of the human and murine CD8+ T-cells CD28, stabilizes the tyrosine kinase Lck activity and pSTAT3-mediated transcription of NKG2D. NKG2D expressing CD8+ T-cells exert cytolytic activity against target tumor cells in vitro and significantly improve the antitumor therapeutic effects in vivo [62]. Even if IL-10 is considered as an immune suppressor it can also increase expansion and cytotoxic activity of CD8+ cells. Tumor-resident CD8+ T-cells express high levels of IL-10R, leading to high levels of activated pSTAT3 and pSTAT1 in response to IL-10 [97]. In contrast, circulating CD8+ T-cells from peripheral blood of HCC patients present high amounts of pSTAT3 which is correlated with high amount of IL-4, IL-6 and IL-10 and low quantity of IFN-γ which may result in abnormal immune surveillance against tumor cells [98]. In murine CD8+ T-cells, STAT3 has been shown to inhibit both IFN-γ-mediated CXCL10 production by myeloid cells and CD8+ T-cells CXCR3 expression (the receptor of CXCL10), blocking the migration of these cells to the tumor site [60].

In an adoptive transfer therapeutic strategy in mice, ablating STAT3 in CD8+ T-cells prior to transfer, allows efficient tumor infiltration and robust CD8+ T-cell proliferation, resulting in increased tumor antigen-specific T-cell activity and tumor growth inhibition [61].

Altogether STAT3 seems to inhibit CD8+ T-cell expansion and cytolytic activity except in some particular conditions.

3. STAT3 and Myeloid Cells

APCs dictate immune system response, since these cells have been shown to capture antigens in the periphery, migrate to the lymphoid organs, and present processed peptides to T-cells in a way that may lead either to priming or tolerance induction [99]. Among myeloid cells, different subsets have been described (Macrophages, DCs, Myeloid-Derived Suppressor Cells (MDSCs)) with distinct functions that could be regulated by STAT3 (Table 2).
Table 2. Impact of STAT3 in myeloid cells.

| Immune Cell Family | STAT3 Role in | STAT3 Modulators | Effects | Reference |
|--------------------|---------------|------------------|---------|-----------|
| Myeloid cells      |               |                  |         |           |
| Macrophages        |               | KO STAT3         | Inflammatory macrophages |
|                    |               | STAT3 oxerexpression | CTL activation |
|                    |               | cancer cells (PAI-1, BMP6, IL-6) | TLR9 pathway (IFN-γ, TNF-α, IL-12) |
|                    |               | Tumor exosomes | IL-23 and ↓ IL-12 |
|                    |               | Corosolic acid, oleic acid | CD163 (M2 marker) |
|                    |               | ERK5             | pSTAT3 \(\rightarrow\) polarization of M1 into M2 (CD163) |
|                    |               | M-CSF            | pSTAT3 \(\rightarrow\) IL-6, IL-10, CCL2 |
|                    |               | KO SOCS3         | pSTAT3 \(\rightarrow\) pro-tumor macrophages |
|                    |               | Tumor cells      | pSTAT3 \(\rightarrow\) anti-tumor macrophages |
| Dendritic Cells    | KO STAT3 or siRNA or shRNA | DCs APC function and cytokine production (↑ IL-12, TNF-α and ↓ IL-10) |
|                    | Constitutive STAT3 activation | ↓ MHC class II, ID-2 |
|                    | Tumor-derived exosomes and IL-6 | ↓ PKCβII \(\rightarrow\) DCs activation and differentiation |
|                    | KO STAT3 or siRNA or anti-sense oligonucleotides | ↓/↑ C/EBPβ |
|                    | Tumor-derived exosomes (HSP70) | \(\rightarrow\) MDSCs differentiation into DCs |
|                    | CCL2           | \(\rightarrow\) NOX2 \(\rightarrow\) ROS \(\rightarrow\) immunosuppression |
|                    | IL-6           | \(\rightarrow\) immunosuppressive functions (with an IL-6 amplification loop) |
|                    | G-CSF          | \(\rightarrow\) pSTAT3 \(\rightarrow\) IDO \(\rightarrow\) immunosuppression |
|                    | GM-CSF         | \(\rightarrow\) pSTAT3 \(\rightarrow\) arginase-1 \(\rightarrow\) immunosuppression |
|                    | siRNA or STATISTIC | \(\rightarrow\) pSTAT3 \(\rightarrow\) IDO \(\rightarrow\) immunosuppression |
|                    | JSI-124 (STAT3 inhibitor) | \(\rightarrow\) pSTAT3 \(\rightarrow\) M-MDSCs-mediated T-cell suppression |
|                    | CD45           | \(\rightarrow\) Early-stage MDSCs accumulation |
|                    | Embelin, PM01183, alisertib, STATISTIC or BBI608 | \(\rightarrow\) pSTAT3 |
|                    | Tumor cells    | \(\rightarrow\) VEGF, βFGF \(\rightarrow\) angiogenesis |

References:
[100], [101], [102], [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142].
3.1. Macrophages

Tumor-associated macrophages (TAMs) are subdivided into two subsets, M1 and M2 macrophages, based on their capacity to express or produce Nitric Oxide Synthase/IL-12/TNF-α or arginase-1/IL-10/TGF-β, respectively. M1 has potent microbicidal properties and promotes Th1 responses, whereas M2 supports Th2-associated effector functions [143,144]. M2 macrophages includes M2a, M2b or M2c subtypes. Tumor-derived signals, such as Macrophage-Colony Stimulating Factor (M-CSF/CSF-1), Monocyte Chemoattractant Protein-1 (MCP-1), or Chemokine (C-C motif) Ligand-2 (CCL2) entails the accumulation of M2 at the tumor site. M2 macrophages participate in tumor growth by releasing proangiogenic cytokines and growth factors, e.g. Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Colony Stimulating Factor-1 (CSF-1), and basic Fibroblast Growth Factor (βFGF). They also generate arginase-1, IL-10 and TGF-β. These molecular messengers will inhibit the antitumor function of T-cells and NK cells. This will favor tumor tolerance and impairment of antitumor immunotherapies efficacy [145–147].

IL-6 inhibition of M-CSF-induced colony formation observed in animals was abolished in mice mutated for the gp130-STAT1/3 signaling, suggesting that the IL-6/STAT3 pathway could regulate macrophage homeostasis [148]. Moreover, breast cancer-derived exosomes are capable of inducing IL-6 secretion and a pro-tumoral phenotype (IL-6, IL-10, CCL2 production) in macrophages, partially via gp130/STAT3 signaling [106]. More particularly, STAT3 directly induces the expression of the M2 marker CD163, both in macrophages and tumor cells [103]. Prostate-cancer cells induce a change in macrophage phenotype from M1 into M2, through STAT3 activation [104]. This can be induced by Plasminogen Activating Inhibitor (PAI)-1 secreted by cancer cells [105].

The inhibition of STAT3 signaling in either macrophages or bone marrow-derived DCs is of great importance in cancer immunotherapy, because it allows these APCs to restore the responsiveness of tolerant T-cells from tumor-bearing mice. STAT3 signaling is a negative regulator in peritoneal elicited macrophages, as its targeted disruption gives a constitutively activated phenotype and an increased ability to produce inflammatory mediators in response to LPS. This may be the consequence of an increased STAT1 activity (leading to high production of inflammatory factors) or a lack of IL-10 production [100]. Moreover, macrophages derived from conditional STAT3 knockout mice are better than wild-type macrophages to prime cognate CTL responses and to cross-present tumor-derived antigen to CTLs in vitro. This leads to a more important proliferation of CTLs and an increased production of IFN-γ and TNF-α. Similarly, removing STAT3 in hematopoietic cells, leads to rapid activation of innate immunity by CpG (a TLR9 ligand), with enhanced activation of macrophages, neutrophils and NK cells and production of IFN-γ, TNF-α, IL-12 to eradicate B16 melanoma tumors [102]. Targeting STAT3 signaling therefore represents an attractive strategy to increase CTL responses in the tumor-bearing host [101]. Immunosuppressive activities of TAMs correlate with over-activated STAT3 signaling, whereas disruption of TAMs STAT3 activity can enhance rat immune response to breast cancer [149]. In glioblastoma patients, tumor-infiltrating macrophages were shown to be predominantly STAT3-positive M2 macrophages, which are associated with a poor prognosis [150]. The same team proposed that corosolic acid and oleic acid can prevent tumor formation through their capacity to suppress macrophages M2 polarization and tumor cell proliferation by inhibiting STAT3 activation [107,108]. CD163-targeted corosolic acid-containing liposomes were also shown to reprogram M2 macrophages into M1 (increased expression of TNF-α, IFN-γ, IL-12, IL-2 and decreased expression of IL-10) [109]. Since ERK5 mediates Y705 phosphorylation of STAT3 in myeloid cells, blocking ERK5 might constitute a treatment strategy to reprogram macrophages toward an antitumor state by inhibiting STAT3-induced gene expression [110]. In intrahepatic cholangiocarcinoma (ICC), patients with high counts of CD163+ M2 macrophages showed poor disease-free survival. Tumor cell supernatant from HuCCT1 ICC cell lines induces the production of IL-10 and VEGF-A by macrophages through activation of STAT3 and polarization towards the M2 phenotype [113]. Similarly, renal cell carcinoma-derived BMP (Bone Morphogenetic Protein)-6 mediates IL-10 expression in macrophages through Smad5 and STAT3, and M2 polarization [114]. These observations were confirmed by the fact
that macrophages isolated from mouse tumors displayed activated STAT3 and induced angiogenesis in an in vitro tube formation assay via STAT3 induction of angiogenic factors, including VEGF and βFGF [115]. STAT3 signaling within the tumor microenvironment induces the production of IL-23, a procarcinogenic cytokine, via direct transcriptional activation of the IL-23/p19 gene in TAMs, while inhibiting the production of IL-12, a central ant carcinogenic cytokine, thereby shifting the balance of tumor immunity towards carcinogenesis [44]. The M-CSF-inducible DC-SIGN (Dendritic cell-specific ICAM-3-grabbing nonintegrin or CD209) expression along monocyte-to-macrophage differentiation is dependent on JNK and STAT3 activation. DC-SIGN contributes to the release of IL-10 that would maintain STAT3 activation in tumor cells, thus implying that DC-SIGN favors the maintenance of an activated STAT3 context in the tumor stroma. This will compromise the ability of TAMs and DCs to generate an effective antitumor response and to maintain an immunosuppressive environment [111]. This effect is potentiated by STAT3-activating cytokines IL-6 and IL-10 produced by STAT3-activated tumor cells. In the same way, IL-6-derived from gastric cancer cells induces normal macrophages differentiation to M2 macrophages with higher IL-10 and TGF-β expression, and lower IL-12 expression, via STAT3 phosphorylation. IL-6-induced M2 macrophages exert a pro-tumor function by promoting GC cell proliferation and migration [151].

However, an anti-tumoral role of STAT3 in macrophages has also been proposed, based on studies that investigated the importance of STAT3 in macrophages through an indirect manner, using SOCS3 conditional knockout mice in macrophages. Hyperactivation of STAT3 in myeloid cells simultaneously exerted anti-inflammatory as well as anti-tumor effects [112]. Thus, Lipoxin A4 induces STAT3 phosphorylation and mediates differentiation of monocytic-like cells into M2 subtypes with anti-tumorigenic activities [152]. The discrepancies between these studies could be explained by the fact that SOCS3 and lipoxin signaling should regulate other pathways such as NF-κB.

3.2. Dendritic Cells (DCs)

DCs are another differentiated stage of monocytes and are the key APCs of the immune system. DCs play a main role as immune sentinels in the initiation of T-cell response against microbial pathogens, tumors and inflammation [153,154].

The first evidence that STAT3 is important for DCs fate was made in mice lacking STAT3 expression in hematopoietic progenitors. These animals present a profound deficiency in DCs which are unresponsive to Flt3L stimulation [116]. However, the same mice bearing a tumor, present enhanced DC, T-cell, NK cell and neutrophil functions and a decreased tumor progression [117]. DCs derived from LysMcre/STAT3flox/flox mice display higher cytokine production in response to TLR stimulation and activate more efficiently T-cells. Intratumoral administration of these DCs significantly inhibits MC38 tumor growth [119]. Moreover, ablating STAT3 in myeloid cells increases CpG-induced DCs maturation, T-cell activation, tumor antigen-specific T-cells generation and long-lasting antitumor immunity in B16 melanoma tumor model [102]. Similarly, CpG was used to administer STAT3 siRNA specifically to myeloid and B cells. Ablation of STAT3 in these cells increases DC engagement and adoptively transferred CD8+ T-cells effector functions in vivo, with an upregulation of effector molecules such as perforin, granzym B, and IFN-γ [118]. Mice without STAT3 in myeloid compartment of tumor stroma, including DCs and macrophages, present reduced numbers of tumor-infiltrating CD4+CD25+/FOXP3+/LAG3+ Tregs, along with an increase in CD8+ effector T-cells [117]. Constitutive STAT3 activation in tumor-residing DCs reduces expression of MHC class II and costimulatory molecules, impairs the antigen-presenting function of DC and contributes to the expansion of tumor-infiltrating FOXP3+ T-cells and attenuates CD4+ Th cell responses [117,122,123]. This can be partly explained by the fact that STAT3 inhibits the ID2 (inhibitor of differentiation 2) expression which promotes tumor immunity [124]. Finally, IL-6 is a suppressor of bone marrow-derived DC activation/maturation and a regulator of DC differentiation in vivo, through STAT3 phosphorylation. Then, DC differentiation/maturation is controlled by IL-6-gp130-STAT3, suggesting that this amplification loop may represent a target for controlling T-cell-mediated immune responses [155]. Similarly, mammary
tumor-derived exosomes inhibit the differentiation of murine myeloid precursor cells into DCs in vitro. This was correlated with an increased IL-6 level and phosphorylated STAT3 and was blocked in bone marrow cells derived from IL-6 knockout mice. This suggests that tumor cells can dampen DCs differentiation through an autocrine activation of STAT3 by IL-6 [125].

In humans, tumor-derived factors suppress DC generation through STAT3-mediated PKCβII reduced expression [156]. STAT3-depleted DCs with adenoviral STAT3 short hairpin RNA (shRNA) or siRNA presented an altered cytokines production profile under TLR stimulation (such as more IL-12 and TNF-α and less IL-10), and induced tumor Ag-specific T-cells and IFN-γ-producing γδ T lymphocytes more efficiently than control DCs [119–121]. The impact on IL-12 can be explained by a competition of STAT3 with CDK9 on a binding site on the IL-12p35 promoter [157]. The effects of STAT3 on IL-10 expression can be explained by the fact that HDAC6 forms a complex with STAT3, recruited to a specific DNA sequence element in the Il10 gene promoter [158].

3.3. Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs have been identified in humans and mice as a population of immature myeloid cells with the ability to suppress T-cell activation [159]. In tumor-bearing mice, these cells have been shown to markedly expand in lymphoid organs and blood [160]. In addition, an increased MDSCs frequency was detected in the blood of patients with different types of cancers [161,162]. In mice and humans, MDSCs from tumor bearers induce antigen-specific MHC class I restricted tolerance of CD8+ T-cells and are one of the major suppressors of antitumor immunity [163]. In humans the phenotype of MDSCs is a matter of debate. However, two major subsets of MDSCs have been identified: monocytic MDSCs (M-MDSCs), similar to monocytes and polymorphonuclear MDSCs (PMN-MDSCs) sharing phenotypic and morphologic features with neutrophils [164].

STAT3 is probably one of the main transcription factors that regulate MDSCs functions. MDSCs from tumor-bearing mice present high levels of phosphorylated STAT3, compared with immature myeloid cells from naive mice [128]. Moreover, ablation of STAT3 expression through the use of conditional knockout mice or selective STAT3 inhibitors (JSI-124) markedly reduce the expansion of MDSCs, promote accumulation of DCs and increase T-cell responses in tumor-bearing mice [117,127,128]. In mice, when STAT3 was specifically deleted in myeloid cells, the ability of MDSCs to inhibit CD4+ and CD8+ T-cell-dependent apoptosis by cell-cell contact and to induce Treg polarization through TGF-β, IL-10 and NOX2 secretion was decreased [131]. When STAT3 was specifically turned off in myeloid cells expressing TLR9 from prostate cancer patients, using a CpG-STAT3 siRNA or CpG-STAT3 antisense oligonucleotides, it abrogated the immunosuppressive effects of patient-derived MDSCs on effector CD8+ T-cells [129,130]. In contrast, deletion of SOCS3 in myeloid cells leads to an increased activation of the STAT3 and to differentiation into Gr-1+CD11b+Ly6G+ MDSCs, enhancing tumor growth [165]. STAT3 can also be regulated in MDSCs by the epigenetic-associated protein, p66α, which may physically interact with STAT3 to suppress its activity through posttranslational modification [166]. We have shown that tumor-derived exosome (TDE)-associated HSP70 led to STAT3 activation in MDSCs. This activation depends on TLR2/MyD88 and autocrine production of IL-6. TDEs from human tumor cell lines activate human MDSCs suppressive functions but not their expansion in an HSP70/TLR2-dependent manner, showing that the mechanism described in mice is also relevant in cancer patients [133]. In tumor cell supernatants, tumor soluble factors induce activation of ERK, which results in MDSCs expansion, while TDEs trigger STAT3 activation without promoting MDSCs expansion [133]. How can these discrepancies be explained? It is well known that STAT3 signaling in myeloid cells, entails the expression of Bcl-xL, c-myc, cyclin D1 or survivin, which favors cell proliferation and inhibits cell apoptosis and differentiation to mature cell types [15,167].

STAT3 controls the G-CSF-and G-MCSF responsive induction of C/EBPβ (CCAAT-enhancer-binding protein β) expression and the interferon regulatory factor 8 (IRF8) downregulation in myeloid cells [126,134]. The transcription factor C/EBPβ was reported to play a crucial role in controlling the differentiation of myeloid precursors to functional MDSCs [126] whereas IRF8 attenuated MDSC
accumulation, phenotype and function [134]. These data suggest also a link between CSF and STAT3 pathway in the regulation of MDSC biology.

Finally, recent studies highlighted the importance of signaling pathways downstream STAT3 in MDSCs differentiation. MDSCs isolated from mouse tumors present activated STAT3. STAT3 favors the production of angiogenic factors, including VEGF and βFGF to induce angiogenesis in an in vitro tube formation assay [115]. STAT3 as well as STAT5 control the cytokine-induced expression of the cytoplasmic NADPH oxidase NOX2 [168], being e.g., crucial for DNA damage response in AML cells, leading together with mitochondrial ROS production, which is a predominant STAT3 affair to the production of ROS, responsible for MDSCs-induced immune suppression in murine colon, lung, mammary carcinoma, thymoma, sarcoma models and in patients with head and neck cancers [132]. STAT3 also favors immunosuppressive functions of MDSCs by inducing the expression and the activity of IDO (Indoleamine 2,3-dioxygenase 1) in breast [137] and liver [135] cancers or arginase-1 in head and neck squamous cell carcinoma [136]. STAT3-inducible up-regulation of the myeloid-related protein S100A9 enhances MDSCs production in cancer. Mice lacking this protein mount potent antitumor immune responses and reject implanted tumors, an effect reversed by administration of wild-type MDSCs [169].

However, STAT3 activity can be endogenously controlled in intra-tumoral MDSCs. Thus, tumor hypoxia led to CD45 protein tyrosine phosphatases activation, resulting in STAT3 activity downregulation and in M-MDSC differentiation into tumor-promoting TAMs [138].

Moreover, many inhibitors were proposed such as the XIAP inhibitor embelin [139], PM01183 a novel synthetic agent derived from trabectedin [140], alisertib (MLN8237), a small-molecule inhibitor of Auror-A kinase [141], STATTIC or BBI608 [142] to inhibit STAT3 in MDSCs with a potential clinical application to favor anti-tumor response.

4. STAT3 and Check Points Inhibitors

The emergence of immune ‘checkpoint inhibitors’, blocking negative regulators of T-cell immunity opened new clinical applications of cancer immunotherapies. The more widely studied are cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death receptor 1 (PD-1). CTLA-4 is mainly expressed on T helper and Treg cells and binds to its ligands B7-1 (CD80) and B7-2 (CD86) on APCs [170]. PD-1 expression is induced both on activated CD8+ T-cells, Tfh and Treg present in tumor microenvironment, and on activated B cells and NK cells. PD-1 has two ligands: PD-L1 (B7-H1) and PD-L2 (B7-DC). PD-1 signaling contributes to T-cell exhaustion [170]. Other checkpoints can also be implicated in tumor immune escape such as Lymphocyte activation gene 3 protein (LAG-3) and T-cell immunoglobulin and mucin domain-containing 3 (TIM-3), IDO1, B- and T-lymphocyte attenuator (BTLA), V-domain immunoglobulin suppressor of T-cell activation (VISTA) and the A2A adenosine receptor (A2A-R) [170,171].

STAT3 can bind the promoter of murine Pdcd1 gene coding for PD-1 in T-cells [172]. STAT3 has been demonstrated to bind to the Pdcd111 promoter (coding for PD-L1) to regulate its transcriptional expression in cancer cells. It requires either mutated oncogene chimeric nucleophosmin/anaplastic lymphoma kinase (ALK) in T-cell lymphoma [173], Latent membrane protein-1 (LMP1) of Epstein–Barr virus in nasopharyngeal carcinoma [174], HDAC6 in osteosarcoma [175], NF-κB in melanoma [176] or HIF-1α in pulmonary adenocarcinoma [177]. In contrast, a study shows that STAT3 is necessary for docetaxel-mediated inhibition of PD-1 expression [178].

In CRC patients, FGFR2 expression is correlated to PD-L1 expression. FGFR2 stimulation leads to STAT3 activation, PD-L1 expression and colon cancer cell death [179]. The EGFR signaling pathway can also regulate PD-L1 expression through the IL-6/JAK/STAT3 pathway in non-small cell lung cancer (NSCLC) cells [180,181]. The expression of PD-L1 is associated with a poor prognosis and inhibition of PD-L1 expression (e.g., through STAT3 or its partner inhibition) is associated to a decrease in cell proliferation and/or an increase in tumor cell death in most of these studies. However, the effects on T-cell anti-tumor response were not tested here.
PD-L1/L2 can be expressed in non-tumoral cells. In liver MDSCs, GM-CSF is responsible for STAT3 activation which in turn induces PD-L1 and IDO1 expression [135]. GBM cells secrete IL-6 which in turn activates STAT3 in infiltrated myeloid cells leading to STAT3 activation and PD-L1 expression. An anti-IL-6 therapy decreases PD-L1 expression and tumor size in a CD8$^+$ T-cell-dependent manner [182]. In HCC, a similar regulation was observed. In this setting, the HCC-associated fibroblasts produce IL-6 which in turn increases PD-L1 expression in neutrophils [183]. Similarly, in prostate carcinoma, DC generated in the presence of stromal myofibroblasts factors expressed significantly elevated levels of PD-L1 in a STAT3 and IL-6-dependent manner [184]. In chronic lymphocytic leukemia (CLL), STAT3 is required to PD-L1 expression and IL-10 production which in turn seems to be responsible for PD-1 expression in CD4$^+$ and CD8$^+$ T-cells [185]. In adult T-cell lymphoma, IL-27B production by Lymphoma cells and IL-27p28 production by macrophages lead to STAT3 activation and PD-L1/L2 expression in macrophages [186]. TGF-$\beta$ is another cytokine secreted by inflammatory or tumor cells that can increase PD-L1 expression in DC in a STAT3-dependent manner [187]. The use of IFN-$\alpha$ in clinical oncology for many types of cancers is reconsidered, as IFN-$\alpha$ induces the expression of PD-L1 molecule, in the majority of the specific immune cell populations, particularly in DCs [188]. However, it should be noted that interferons are highly liver toxic and they act on all cell types in the body, where many unwanted side effects from neurotoxic problems to fever symptoms were reported in therapy, making their window of opportunity in fragile patients delicate.

Little is known about the ability of STAT3 to regulate other checkpoints. One study shows that STAT3/IRF1 are required for PD-L2 expression in melanoma cells [189]. In a non-cancerous context, it has been shown that CTLA-4 as well as PD-1, LAG-3 and TIM-3 expression is induced in HIV-infected DCs in a STAT3-dependent manner [190].

In contrast, the immunosuppressive effect of these checkpoints can be dependent on STAT3 activation in target-cells. For example, IDO1 may promote EMT (Epithelial-Mesenchymal Transition) by activation of the IL-6/STAT3/PD-1 signaling pathway [191]. TIM-3$^+$ endothelial cells modulate T-cell response to lymphoma surrogate antigens by suppressing activation of CD4$^+$ T lymphocytes through the activation of the IL-6-STAT3 pathway, inhibiting Th1 polarization and providing protective immunity [192]. Finally, CTLA-4 critically shapes the characteristics of IL-17 producing CD8$^+$ cells (Tc17 a pro-tumoral population) in a STAT3 activation-dependent manner and inhibition of CTLA-4-induced STAT3 activity reverses Tc17 signature to Tc1-like cells with enhanced cytotoxic potential [193].

5. Conclusions

STAT3 regulates genes involved in biological functions of cancer and immune cells, rendering this pathway an interesting therapeutic target. STAT3 could be inhibited directly by peptides or natural compounds or indirectly by blocking upstream signaling pathways such as IL-6 and JAK2 pathways (For review see [194,195]). However, the complexity of STAT3 biology and its broad effects may render its clinical development complex. This review underlines the ambivalent effects of STAT3 on the antitumoral immune response, with both positive or negative effects, depending on the context or cell types involved. Additional translational studies on patients treated with STAT3 inhibitors are awaited to understand their effects on the complexity of tumor biology.

Funding: This research was funded by Ligue Nationale Contre le Cancer.

Acknowledgments: We thank Isabel Gregoire for carefully reading the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Kosack, L.; Wingelhofer, B.; Popa, A.; Orlova, A.; Agerer, B.; Vilagos, B.; Majek, P.; Parapatics, K.; Lercher, A.; Ringler, A.; et al. The ERBB-STAT3 Axis Drives Tasmanian Devil Facial Tumor Disease. Cancer Cell 2019, 35, 125–139. [CrossRef] [PubMed]
2. Yoshimura, A.; Naka, T.; Kubo, M. SOCS proteins, cytokine signalling and immune regulation. *Nat. Rev. Immunol.* 2007, 7, 454–465. [CrossRef] [PubMed]

3. Hirano, T.; Ishihara, K.; Hibi, M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. *Oncogene* 2000, 19, 2548–2556. [CrossRef] [PubMed]

4. Yuan, Z.L.; Guan, Y.J.; Chatterjee, D.; Chin, Y.E. Stat3 dimerization regulated by reversible acetylation of a single lysine residue. *Science* 2005, 307, 269–273. [CrossRef] [PubMed]

5. Meier, J.A.; Larner, A.C. Toward a new STATe: The role of STATs in mitochondrial function. *Semin. Immunol.* 2014, 26, 20–28. [CrossRef]

6. Avalle, L.; Poli, V. Nucleus, Mitochondrion, or Reticulum? STAT3 a La Carte. *Int. J. Mol. Sci.* 2018, 19, 2820. [CrossRef] [PubMed]

7. Shuai, K.; Liu, B. Regulation of gene-activation pathways by PIAS proteins in the immune system. *Nat. Rev. Immunol.* 2005, 5, 593–605. [CrossRef]

8. Alexander, W.S.; Hilton, D.J. The role of suppressors of cytokine signaling (SOCS) proteins in regulation of the immune response. *Annu Rev. Immunol.* 2004, 22, 503–529. [CrossRef]

9. Migone, T.S.; Cacalano, N.A.; Taylor, N.; Yi, T.; Waldmann, T.A.; Johnston, J.A. Recruitment of SH2-containing protein tyrosine phosphatase SHP-1 to the interleukin 2 receptor; loss of SHP-1 expression in human T-lymphotropic virus type I-transformed T cells. *Proc. Natl. Acad. Sci. USA* 1998, 95, 3845–3850. [CrossRef]

10. Schaper, F.; Gendo, C.; Eck, M.; Schmitz, J.; Grimm, C.; Anhuf, D.; Kerr, I.M.; Heinrich, P.C. Activation of the protein tyrosine phosphatase SHP2 via the interleukin-6 signal transducing receptor protein gp130 requires tyrosine kinase Jak1 and limits acute-phase protein expression. *Biochem. J.* 2000, 405, 349–354. [CrossRef] [PubMed]

11. Daino, H.; Matsumura, I.; Takada, K.; Odajima, J.; Tanaka, H.; Ueda, S.; Shibayama, H.; Ikeda, H.; Hibi, M.; Machii, T.; et al. Induction of apoptosis by extracellular ubiquitin in human hematopoietic cells: Possible involvement of STAT3 degradation by proteasome pathway in interleukin 6-dependent hematopoietic cells. *Blood* 2000, 95, 2577–2585. [PubMed]

12. Delgoffe, G.M.; Vignali, D.A. STAT heterodimers in immunity: A mixed message or a unique signal? *JAKSTAT* 2013, 2, e23060. [CrossRef] [PubMed]

13. Bromberg, J.; Darnell, J.E., Jr. The role of STATs in transcriptional control and their impact on cellular function. *Oncogene* 2000, 19, 2468–2473. [CrossRef] [PubMed]

14. Yu, H.; Pardoll, D.; Jove, R. STATs in cancer inflammation and immunity: A leading role for STAT3. *Nat. Rev. Cancer* 2009, 9, 798–809. [CrossRef] [PubMed]

15. Rebe, C.; Vegran, F.; Berger, H.; Ghiringhelli, F. STAT3 activation: A key factor in tumor immunoevasion. *JAKSTAT* 2013, 2, e23010. [CrossRef]

16. Zhang, H.F.; Lai, R. STAT3 in Cancer-Friend or Foe? *Cancers* 2014, 6, 1408–1440. [CrossRef] [PubMed]

17. Burchill, M.A.; Goetz, C.A.; Prlic, M.; O’Neil, J.J.; Harmon, I.R.; Bensinger, S.J.; Turka, L.A.; Brennan, P.; Jameson, S.C.; Farrar, M.A. Distinct effects of STAT5 activation on CD4+ and CD8+ T cell homeostasis: Development of CD4+CD25+ regulatory T cells versus CD8+ memory T cells. *J. Immunol.* 2003, 171, 5853–5864. [CrossRef]

18. Agnello, D.; Lankford, C.S.; Bream, J.; Morinobu, A.; Gadina, M.; O’Shea, J.J.; Frucht, D.M. Cytokines and transcription factors that regulate T helper cell differentiation: New players and new insights. *J. Clin. Immunol.* 2003, 23, 147–161. [CrossRef]

19. Yao, Z.; Kanno, Y.; Kerenyi, M.; Stephens, G.; Durant, L.; Watford, W.T.; Laurence, A.; Robinson, G.W.; Shevach, E.M.; Morrigl, R.; et al. Nonredundant roles for Stat5a/b in directly regulating Foxp3. *Blood* 2007, 109, 4368–4375. [CrossRef]

20. Shiku, H. Importance of CD4+ helper T-cells in antitumor immunity. *Int. J. Hematol.* 2003, 77, 435–438. [CrossRef] [PubMed]

21. Galon, J.; Costes, A.; Sanchez-Cabo, F.; Kirilovsky, A.; Mlecnik, B.; Lagorce-Pages, C.; Tosolini, M.; Camus, M.; Berger, A.; Wind, P.; et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. *Science* 2006, 313, 1960–1964. [CrossRef] [PubMed]
23. Marrogi, A.J.; Munshi, A.; Merogi, A.J.; Ohadike, Y.; El-Habashi, A.; Marrogi, O.L.; Freeman, S.M. Study of tumor infiltrating lymphocytes and transforming growth factor-beta as prognostic factors in breast carcinoma. *Int. J. Cancer* 1997, 74, 492–501. [CrossRef]

24. Hiraoka, K.; Miyamoto, M.; Cho, Y.; Suzuki, M.; Oshikiri, T.; Nakakubo, Y.; Itoh, T.; Obuchi, T.; Kondo, S.; Katoh, H. Concurrent infiltration by CD8+ T cells and CD4+ T cells is a favourable prognostic factor in non-small-cell lung carcinoma. *Br. J. Cancer* 2006, 94, 275–280. [CrossRef] [PubMed]

25. Tutting, T.; Storkus, W.J.; Lotze, M.T. Gene-based strategies for the immunotherapy of cancer. *J. Mol. Med.* 1997, 75, 478–491. [CrossRef]

26. Knutson, K.L.; Disis, M.L. Tumor antigen-specific T helper cells in cancer immunity and immunotherapy. *Cancer Immunol. Immunother.* 2005, 54, 721–728. [CrossRef]

27. Owaki, T.; Asakawa, M.; Morishima, N.; Mizoguchi, I.; Fukai, F.; Takeda, K.; Mizuguchi, J.; Yoshimoto, T. Modulation. *Cancer Res.* 1997, 54, 721–728. [CrossRef]

28. Ma, C.S.; Wong, N.; Rao, G.; Nguyen, A.; Avery, D.T.; Payne, K.; Torpy, J.; O'Young, P.; Deenick, E.; Laurence, A.; Tato, C.M.; Davidson, T.S.; Kanno, Y.; Chen, Z.; Yao, Z.; Blank, R.B.; Meylan, F.; Siegel, R.; Laurence, A.; Tato, C.M.; Davidson, T.S.; Kanno, Y.; Chen, Z.; Yao, Z.; Blank, R.B.; Meylan, F.; Siegel, R.; Mauldin, I.S.; Tung, K.S.; Lorenz, U.M. The tyrosine phosphatase SHP-1 dampens murine Th17 development. *Blood* 2012, 120, 2961–2970. [CrossRef] [PubMed]

29. Owaki, T.; Asakawa, M.; Morishima, N.; Mizoguchi, I.; Fukai, F.; Takeda, K.; Mizuguchi, J.; Yoshimoto, T. STAT3 Deacetylation. *Cell Rep.* 2017, 19, 746–759. [CrossRef]

30. Zhang, Y.; Ma, C.A.; Lawrence, M.G.; Break, T.J.; O'Connell, M.P.; Lyons, J.J.; Lopez, D.B.; Barber, J.S.; Harris, T.J.; Grosso, J.F.; Yen, H.R.; Xin, H.; Kortylewski, M.; Albesiano, E.; Hipkiss, E.L.; Getnet, D.; Marrogi, A.J.; Munshi, A.; Merogi, A.J.; Ohadike, Y.; El-Habashi, A.; Marrogi, O.L.; Freeman, S.M. Study of pathways. *Nat. Immunol.* 2007, 8, 967–974. [CrossRef] [PubMed]

31. Nishihara, M.; Ogura, H.; Ueda, N.; Tsuruoka, M.; Kitabayashi, C.; Tsuji, F.; Aono, H.; Ishihara, K.; Huseby, E.; Betz, U.A.; et al. IL-6-gp130-STAT3 in T cells directs the development of IL-17+ Th with a minimum effect on that of Treg in the steady state. *Int. Immunol.* 2007, 19, 695–702. [CrossRef] [PubMed]

32. Zhou, L.; Ivanov, I.I.; Spolski, R.; Min, R.; Shenderov, K.; Egawa, T.; Levy, D.E.; Leonard, W.J.; Littman, D.R. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat. Immunol.* 2007, 8, 967–974. [CrossRef] [PubMed]

33. Zhang, Y.; Ma, C.A.; Lawrence, M.G.; Break, T.J.; O'Connell, M.P.; Lyons, J.J.; Lopez, D.B.; Barber, J.S.; Zhao, Y.; Barber, D.L.; et al. PD-L1 up-regulation restrains Th17 cell differentiation in STAT3 loss- and STAT1 gain-of-function patients. *J. Exp. Med.* 2017, 214, 2523–2533. [CrossRef]

34. Laurence, A.; Tato, C.M.; Davidson, T.S.; Kanno, Y.; Chen, Z.; Yao, Z.; Blank, R.B.; Meylan, F.; Siegel, R.; Nishihara, M.; Ogura, H.; Ueda, N.; Tsuruoka, M.; Kitabayashi, C.; Tsuji, F.; Aono, H.; Ishihara, K.; Huseby, E.; Betz, U.A.; et al. IL-6-gp130-STAT3 in T cells directs the development of IL-17+ Th with a minimum effect on that of Treg in the steady state. *Int. Immunol.* 2007, 19, 695–702. [CrossRef] [PubMed]

35. Marrogi, A.J.; Munshi, A.; Merogi, A.J.; Ohadike, Y.; El-Habashi, A.; Marrogi, O.L.; Freeman, S.M. Study of tumor infiltrating lymphocytes and transforming growth factor-beta as prognostic factors in breast carcinoma. *Int. J. Cancer* 1997, 74, 492–501. [CrossRef]

36. Laurence, A.; Tato, C.M.; Davidson, T.S.; Kanno, Y.; Chen, Z.; Yao, Z.; Blank, R.B.; Meylan, F.; Siegel, R.; Hennighausen, L.; et al. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity* 2007, 26, 371–381. [CrossRef] [PubMed]

37. Yang, X.O.; Panopoulos, A.D.; Nurieva, R.; Chang, S.H.; Wang, D.; Watowich, S.S.; Dong, C. STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. *J. Biol Chem* 2007, 282, 9358–9363. [CrossRef] [PubMed]

38. Yang, X.O.; Panopoulos, A.D.; Nurieva, R.; Chang, S.H.; Wang, D.; Watowich, S.S.; Dong, C. STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. *J. Biol Chem* 2007, 282, 9358–9363. [CrossRef] [PubMed]

39. Yang, X.O.; Panopoulos, A.D.; Nurieva, R.; Chang, S.H.; Wang, D.; Watowich, S.S.; Dong, C. STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. *J. Biol Chem* 2007, 282, 9358–9363. [CrossRef] [PubMed]

40. Chalmin, F.; Mignot, G.; Bruchard, M.; Chevriaux, A.; Vegran, F.; Hichami, A.; Ladoire, S.; Derangere, V.; Vincent, J.; Masson, D.; et al. STAT3 and Gfi-1 transcription factors control Th17 cell immunosuppressive activity via the regulation of ectonucleotidase expression. *Immunity* 2012, 36, 362–373. [CrossRef]
41. Zhou, J.; Li, X.; Wu, X.; Zhang, T.; Zhu, Q.; Wang, X.; Wang, H.; Wang, K.; Lin, Y.; Wang, X. Exosomes Released from Tumor-Associated Macrophages Transfer miRNAs That Induce a Treg/Th17 Cell Imbalance in Epithelial Ovarian Cancer. Cancer Immunol. Res. 2018, 6, 1578–1592. [CrossRef] [PubMed]

42. Zorn, E.; Nelson, E.A.; Mohseni, M.; Porcheray, F.; Kim, H.; Litsa, D.; Bellucci, R.; Raderschall, E.; Canning, C.; Soiffer, R.J.; et al. IL-2 regulates FOXP3 expression in human CD4+CD25+ regulatory T cells through a STAT3-dependent mechanism and induces the expansion of these cells in vivo. Blood 2006, 108, 1571–1579. [CrossRef] [PubMed]

43. Kortylewski, M.; Xin, H.; Kujawski, M.; Lee, H.; Liu, Y.; Harris, T.; Drake, C.; Pardoll, D.; Yu, H. Regulation of the IL-23 and IL-12 balance by Stat3 signaling in the tumor microenvironment. Cancer Cell 2009, 15, 114–123. [CrossRef] [PubMed]

44. Chen, M.M.; Xiao, X.; Lao, X.M.; Wei, Y.; Liu, R.X.; Zeng, Q.H.; Wang, J.C.; Ouyang, F.Z.; Chen, D.P.; Oweida, A.J.; Darragh, L.; Phan, A.; Binder, D.; Bhatia, S.; Mueller, A.; Van Court, B.; Milner, D.; Raben, D.; Woessner, R.; et al. The role of regulatory T cells in the response to radiation therapy in head and neck cancer. J. Natl. Cancer Inst. 2018, 110, 1145–1158. [CrossRef] [PubMed]

45. Hercor, M.; Anciaux, M.; Denanglaire, S.; Debuisson, D.; Leo, O.; Andris, F. Antigen-presenting cell-derived IL-6 restricts the expression of GATA3 and IL-4 by follicular helper T cells. J. Leukoc. Biol. 2012, 92, 3297–3304. [CrossRef] [PubMed]

46. Huber, M.; Steinwald, V.; Guralnik, A.; Brustle, A.; Kleemann, P.; Rosenplanter, C.; Decker, T.; Lohoff, M. IL-27 inhibits the development of regulatory T cells via STAT3. Cell Rep. 2015, 15, 14615. [CrossRef] [PubMed]

47. Lam, E.; Choi, S.H.; Pareek, T.K.; Kim, B.G.; Letterio, J.J. Cyclin-dependent kinase 5 represses Foxp3 gene expression and Treg development through specific phosphorylation of Stat3 at Ser 727. Mol. Immunol. 2015, 67, 317–324. [CrossRef] [PubMed]

48. Li, D.; Kong, C.; Tsun, A.; Chen, C.; Song, H.; Shi, G.; Pan, W.; Dai, D.; Shen, N.; Li, B. MiR-125a-5p Decreases the Sensitivity of Treg cells Toward IL-6-Mediated Conversion by Inhibiting IL-6R and STAT3 Expression. Sci Rep. 2015, 5, 14615. [CrossRef] [PubMed]

49. Xiao, W.; Yin, M.; Wu, K.; Lu, G.; Deng, B.; Zhang, Y.; Qian, L.; Jia, X.; Ding, Y.; Gong, W. High-dose wogonin exacerbates DSS-induced colitis by up-regulating effector T cell function and inhibiting Treg cell. J. Cell Mol. Med. 2017, 21, 286–298. [CrossRef] [PubMed]

50. Kong, L.Y.; Wei, J.; Sharma, A.K.; Barr, J.; Abou-Ghazal, M.K.; Fokt, I.; Weinberg, J.; Rao, G.; Grimm, E.; Priebe, W.; et al. A novel phosphorylated STAT3 inhibitor enhances T cell cytotoxicity against melanoma through inhibition of regulatory T cells. Cancer Immunol. Immunother. 2009, 58, 1023–1032. [CrossRef] [PubMed]

51. He, W.; Zhu, Y.; Mu, R.; Xu, J.; Zhang, X.; Wang, C.; Li, Q.; Huang, Z.; Zhang, J.; Pan, Y.; et al. A Jak2-selective inhibitor potently reverses the immune suppression by modulating the tumor microenvironment for cancer immunotherapy. Biochem. Pharmacol. 2017, 145, 132–146. [CrossRef] [PubMed]

52. Oweida, A.J.; Darragh, L.; Phan, A.; Binder, D.; Bhatia, S.; Mueller, A.; Van Court, B.; Milner, D.; Raben, D.; Woessner, R.; et al. The role of regulatory T cells in the response to radiation therapy in head and neck cancer. J. Natl. Cancer Inst. 2019. [CrossRef] [PubMed]

53. Schmitt, N.; Liu, Y.; Bentebibel, S.E.; Munagala, I.; Bourdery, L.; Venuprasad, K.; Banchereau, J.; Ueno, H. The cytokine TGF-beta co-opts signaling via STAT3-STAT4 to promote the differentiation of human TFF cells. Nat. Immunol. 2014, 15, 856–865. [CrossRef] [PubMed]

54. Ma, C.S.; Avery, D.T.; Chan, A.; Batten, M.; Bustamante, J.; Boisson-Dupuis, S.; Arkwright, P.D.; Kreins, A.Y.; Averbuch, D.; Engelhard, D.; et al. Functional STAT3 deficiency compromises the generation of human T follicular helper cells. Blood 2012, 119, 3997–4008. [CrossRef] [PubMed]

55. Hiscott, M.; Aniaux, M.; Denanglaire, S.; Debuissin, D.; Leo, O.; Andris, F. Antigen-presenting cell-derived IL-6 restricts the expression of GATA3 and IL-4 by follicular helper T cells. J. Leukoc. Biol. 2017, 101, 5–14. [CrossRef] [PubMed]

56. Chen, M.M.; Xiao, X.; Lao, X.M.; Wei, Y.; Liu, R.X.; Zeng, Q.H.; Wang, J.C.; Ouyang, F.Z.; Chen, D.P.; Chan, K.W.; et al. Polarization of Tissue-Resident TFH-Like Cells in Human Hepatoma Bridges Innate Monocyte Inflammation and M2b Macrophage Polarization. Cancer Discov. 2016, 6, 1182–1195. [CrossRef] [PubMed]

57. Olson, M.R.; Verdan, F.F.; Hufford, M.M.; Dent, A.L.; Kaplan, M.H. STAT3 Impairs STAT5 Activation in the Development of IL-9-Secreting T Cells. J. Immunol. 2016, 196, 3297–3304. [CrossRef] [PubMed]

58. Ulrich, B.J.; Verdan, F.F.; McKenzie, A.N.; Kaplan, M.H.; Olson, M.R. STAT3 Activation Impairs the Stability of Th9 Cells. J. Immunol. 2017, 198, 2302–2309. [CrossRef] [PubMed]
59. Zhang, Y.; Siegel, A.M.; Sun, G.; Dimaggio, T.; Freeman, A.F.; Milner, J.D. Human TH9 differentiation is dependent on signal transducer and activator of transcription (STAT) 3 to restrain STAT1-mediated inhibition. J. Allergy Clin. Immunol. 2019, 143, 1108–1118. [CrossRef]

60. Yue, C.; Shen, S.; Deng, J.; Priceman, S.J.; Li, W.; Huang, A.; Yu, H. STAT3 in CD8+ T Cells Inhibits Their Tumor Accumulation by Downregulating CXCR3/CXCL10 Axis. Cancer Immunol. Res. 2015, 3, 864–870. [CrossRef]

61. Kujawski, M.; Zhang, C.; Herrmann, A.; Reckamp, K.; Scuto, A.; Jensen, M.; Deng, J.; Forman, S.; Figlin, R.; Yu, H. Targeting STAT3 in adoptively transferred T cells promotes their in vivo expansion and antitumor effects. Cancer Res. 2010, 70, 9599–9610. [CrossRef] [PubMed]

62. Hu, J.; Bath, I.S.; Xia, X.; Li, S. Regulation of NKG2D(+)CD8(+) T-cell-mediated antitumor immune surveillance: Identification of a novel CD28 activation-mediated, STAT3 phosphorylation-dependent mechanism. OncolImmunology 2016, 5, e1252012. [CrossRef] [PubMed]

63. Tosolini, M.; Kirilovsky, A.; Mlecnik, B.; Fredriksen, T.; Mauger, S.; Bindea, G.; Berger, A.; Bruneval, P.; Fridman, W.H.; Pages, F.; et al. Clinical impact of different classes of infiltrating T cytokotic and helper cells (Th1, Th2, Treg, Th17) in patients with colorectal cancer. Cancer Res. 2011, 71, 1263–1271. [CrossRef] [PubMed]

64. Szabo, S.J.; Kim, S.T.; Costa, G.L.; Zhang, X.; Fathman, C.G.; Glimcher, L.H. A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell 2000, 100, 655–669. [CrossRef]

65. Zheng, W.; Flavell, R.A. The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. Cell 1997, 89, 587–596. [CrossRef]

66. Yoshimoto, T.; Yasuda, K.; Mizuguchi, J.; Nakanishi, K. IL-27 suppresses Th2 cell development and Th2 cytokines production from polarized Th2 cells: A novel therapeutic way for Th2-mediated allergic inflammation. J. Immunol. 2007, 179, 4415–4423. [CrossRef] [PubMed]

67. Chen, Z.; O’Shea, J.J. Th17 cells: A new fate for differentiating helper T cells. Immunol. Res. 2008, 41, 87–102. [CrossRef]

68. Van den Berg, W.B.; Miossec, P. IL-17 as a future therapeutic target for rheumatoid arthritis. Nat. Rev. Rheumatol. 2009, 5, 549–553. [CrossRef]

69. Su, X.; Ye, J.; Hsueh, E.C.; Zhang, Y.; Hoft, D.F.; Peng, G. Tumor microenvironments direct the recruitment and expansion of human Th17 cells. J. Immunol. 2010, 184, 1630–1641. [CrossRef]

70. Hemdan, N.Y. Anti-cancer versus cancer-promoting effects of the interleukin-17-producing T helper cells. Immunol. Lett. 2013, 149, 123–133. [CrossRef]

71. Ivanov, I.I.; McKenzie, B.S.; Zhou, L.; Tadokoro, C.E.; Lepelley, A.; Lafaille, J.J.; Cua, D.J.; Littman, D.R. The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. Cell 2006, 126, 1121–1133. [CrossRef] [PubMed]

72. Jiang, Y.; Liu, Y.; Lu, H.; Sun, S.C.; Jin, W.; Wang, X.; Dong, C. Epigenetic activation during Th helper 17 cell differentiation is mediated by Tripartite motif containing 28. Nat. Commun. 2018, 9, 1424. [CrossRef]

73. Fang, S.; Liu, B.; Sun, Q.; Zhao, J.; Qi, H.; Li, Q. Platelet factor 4 inhibits IL-17/Stat3 pathway via upregulation of SOCS3 expression in melanoma. Inflammation 2014, 37, 1744–1750. [CrossRef] [PubMed]

74. Ghoreschi, K.; Laurence, A.; Yang, X.P.; Tato, C.M.; McGechy, M.J.; Konkel, J.E.; Ramos, H.L.; Wei, L.; Davidson, T.S.; Bouladoux, N.; et al. Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature 2010, 467, 967–971. [CrossRef] [PubMed]

75. Sakaguchi, S. Regulatory T cells: Key controllers of Immunologic self-tolerance. Cell 2000, 101, 455–458. [CrossRef]

76. Shevach, E.M. CD4+ CD25+ suppressor T cells: More questions than answers. Nat. Rev. Immunol. 2002, 2, 389–400. [CrossRef] [PubMed]

77. Chen, W.; Jin, W.; Hardegen, N.; Lei, K.J.; Li, L.; Marinos, N.; McGrady, G.; Wahl, S.M. Conversion of peripheral CD4+CD25− naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J. Exp. Med. 2003, 198, 1875–1886. [CrossRef] [PubMed]

78. Nishikawa, H.; Sakaguchi, S. Regulatory T cells in tumor immunity. Int. J. Cancer 2010, 127, 759–767. [CrossRef] [PubMed]

79. Curiel, T.J.; Coukos, G.; Zou, L.; Alvarez, X.; Cheng, P.; Mottram, P.; Evdemon-Hogan, M.; Conejo-Garcia, J.R.; Zhang, L.; Burow, M.; et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat. Med. 2004, 10, 942–949. [CrossRef]
80. Bates, G.J.; Fox, S.B.; Han, C.; Leek, R.D.; Garcia, J.F.; Harris, A.L.; Banham, A.H. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. *J. Clin. Oncol.* 2006, 24, 5373–5380. [CrossRef]

81. Perrone, G.; Ruffini, P.A.; Catalano, V.; Spino, C.; Santini, D.; Muretto, P.; Spoto, C.; Zingaretti, C.; Sisti, V.; Alessandroni, P.; et al. Intratumoural FOXP3-positive regulatory T cells are associated with adverse prognosis in radically resected gastric cancer. *Eur. J. Cancer* 2008, 44, 1875–1882. [CrossRef] [PubMed]

82. Chaudhry, A.; Rudra, D.; Treuting, P.; Samstein, R.M.; Liang, Y.; Kas, A.; Rudensky, A.Y. CD4+ regulatory T cells control TH17 responses in a Stat3-dependent manner. *Science* 2009, 326, 986–991. [CrossRef] [PubMed]

83. Wuest, T.Y.; Willette-Brown, J.; Durum, S.K.; Hurwitz, A.A. The influence of IL-2 family cytokines on activation and function of naturally occurring regulatory T cells. *J. Leukoc. Biol.* 2008, 84, 973–980. [CrossRef] [PubMed]

84. Xu, L.; Kitani, A.; Stuelten, C.; McGrady, G.; Strober, W. Positive and negative transcriptional regulation of the Foxp3 gene is mediated by access and binding of the Smad3 protein to enhancer I. *Immunity* 2010, 33, 313–325. [CrossRef] [PubMed]

85. Laurence, A.; Amarnath, S.; Mariotti, J.; Kim, Y.C.; Foley, J.; Eckhaus, M.; O’Shea, J.J.; Fowler, D.H. STAT3 Transcription Factor Promotes Instability of nTreg Cells and Limits Generation of iTreg Cells during Acute Murine Graft-versus-Host Disease. *Immunity* 2012, 37, 209–222. [CrossRef] [PubMed]

86. Eivazi, S.; Bagheri, S.; Hashemzadeh, M.S.; Ghalavand, M.; Qamsari, E.S.; Dorostkar, R.; Yasemi, M. Development of T follicular helper cells and their role in disease and immune system. *Biomed. Pharmacother.* 2016, 84, 1668–1678. [CrossRef] [PubMed]

87. Qin, L.; Waseem, T.C.; Sahoo, A.; Bieerkehazbi, S.; Zhou, H.; Galkina, E.V.; Nurieva, R. Insights Into the Molecular Mechanisms of T Follicular Helper-Mediated Immunity and Pathology. *Front. Immunol.* 2018, 9, 1884. [CrossRef] [PubMed]

88. Gu-Trantien, C.; Loi, S.; Garaud, S.; Equeter, C.; Libin, M.; de Wind, A.; Ravoet, M.; Le Buanc, H.; Sibille, C.; Manfouo-Foutsop, G.; et al. CD4(+) follicular helper T cell infiltration predicts breast cancer survival. *J. Clin. Invest.* 2013, 123, 2873–2892. [CrossRef] [PubMed]

89. Bindea, G.; Micenk, B.; Tosolini, M.; Kirilovsky, A.; Waldner, M.; Obenauf, A.C.; Angell, H.; Fredriksen, T.; Lafontaine, L.; Berger, A.; et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. *Immunity* 2013, 39, 782–795. [CrossRef]

90. Alshekaili, J.; Chand, R.; Lee, C.E.; Corley, S.; Li, S.; Papa, I.; Fulcher, D.A.; Randall, K.L.; Leiding, J.W.; Ma, C.S.; et al. STAT3 regulates cytotoxicity of human CD57+ CD4+ T cells in blood and lymphoid follicles. *Sci. Rep.* 2018, 8, 3529. [CrossRef]

91. Ray, J.P.; Marshall, H.D.; Laidlaw, B.J.; Staron, M.M.; Kaech, S.M.; Craft, J. Transcription factor STAT3 and type I interferons are corepressors of differentiation for follicular helper and T helper 1 cells. *Immunity* 2014, 40, 367–377. [CrossRef] [PubMed]

92. Wu, H.; Xu, L.L.; Teuscher, P.; Liu, H.; Kaplan, M.H.; Dent, A.L. An Inhibitory Role for the Transcription Factor Stat3 in Controlling IL-4 and Bcl6 Expression in Follicular Helper T Cells. *J. Immunol.* 2015, 195, 2080–2089. [CrossRef] [PubMed]

93. Read, K.A.; Powell, M.D.; Baker, C.E.; Sreekumar, B.K.; Ringel-Scaia, V.M.; Bachus, H.; Martin, R.E.; Cooley, I.C.; Allen, I.C.; Ballesteros-Tato, A.; et al. Integrated STAT3 and Ikaros Zinc Finger Transcription Factor Activities Regulate Bcl-6 Expression in CD4(+) Th Cells. *J. Immunol.* 2017, 199, 2377–2387. [CrossRef] [PubMed]

94. Chen, W.; Nyuydze, M.S.; Weiss, J.M.; Zhang, J.; Waksal, S.D.; Zanin-Zhorov, A. ROCK2, but not ROCK1 interacts with phosphorylated STAT3 and co-occupies TH17/TFH gene promoters in TH17-activated human T cells. *Sci. Rep.* 2018, 8, 16636. [CrossRef]

95. Rivera Vargas, T.; Humblin, E.; Vegran, F.; Ghiringhelli, F.; Apetoh, L. TH9 cells in anti-tumor immunity. *Semin. Immunopathol.* 2017, 39, 39–46. [CrossRef]

96. Durgeau, A.; Virk, Y.; Corgnac, S.; Mami-Chouaib, F. Recent Advances in Targeting CD8 T-Cell Immunity for More Effective Cancer Immunotherapy. *Front. Immunol.* 2018, 9, 14. [CrossRef] [PubMed]

97. Emmerich, J.; Mumm, J.B.; Chan, I.H.; LaFace, D.; Truong, H.; McManus, T.; Gorman, D.M.; Oft, M. IL-10 directly activates and expands tumor-resident CD8(+) T cells without de novo infiltration from secondary lymphoid organs. *Cancer Res.* 2012, 72, 3570–3581. [CrossRef] [PubMed]

98. Wang, X.; Xin, W.; Zhang, H.; Zhang, F.; Gao, M.; Yuan, L.; Xu, X.; Hu, X.; Zhao, M. Aberrant expression of p-STAT3 in peripheral blood CD4+ and CD8+ T cells related to hepatocellular carcinoma development. *Mol. Med. Rep.* 2014, 10, 2649–2656. [CrossRef] [PubMed]
117. Kortylewski, M.; Kujawski, M.; Wang, T.; Wei, S.; Zhang, S.; Pilon-Thomas, S.; Niu, G.; Kay, H.; Mule, J.; Kerr, W.G.; et al. Inhibiting Stat3 signaling in the hematopoietic system elicits multicomponent antitumor immunity. *Nat. Med.* **2005**, *11*, 1314–1321. [CrossRef]

118. Herrmann, A.; Kortylewski, M.; Kujawski, M.; Zhang, C.; Reckamp, K.; Armstrong, B.; Wang, L.; Kowolik, C.; Deng, J.; Figlin, R.; et al. Targeting Stat3 in the myeloid compartment drastically improves the in vivo antitumor functions of adoptively transferred T cells. *Cancer Res.* **2010**, *70*, 7455–7464. [CrossRef]

119. Iwata-Kajihara, T.; Sumimoto, H.; Kawamura, N.; Ueda, R.; Takahashi, T.; Mizuguchi, H.; Miyagishi, M.; Takeda, K.; Kawakami, Y. Enhanced cancer immunotherapy using STAT3-depleted dendritic cells with high Th1-inducing ability and resistance to cancer cell-derived inhibitory factors. *J. Immunol.* **2011**, *187*, 27–36. [CrossRef]

120. Sanseverino, I.; Purificato, C.; Varano, B.; Conti, L.; Gessani, S.; Gauzzi, M.C. STAT3-silenced human dendritic cells have an enhanced ability to prime IFN gamma production by both alpha-beta and gamma delta T lymphocytes. *Immunobiology* **2014**, *219*, 503–511. [CrossRef]

121. Hoentjen, F.; Sartor, R.B.; Ozaki, M.; Jobin, C. STAT3 regulates NF-kappaB recruitment to the IL-12p40 promoter in dendritic cells. *Blood* **2005**, *105*, 689–696. [CrossRef] [PubMed]

122. Kitamura, H.; Kamon, H.; Sawa, S.; Park, S.J.; Katunuma, N.; Ishihara, K.; Murakami, M.; Hirano, T. IL-6-STAT3 controls intracellular MHC class II alpha beta dimer level through cathepsin S activity in dendritic cells. *Immunity* **2005**, *23*, 491–502. [CrossRef] [PubMed]

123. Ohno, Y.; Kitamura, H.; Takahashi, N.; Ohtake, J.; Kaneumi, S.; Sumida, K.; Homma, S.; Kawamura, H.; Minagawa, N.; Shibasaki, S.; et al. IL-6 down-regulates HLA class II expression and IL-12 production of human dendritic cells to impair activation of antigen-specific CD4 (+) T cells. *Cancer Immunol. Immunother.* **2016**, *65*, 193–204. [CrossRef] [PubMed]

124. Li, H.S.; Liu, C.; Xiao, Y.; Chu, F.; Liang, X.; Peng, W.; Hu, J.; Neelapu, S.S.; Sun, S.C.; Hwu, P.; et al. Bypassing STAT3-mediated inhibition of the transcriptional regulator ID2 improves the antitumor efficacy of dendritic cells. *Sci. Signal.* **2016**, *9*, ra94. [CrossRef] [PubMed]

125. Yu, S.; Liu, C.; Su, K.; Wang, J.; Liu, Y.; Zhang, L.; Li, C.; Cong, Y.; Kimberly, R.; Grizzle, W.E.; et al. Tumor exosomes inhibit differentiation of bone marrow dendritic cells. *J. Immunol.* **2007**, *178*, 6867–6875. [CrossRef]

126. Zhang, H.; Nguyen-Jackson, H.; Panopoulos, A.D.; Li, H.S.; Murray, P.J.; Watowich, S.S. STAT3 controls myeloid progenitor growth during emergency granulopoiesis. *Blood* **2010**, *116*, 2462–2471. [CrossRef] [PubMed]

127. Nefedova, Y.; Huang, M.; Kusmartsev, S.; Bhattacharya, R.; Cheng, P.; Salup, R.; Jove, R.; Gabrilovich, D. Hyperactivation of STAT3 is involved in abnormal differentiation of dendritic cells in cancer. *J. Immunol.* **2004**, *172*, 464–474. [CrossRef] [PubMed]

128. Nefedova, Y.; Nagaraj, S.; Rosenbauer, A.; Muro-Cacho, C.; Sebti, S.M.; Gabrilovich, D.I. Regulation of dendritic cell differentiation and antitumor immune response in cancer by pharmacologic-selective inhibition of the janus-activated kinase 2 signal transducers and activators of transcription 3 pathway. *Cancer Res.* **2005**, *65*, 9525–9535. [CrossRef]

129. Hossain, D.M.; Pal, S.K.; Moreira, D.; Duttatgupta, P.; Zhang, Q.; Won, H.; Jones, J.; D’Apuzzo, M.; Forman, S.; Kortylewski, M. TLR9-Targeted STAT3 Silencing Abrogates Immunosuppressive Activity of Myeloid-Derived Suppressor Cells from Prostate Cancer Patients. *Clin. Cancer Res.* **2015**, *21*, 3771–3782. [CrossRef]

130. Moreira, D.; Adamus, T.; Zhao, X.; Su, Y.L.; Zhang, Z.; White, S.V.; Remy-Martin, J.P.; Boireau, W.; Rout, A.; Simon, B.; Lanneau, D.; et al. Membrane-associated Hsp72 from tumor-derived exosomes mediates STAT3-dependent immunosuppressive function of mouse and human myeloid-derived suppressor cells. *J. Clin. Invest.* **2010**, *120*, 457–471. [CrossRef] [PubMed]
134. Waight, J.D.; Netherby, C.; Hensen, M.L.; Miller, A.; Hu, Q.; Liu, S.; Bogner, P.N.; Farren, M.R.; Lee, K.P.; Liu, K.; et al. Myeloid-derived suppressor cell development is regulated by a STAT/IRF-8 axis. *J. Clin. Invest.* 2013, 123, 4464–4478. [CrossRef] [PubMed]

135. Thorn, M.; Guha, P.; Cunetta, M.; Espat, N.J.; Miller, G.; Junghans, R.P.; Katz, S.C. Tumor-associated GM-CSF overexpression induces immunoinhibitory molecules via STAT3 in myeloid-suppressor cells infiltrating liver metastases. *Cancer Gene Ther.* 2016, 23, 188–198. [CrossRef] [PubMed]

136. Vasquez-Dunddel, D.; Pan, F.; Zeng, Q.; Gorbounov, M.; Albesiano, E.; Fu, J.; Blosser, R.L.; Tam, A.J.; Bruno, T.; Zhang, H.; et al. STAT3 regulates arginase-I in myeloid-derived suppressor cells from cancer patients. *J. Clin. Invest.* 2013, 123, 1580–1589. [CrossRef]

137. Yu, J.; Du, W.; Yan, F.; Wang, Y.; Li, H.; Cao, S.; Yu, W.; Shen, C.; Liu, J.; Ren, X. Myeloid-derived suppressor cells suppress antitumor immune responses through IDO expression and correlate with lymph node metastasis in patients with breast cancer. *J. Immunol.* 2013, 190, 3783–3797. [CrossRef]

138. Kumar, V.; Cheng, P.; Condamine, T.; Mony, S.; Languino, L.R.; McCaffrey, J.C.; Hockstein, N.; Guarino, M.; Masters, G.; Penman, E.; et al. CD45 Phosphatase Inhibits STAT3 Transcription Factor Activity in Myeloid Cells and Promotes Tumor-Associated Macrophage Differentiation. *Immunity* 2016, 44, 303–315. [CrossRef]

139. Wu, T.; Wang, C.; Wang, W.; Hui, Y.; Zhang, R.; Qiao, L.; Dai, Y. Embelin impairs the accumulation and differentiation of MDSCs in colitis-associated tumorigenesis. *OncoImmunology* 2018, 7, e1498437. [CrossRef]

140. Kuroda, H.; Mabuchi, S.; Kozasa, K.; Yokoi, E.; Matsumoto, Y.; Komura, N.; Kawano, M.; Hashimoto, K.; Crowley, M.; Inaba, K.; Steinman, R.M. Dendritic cells are the principal cells in mouse spleen bearing immunogenic fragments of foreign proteins. *J. Exp. Med.* 1990, 172, 383–386. [CrossRef] [PubMed]

141. Yin, T.; Zhao, Z.B.; Guo, J.; Wang, T.; Yang, J.B.; Wang, C.; Long, J.; Ma, S.; Huang, Q.; Zhang, K.; et al. Aurora-A inhibition eliminates myeloid cell-mediated immunosuppression and enhances the efficacy of anti-PD-L1 therapy in breast cancer. *Cancer Res.* 2019. [CrossRef] [PubMed]

142. Guha, P.; Gardell, J.; Darpolor, J.; Cunetta, M.; Lima, M.; Miller, G.; Espat, N.J.; Junghans, R.P.; Katz, S.C. STAT3 inhibition induces Bax-dependent apoptosis in liver tumor myeloid-derived suppressor cells. *Oncogene* 2019, 38, 533–548. [CrossRef] [PubMed]

143. Mills, C.D.; Kincaid, K.; Alt, J.M.; Heilman, M.J.; Hill, A.M. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J. Immunol.* 2000, 164, 6166–6173. [CrossRef] [PubMed]

144. Martinez, F.O.; Sica, A.; Mantovani, A.; Locati, M. Macrophage activation and polarization. *Front. Biosci.* 2008, 13, 453–461. [CrossRef] [PubMed]

145. Pollard, J.W. Tumour-educated macrophages promote tumour progression and metastasis. *Nat. Rev. Cancer* 2004, 4, 71–78. [CrossRef] [PubMed]

146. Sica, A.; Schioppa, T.; Mantovani, A.; Allavena, P. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour progression: Potential targets of anti-cancer therapy. *Eur. J. Cancer* 2006, 42, 717–727. [CrossRef]

147. Lewis, C.E.; Pollard, J.W. Distinct role of macrophages in different tumor microenvironments. *Cancer Res.* 2006, 66, 605–612. [CrossRef]

148. Jenkins, B.J.; Gail, D.; Inglese, M.; Quilici, C.; Bozinovski, S.; Wong, P.; Ernst, M. Imbalanced gp130-dependent signaling in macrophages alters macrophage colony-stimulating factor responsiveness via regulation of c-fms expression. *Mol. Cell Biol.* 2004, 24, 1453–1463. [CrossRef]

149. Sun, Z.; Yao, Z.; Liu, S.; Tang, H.; Yan, X. An oligonucleotide decoy for Stat3 activates the immune response of macrophages to breast cancer. *Immunobiology* 2006, 211, 199–209. [CrossRef]

150. Komohara, Y.; Ohnishi, K.; Kuratsu, J.; Takeya, M. Possible involvement of the M2 anti-inflammatory macrophage phenotype in growth of human gliomas. *J. Pathol.* 2008, 216, 15–24. [CrossRef]

151. Fu, X.L.; Duan, W.; Su, C.Y.; Mao, F.Y.; Lv, Y.P.; Teng, Y.S.; Yu, P.W.; Zhuang, Y.; Zhao, Y.L. Interleukin 6 induces M2 macrophage differentiation by STAT3 activation that correlates with gastric cancer progression. *Cancer Immunol. Immunother.* 2017, 66, 1597–1608. [CrossRef] [PubMed]

152. Li, Y.; Cai, L.; Wang, H.; Wu, P.; Gu, W.; Chen, Y.; Hao, H.; Tang, K.; Yi, P.; Liu, M.; et al. Pleiotropic regulation of macrophage polarization and tumorigenesis by formyl peptide receptor-2. *Oncogene* 2011, 30, 3887–3899. [CrossRef] [PubMed]

153. Crowley, M.; Inaba, K.; Steinman, R.M. Dendritic cells are the principal cells in mouse spleen bearing immunogenic fragments of foreign proteins. *J. Exp. Med.* 1990, 172, 383–386. [CrossRef] [PubMed]
Cancers 2019, 11, 1280

174. Fang, W.; Zhang, J.; Hong, S.; Zhan, J.; Chen, N.; Qin, T.; Tang, Y.; Zhang, Y.; Kang, S.; Zhou, T.; et al. EBV-driven LMP1 and IFN-gamma up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. *Oncotarget* 2014, 5, 12189–12202. [CrossRef] [PubMed]

175. Keremu, A.; Aimaiti, A.; Liang, Z.; Zou, X. Role of the HDAC6/STAT3 pathway in regulating PD-L1 expression in osteosarcoma cell lines. *Cancer Chemother. Pharmacol.* 2019, 83, 255–264. [CrossRef] [PubMed]

176. Gowrishankar, K.; Gunatilake, D.; Gallagher, S.J.; Tiffen, J.; Rizos, H.; Hersey, P. Inducible but not constitutive expression of PD-L1 in human melanoma cells is dependent on activation of NF-kappaB. *PLoS ONE* 2015, 10, e0123410. [CrossRef]

177. Koh, J.; Jang, J.Y.; Keam, B.; Kim, S.; Kim, M.Y.; Go, H.; Kim, T.M.; Kim, D.W.; Jeon, Y.K.; et al. EML4-ALK enhances programmed cell death-ligand 1 expression in pulmonary adenocarcinoma via hypoxia-inducible factor (HIF)-1alpha and STAT3. *OncolImmunology* 2016, 5, e1108514. [CrossRef] [PubMed]

178. Zhang, C.; Li, F.; Li, J.; Xu, Y.; Wang, L.; Zhang, Y. Docetaxel Down-Regulates PD-1 Expression via STAT3 in T Lymphocytes. *Clin. Lung. Cancer* 2018, 19, e675–e683. [CrossRef]

179. Li, F.; Huang, T.; Zou, Q.; Liu, D.; Wang, Y.; Tan, X.; Wei, Y.; Qiu, H. FGFR2 Promotes Expression of PD-L1 in Colorectal Cancer via the JAK/STAT3 Signaling Pathway. *J. Immunol.* 2019. [CrossRef] [PubMed]

180. Zhang, N.; Zeng, Y.; Du, W.; Zhu, J.; Shen, D.; Liu, Z.; Huang, J.A. The EGFR pathway is involved in the regulation of PD-L1 expression via the IL-6/JAK/STAT3 signaling pathway in EGFR-mutated non-small cell lung cancer. *Int. J. Oncol.* 2016, 49, 1360–1368. [CrossRef]

181. Abdelhamed, S.; Ogura, K.; Yokoyama, S.; Saiki, I.; Hayakawa, Y. AKT-STAT3 Pathway as a Downstream Target of EGFR Signaling to Regulate PD-L1 Expression on NSCLC cells. *J. Cancer* 2016, 7, 1579–1586. [CrossRef] [PubMed]

182. Lamano, J.B.; Lamano, J.B.; Li, Y.D.; DiDomenico, J.D.; Choy, W.; Veliceasa, D.; Oyon, D.E.; Fakurnejad, S.; Ampie, L.; Kesavabhotla, K.; et al. Glioblastoma-Derived IL-6 Induces Immunosuppressive Peripheral Myeloid Cell PD-L1 and Promotes Tumor Growth. *Clin. Cancer Res.* 2019. [CrossRef] [PubMed]

183. Cheng, Y.; Li, H.; Deng, Y.; Tai, Y.; Zeng, K.; Zhang, Y.; Liu, W.; Zhang, Q.; Yang, Y. Cancer-associated fibroblasts induce PDL1+ neutrophils through the IL6-STAT3 pathway that foster immune suppression in hepatocellular carcinoma. *Cell Death Dis.* 2018, 9, 422. [CrossRef] [PubMed]

184. Sparry, L.K.; Salimu, J.; Webber, J.P.; Clayton, A.; Mason, M.D.; Tabi, Z. Tumor stroma-derived factors skew monocyte to dendritic cell differentiation toward a suppressive CD14(+)/PD-L1(+) phenotype in prostate cancer. *OncoImmunology* 2014, 3, e955331. [CrossRef] [PubMed]

185. Kondo, K.; Shaim, H.; Thompson, P.A.; Burger, J.A.; Keating, M.; Estrov, Z.; Harris, D.; Kim, E.; Ferrajoli, A.; Daher, M.; et al. Ibrutinib modulates the immunosuppressive CLL microenvironment through STAT3-mediated suppression of regulatory B-cell function and inhibition of the PD-1/PD-L1 pathway. *Leukemia* 2018, 32, 960–970. [CrossRef] [PubMed]

186. Horlad, H.; Ma, C.; Yano, H.; Pan, C.; Ohnishi, K.; Fujiwara, Y.; Endo, S.; Kikukawa, Y.; Okuno, Y.; Matsuoka, M.; et al. An IL-27/Stat3 axis induces expression of programmed cell death 1 ligands (PD-L1/2) on infiltrating macrophages in lymphoma. *Cancer Sci.* 2016, 107, 1696–1704. [CrossRef]

187. Song, S.; Yuan, P.; Wu, H.; Chen, J.; Fu, J.; Li, P.; Lu, J.; Wei, W. Dendritic cells with an increased PD-L1 by PD-L1 pathway. *Front. Immunol.* 2018, 9, 2129. [CrossRef]

188. Bazhin, A.V.; von Ahn, K.; Fritz, J.; Werner, J.; Karakhanova, S. Interferon-alpha Up-Regulates the Expression of PD-L1 Molecules on Immune Cells Through STAT3 and p38 Signaling. *Front. Immunol.* 2018, 9, 2129. [CrossRef]

189. Garcia-Diaz, A.; Shin, D.S.; Moreno, B.H.; Saco, J.; Esquin-Ordinas, H.; Rodriguez, G.A.; Zaretsky, J.M.; Sun, L.; Hugo, W.; Wang, X.; et al. Interferon Receptor Signaling Pathways Regulating PD-L1 and PD-L2 Expression. *Cell Rep.* 2017, 19, 1189–1201. [CrossRef]

190. Che, K.F.; Shankar, E.M.; Muthu, S.; Zandi, S.; Sigvardsson, M.; Hinkula, J.; Messmer, D.; Larsson, M. p38 Mitogen-activated protein kinase/signal transducer and activator of transcription-3 pathway signaling regulates expression of inhibitory molecules in T cells activated by HIV-1-exposed dendritic cells. *Mol. Med.* 2012, 18, 1169–1182. [CrossRef]

191. Zhang, W.; Zhang, J.; Zhang, Z.; Guo, Y.; Wu, Y.; Wang, R.; Wang, L.; Mao, S.; Yao, X. Overexpression of Indoleamine 2,3-Dioxygenase 1 Promotes Epithelial-Mesenchymal Transition by Activation of the IL-6/STAT3/PD-L1 Pathway in Bladder Cancer. *Transl. Oncol.* 2019, 12, 485–492. [CrossRef] [PubMed]
192. Huang, X.; Bai, X.; Cao, Y.; Wu, J.; Huang, M.; Tang, D.; Tao, S.; Zhu, T.; Liu, Y.; Yang, Y.; et al. Lymphoma endothelium preferentially expresses Tim-3 and facilitates the progression of lymphoma by mediating immune evasion. J. Exp. Med. 2010, 207, 505–520. [CrossRef] [PubMed]

193. Arra, A.; Lingel, H.; Kuropka, B.; Pick, J.; Schnoeder, T.; Fischer, T.; Freund, C.; Pierau, M.; Brunner-Weinzierl, M.C. The differentiation and plasticity of Tc17 cells are regulated by CTLA-4-mediated effects on STATs. OncoImmunology 2017, 6, e1273300. [CrossRef] [PubMed]

194. Mankan, A.K.; Greten, F.R. Inhibiting signal transducer and activator of transcription 3: Rationality and rationale design of inhibitors. Expert Opin. Investig. Drugs 2011, 20, 1263–1275. [CrossRef] [PubMed]

195. Shouksmith, A.E.; Gunning, P.T. Targeting Signal Transducer and Activator of Transcription (STAT) 3 with Small Molecules. In Small-Molecule Transcription Factor Inhibitors in Oncology; Khondaker, M.R.D.E.T., Ed.; Royal Society of Chemistry: London, UK, 2019; pp. 147–168.

© 2019 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).