STAT3 in cancer: a double edged sword

by Lidia Avalle, Annalisa Camporeale, Andrea Camperi and Valeria Poli *

Molecular Biotechnology Center, Department of Molecular Biotechnology and Life Sciences, University of Turin, Via Nizza 52, 10126 Turin, Italy.

* Corresponding author: valeria.poli@unito.it

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ABSTRACT

The transcription factor signal transducer and activator of transcription (STAT) 3 is activated downstream of cytokines, growth factors and oncogenes to mediate their functions under both physiological and pathological conditions. In particular, aberrant/unrestrained STAT3 activity is detected in a wide variety of tumors, driving multiple pro-oncogenic functions. For that, STAT3 is widely considered as an oncogene and is the object of intense translational studies. One of the distinctive features of this factor is however, its ability to elicit different and sometimes contrasting effects under different conditions. In particular, STAT3 activities have been shown to be either pro-oncogenic or tumor-suppressive according to the tumor aetiology/mutational landscape, suggesting that the molecular bases underlining its functions are still incompletely understood. Here we discuss some of the properties that may provide the bases to explain STAT3 heterogeneous functions, and in particular how post-translational modifications contribute shaping its sub-cellular localization and activities, the cross talk between these activities and cell metabolic conditions, and finally how its functions can control the behaviour of both tumor and tumor microenvironment cell populations.

1. INTRODUCTION

Signal Transducer and Activator of Transcription (STAT) factors become activated downstream of both extrinsic and intrinsic signals by phosphorylation on a conserved tyrosine residue mainly accomplished by receptor-associated JAK kinases [1, 2]. Tyrosine-phosphorylated (YP)-STATs form active dimers that concentrate in the nucleus to regulate the expression of target genes [3]. The family member STAT3 is canonically activated by YP downstream of numerous cytokines, growth factors and oncogenes, and is accordingly constitutively active in a high percentage of tumors and tumor-derived cell lines of both liquid and solid origin, which often become STAT3 addicted (recently reviewed by [4, 5]). Thus, STAT3 is widely considered as an oncogene and a good target for anti-cancer therapy. In keeping with the wide repertoire of distinct target genes activated in different contexts, STAT3 was reported to exert a plethora of different functions in normal as well as in transformed cells. STAT3 constitutive activity in tumours can promote cell survival and proliferation, down-modulate anti-tumour immune responses and promote tumor angiogenesis, enhance tumour invasion and metastasis by inducing epithelial to mesenchymal transition (EMT), alter the extracellular matrix through the expression of matrix metalloproteinases (MMP) and the enhancement of collagen cross-linking and tissue tension, modify cell energy metabolism and mitochondrial activity. Finally, STAT3 activity can confer tumor-initiating features to cancer cells in a number of solid tumors [4, 6-9].

Not surprisingly therefore, STAT3 transcriptional functions are required for cellular transformation downstream of several oncogenes that trigger its phosphorylation on Y705 such as, for example, Src [10]. However, STAT3 is also required for Ras-mediated tumor transformation, for which YP and transcriptional activities are dispensable [11], suggesting that both transcriptional and non-transcriptional activities of STAT3 promote tumorigenesis. Despite this knowledge, and the wealth of data supporting the concept of STAT3 as an oncogene, several reports have now highlighted its ability to suppress tumor onset and/or progression.

2. STAT3 the oncogene or STAT3 the oncosuppressor?

The first indication that STAT3 tumor-promoting functions may be strongly context-dependent came from the observation that STAT3 plays a dual role in glioblastoma, and this role depends on its mutational status. While in the context of tumors driven by the type III epidermal growth factor receptor (*EGFRvIII*) mutation STAT3 triggered glial transformation by associating with the mutant receptor in the nucleus, in the context of *PTEN* loss STAT3 inhibited glial tumor transformation and growth [12]. Indeed, the analysis of clinical samples showed that *PTEN* loss and *EGFRvIII* expression define distinct glioblastoma subsets, with down-regulation of STAT3 signaling only associated with the subset demonstrating *PTEN* loss. Also, in the context of a *PTEN* -loss driven mouse model of prostate cancer, STAT3 ablation accelerated metastatic progression by down-modulating $p19^{ARF}$ to bypass senescence [13]. Clinically, reduced IL-6 and STAT3 expression correlated with increased risk of recurrence in prostate cancer patients.

The mutational landscape also appears to determine the role of STAT3 in lung cancer. Indeed, despite a host of literature supporting a pro-oncogenic role of STAT3 in lung cancer, particularly in the context of *EGFR* driver mutations, Casanova and co-authors have recently shown that STAT3 exerts a tumor suppressive role in *KRAS* mutant lung adenocarcinomas, by impairing NF-κB-mediated IL-8 expression, tumor myeloid cell recruitment and vascularization [14]. Indeed, the authors could demonstrate that low STAT3 levels correlate with increased malignant progression and poor prognosis in adenocarcinoma patients with *KRAS* mutation and/or with a smoking history, highlighting how tumor stratification according to mutational status and clinical history may be crucial to determine the involvement of specific signaling pathways.

In the context of colon cancer the etiology also appears to strongly influence STAT3 involvement. While the relevance of the IL-6-STAT3 pathway in promoting inflammation-driven colorectal tumorigenesis is well-documented [15, 16], *Stat3* gene inactivation delayed tumor onset in the Apc^{Min} mouse model of intestinal cancer, while promoting faster progression of more

invasive tumors, via transcriptional regulation of the adhesion molecule CEACAM1 and modulation of Snail1 degradation and EMT [17, 18] .

Finally, in human primary papillary thyroid carcinoma, an inverse relationship was observed between YP-STAT3 and tumor size/metastasis. Accordingly, *STAT3* deficiency in a thyroid carcinoma model enhanced tumor cell proliferation, partly by down regulating the tumor suppressor *IGFBP7* [19].

Certainly, these contrasting actions can be partly explained by STAT3 ability to activate a wide variety of target genes depending on cell type and conditions, which in turn is determined by cell-specific accessibility of genomic STAT3 binding sites, cell- and signal-specific interactions with distinct co-factors, and STAT3's ability to activate transcription by interacting with other transcription factors, modulating or redirecting their activity (see [4, 20] for recent reviews). Other important features influencing STAT3 multifaceted functions are (i) the multiple modifications affecting STAT3 activities/functions that result in many functionally distinct forms of this factor modulating both transcriptional and non-transcriptional activities in different sub-cellular compartments including the nucleus, the cytoplasm or the mitochondrion (Fig. 1); (ii) the reciprocal cross-talk that exists between STAT3's multiple activities and the metabolic and redox states, and (iii) the increasing knowledge that STAT3 is profoundly involved in mediating both cell autonomous and non-cell autonomous functions in tumor cells and tumor stromal components, with both coherent and incoherent effects.

Since the multiple roles of STAT3 in tumors have been extensively described in many excellent recent reviews [4, 5, 20, 21], here we will concentrate on discussing some of these aspects and how they may affect the multitude of apparently contrasting STAT3 biological functions.

3. Post-translational modifications: how many STAT3s are there?

3.1. *Tyrosine phosphorylation*

As mentioned in the introduction, STAT3 canonical activity as a transcription factor mainly depends on JAK kinase-mediated phosphorylation on Y705 (YP), which endows STAT3 dimers with the ability to concentrate in the nucleus, bind to DNA and activate transcription. Upstream signals that can trigger STAT3 YP range from cytokines of the IL-6 family, leptin, IL-12, IL-17, IL-10, Interferons, growth factors such as G-CSF, EGF, PDGF, and a number of oncogenes, the prototype of which are Src family kinases but also including Abl, Sis, Fps, Ros, Met and ErbB2 [5, 22, 23]. Recently, G protein coupled receptors, like the sphingosine-1-phosphate receptor (S1PR)1, and several Toll like receptors have been shown to activate STAT3 (for recent reviews, see [4, 5]). In particular, S1PR1 overexpression has been linked to the maintenance of constitutive STAT3

activity [24]. This vast collection of potential activators offers a glimpse of the variety of conditions that can lead to both physiological and aberrant STAT3 activity.

Under physiological conditions, STAT3 activation is tightly controlled by negative regulators, which mainly fall into three groups: phosphatases, Suppressor Of Cytokine Signaling (SOCS) proteins, and Protein Inhibitor of Activated STAT (PIAS) proteins [25-27]. Phosphatases like SHP-1, SHP-2, PTP1B or T cell PTP terminate STAT3 activation, acting either at the level of JAK kinases or directly in the nucleus [25]. Among SOCS proteins, SOCS3 is a primary transcriptional target of STAT3 and acts as a negative feedback regulator to inhibit JAK activity [28]. Finally, PIAS3 prevents the binding of STAT3 to its target DNA sequence [29]. Persistent STAT3 activation in tumors is known to occur downstream of aberrant upstream stimulation [30], as a result of impaired negative regulation [31] and upon cadherin-mediated cell-cell contacts [32]. More recently, *trans*-activating *STAT3* somatic mutations have been shown to play a role in the pathogenesis of hepatic and hematopoietic malignancies [33-36]. Additionally, un-phosphorylated STAT3 is also thought to be involved in transcriptional regulation, being able to translocate to the nucleus, bind DNA both directly and indirectly, and activate transcription of target genes including several oncogenes [37-39]. Indeed, high levels of nuclear un-phosphorylated STAT3 correlate with a bad prognosis in glioblastoma [40].

3.2. *Serine phosphorylation.*

In addition to YP, STAT3 can undergo several other post-translational modifications, most of which have been correlated with enhanced trans-activating potential. Phosphorylation on serine residue 727 (SP) within the carboxy-terminal transcription activation domain can be carried out by several kinases including MAP kinases and mTOR, downstream of both classical STAT3 activating cytokines/growth factors and of Ras proteins [41, 42]. Although SP is required for optimal induction of a subset of target genes [43], SP-STAT3 appears to mostly function independently of YP in the mitochondrion (see below). Phosphatases leading to S727 dephosphorylation have not been characterized yet. Incidentally, an alternatively spliced form of STAT3, STAT3beta, which lacks S727, is specifically up regulated under inflammatory conditions and regulates an only partially overlapping subset of STAT3 target genes [44, 45].

3.3. *Acetylation.*

STAT3 is also known to be acetylated (Ac) on multiple lysine (K) residues by the CBP/p300 histone acetyltransferase in response to cytokines and growth factor signaling. Acetylation on K685 enhances tyrosine phosphorylation, dimer stability and transcriptional activity [46], leading to DNA methylation and silencing of tumor suppressor genes through recruitment of DNA methyltransferase 1 [47]. Deacetylation can be brought about by the NAD-dependent silent

information regulator protein (SIRT) 1, which is activated under starvation conditions [48]. SIRT1-mediated deacetylation leads to both reduced YP and transcriptional activity and decreased SP-STAT3 mitochondrial localization, likely in an indirect way [49]. In contrast, K87 acetylation downstream of insulin stimulation was recently shown to specifically promote STAT3 mitochondrial translocation and functions [50].

3.4. *Methylation.*

Nuclear STAT3 can be methylated on several residues, with contrasting effects on its activities. The histone methyltransferase SET9 can methylate promoter-bound STAT3 on K140, impairing transcription of its target genes [51]. In contrast, K180 tri-methylation by the EZH2 component of the Polycomb Complex 2 is required for STAT3 YP and transcriptional activity in glioblastoma and prostate cancer cells [52].

3.5. *Oxidation, glutathionylation*.

Finally, STAT3 transcriptional activity can be differentially modulated under conditions of oxidative stress and cytokine signaling, via the oxidation or glutathionylation of multiple cysteine residues, establishing a crucial cross-talk between cell metabolic conditions and STAT3 functions [53-56]. At present, the influence of these modifications on the activity of the other STAT3 modifications is unknown.

The interplay between these multiple functionally distinct STAT3 forms, whose relative levels, localization and activities are reciprocally regulated by multiple signals and by specific metabolic conditions sets the stage for addressing the complexity of the STAT3 functions.

4. STAT3 and energy metabolism: of electron transport complexes and transcription

Energy metabolism plays a central role in tumor progression, with tumor cells often undergoing a metabolic switch known as the Warburg effect, leading to increased aerobic glycolysis and reduced mitochondrial activity [57]. STAT3 is an important player in this switch, since its constitutive transcriptional activity promotes aerobic glycolysis and down regulates mitochondrial activity by inducing HIF1α transcription while reducing the expression of electron transport complexes (ETC) [58]. In turn, this metabolic switch leads to enhanced production of lactate and decreased production of ROS, which contribute to protect cells from apoptosis and senescence. Intriguingly, STAT3 has been shown to regulate mitochondrial activities in a completely different fashion, *via* its localization to this organelle, as observed in a number of cell types and tissues [11, 59-62]. In keeping with its association with distinct ETCs [59, 63], protease

experiments demonstrated that, despite the lack of a mitochondrial targeting sequence, STAT3 is associated with the inner mitochondrial membrane [63]. STAT3 mitochondrial import can be chaperoned by the ETC I component Gene associated with Retinoid Interferon induced cell Mortality (GRIM) 19 [63], and by the heat shock protein 22, at least in cardiomyocytes [64].

Like nuclear STAT3, mitochondrial STAT3 acts as a pro-survival factor that enhances cell fitness under specific stress conditions such as heart ischemia or Ras-mediated transformation [11, 59, 65]. It has been shown to preserve optimal ETC activity, increasing mitochondrial membrane polarization and ATP production, and to enhance lactate dehydrogenase activity while at the same time reducing ROS production, possibly via the interaction with ETC I and II [59, 63, 65-68]. Protection from apoptosis may also stem from its ability to inhibit the opening of the mitochondrial permeability transition pore by interacting with cyclophilin D [69]. The association between increased ETC activity and reduced production of ROS mediated by mitochondrial STAT3, which was confirmed in many cell types including astrocytes, hematopoietic stem cells and activated $CD4^+$ T lymphocytes [60-62], is in apparent contrast with the knowledge that ETC activity is the main source of ROS. A fascinating explanation has been proposed by Rincon and colleagues, who demonstrated that IL-6-induced $CD4^+$ T cell activation occurs via mitochondrial STAT3 and correlates with the formation of ET super complexes, known to minimize electron leakage [62]. In this context, ETC activity increased mitochondrial membrane polarization and raised the levels of mitochondrial Ca^{2+} . Mitochondrial STAT3 can contribute to the control of ROS levels also by indirectly inducing, via an unknown mechanism, the synthesis of the major cellular ROS scavenger glutathione [70].

SP, but not YP, is believed to be required for most, if not all, STAT3 mitochondrial functions, and can be elicited by MAP kinases downstream of Ras stimulation [11, 71], and by PKCε in keratinocytes upon TPA or EGF treatment [68, 72]. Recently however, it was proposed that STAT3 acetylation on lysine residue 87, occurring downstream of insulin signaling, is the modification required for STAT3 to translocate to mitochondria, where it increases mitochondrial membrane potential and ATP production by interacting with pyruvate dehydrogenase complex E1 [50]. While the assessment of how acetylation levels of mitochondrial STAT3 may affect its functions needs to be systematically addressed, it is already evident that SP is not required for mitochondrial import, and that YP STAT3 is abundantly detected within mitochondria [62, 68, 72]. Intriguingly, overexpression of BCL2 in the human colon cancer cell line HCT116 was shown to recruit YP, not SP, STAT3 to mitochondria, leading to increased $\bullet O_2^-$ production and enhanced survival [73]. Additionally, mitochondrial fractions from both activated $CD4^+$ T cells and LIF-

stimulated ES cells appear to be enriched in YP STAT3 [62, 68]. At present, whether mitochondrial STAT3 is phosphorylated on both Y and S or whether YP and SP STAT3 represent two distinct pools is unknown. At any rate, transcriptionally active STAT3 is likely to play a specific role in mitochondria, as suggested by its ability to bind to mitochondrial DNA in both keratinocytes and ESCs. In keratinocytes, STAT3 interacts with the mitochondrial transcription factor TFAM to down-regulate respiratory chain genes [72], leading to reduced ETC activity. In contrast, in ES cells it acts as a transcriptional activator of ETC subunits, leading to increased complexes assembly and enhanced respiratory activity, which is required to promote high proliferative activity downstream of LIF [68]. Although the specific role for S or Y phosphorylation has not been addressed in these contexts, the ability of mitochondrial STAT3 to bind to DNA and the detection of dimeric mitochondrial STAT3 are suggestive of YP STAT3 being involved in these functions [72].

A host of observations supports the idea that several known STAT3 pro-oncogenic activities involve the SP, rather than the YP protein. Indeed, H-RAS driven transformation of MEF cells, K-RAS-driven myeloid malignancy, and pancreatic cancer development driven by Receptor for Advanced Glycation Endproducts (RAGE)-dependent IL-6 signaling were all shown to be dependent on the mitochondrial activities of SP STAT3 that enhance ETC activity, mitochondrial membrane polarization and ATP production [11, 66, 71, 74]. Moreover, SP STAT3 mediates tumor growth and metastatic potential of mammary 4T1 mouse tumor cells via increased complex I coupling and reduced ROS production [67]. Accordingly, decreased STAT3 mitochondrial localization triggered by phospho-valproic acid treatment results in reduced growth of human pancreatic tumor xenografts [75]. Interestingly, expression of the FGFR-R388 single nucleotide polymorphism in pituitary cells leads to SP-STAT3 accumulation in mitochondria, correlating with enhanced cytochrome c oxidase activity and pituitary tumorigenesis [76].

5. STAT3 and redox balance: to be or not to be (oxidized)

Redox homeostasis is maintained thanks to an equilibrium between ROS production and scavenging, whose disruption may result in oxidative stress which in turn contributes to the pathogenesis of cancer, neurodegeneration and aging [77]. While controlled ROS production is involved in the signaling of growth factor and cytokine receptors, an excess of ROS can directly lead to oxidation-mediated inactivation of several protein phosphatases, indirectly activating key proliferation and survival signaling pathways. Thus, a correct balance between functional and toxic effects of ROS is crucial for cell survival and proliferation [77].

STAT3 contributes to intracellular ROS homeostasis in a number of ways. As discussed above, under different cellular contexts both nuclear and mitochondrial STAT3 can lead to reduced

production of ROS and increased ROS scavenging [11, 58, 70]. On the other hand, STAT3 activity itself is affected by ROS concentration. Oxidation and glutathionylation of specific Cys residues under conditions of oxidative stress impair STAT3 DNA binding and transcriptional activity [53-56], while mild ROS production downstream of IGF1, EGF and other growth factor signaling can actually enhance STAT3 YP and nuclear activity [78-81]. Similarly, starvation-induced ROS leads to increased YP STAT3 binding to the IL-6 promoter during autophagy in HeLa cells [82].

STAT3 oxidation appears to be part of a redox relay for ROS signaling downstream of the thiol peroxidase peroxiredoxin-2 (Prx2), one of the major H_2O_2 scavengers within the cell. Upon H_2O_2 treatment, Prx2 transfers oxidative equivalents to Cys residues within the STAT3 DNA binding and transcriptional activation domains, attenuating transcriptional activity [56]. Importantly, Prx2-mediated STAT3 oxidation is also involved in modulating STAT3-mediated transcription downstream of IL-6-type cytokines, as the expression of a redox-insensitive cysteine mutant STAT3 leads to increased STAT3 activity and cell growth rates. This cross-talk between oxidative and non-oxidative STAT3 modifications can integrate exogenous and endogenous H_2O_2 levels and cytokine signaling, affecting the levels, localization and activities of the different forms of STAT3 to control intracellular redox homeostasis as well as cell proliferation and survival. This may be particularly relevant for cancer cells, which often rely on high levels of ROS to promote proliferation, survival and metabolic adaptation, thus depending heavily on efficient antioxidant activities to prevent oxidative stress and apoptosis [83].

6. STAT3 as an autophagy regulator: to eat or not to eat (itself)

Autophagy, and in particular macro-autophagy, is a cellular process that delivers cytoplasmic material to lysosomes for degradation [84], and it plays ambiguous roles in tumor transformation and progression [85]. While an efficient autophagy machinery is essential to protect cells from transformation, cancer cells rely on autophagy for their survival and diffusion. Thus, fine-tuning of the autophagy process may represent an appealing strategy for both prevention and therapy of cancer. The knowledge that STAT3 can both promote and inhibit autophagy adds a further layer of complexity to the functions of this factor in tumorigenesis (recently reviewed in [86]).

STAT3 can inhibit autophagy both from the nucleus and the cytoplasm. Nuclear YP-STAT3 can control the levels and activity of beclin1, an essential autophagy player that is often down-regulated in cancer, both directly by repressing its transcription [87] and indirectly by inducing the beclin1 negative regulators BCL2 and MCL1 [88, 89], or miRNA17, which targets both Beclin1 and ATG7, another essential component of the autophagy pathway [90, 91]. miR17 down-

regulation was shown to promote autophagy and to increase the sensitivity of cancer cells to chemotherapy [92, 93].

From within the cytoplasm, STAT3 was proposed to inhibit autophagy by interacting with protein kinase R, blocking its enzymatic activity [94]. Fatty acids like palmitate trigger STAT3 dissociation from PKR leading to stimulation of the autophagy flux [94, 95]. In addition, un-phosphorylated STAT3 was shown to inhibit FOXO-mediated induction of several autophagy related genes by maintaining FOXO1 and FOXO3 in the cytoplasm of T cells [96, 97]. Finally, SP STAT3 has been shown to inhibit autophagy downstream of mTOR [98].

STAT3 pro-autophagy effects are less direct and strongly linked to hypoxia-related response. STAT3 and HIF1α are connected by a feed-forward loop whereby active YP-STAT3 increases the levels of HIF1α, which in turn helps to maintain STAT3 activation via PKM2-mediated YP [99]. Hypoxic conditions are known to promote HIF1α-dependent autophagy activation, which allows cells to survive during prolonged hypoxia by limiting ROS accumulation, and may well involve STAT3 transcriptional activity [100]. Accordingly, hypoxia was reported to drive STAT3 and HIF1α-dependent autophagy, impairing the susceptibility of tumor cells to CTL-mediated cell lysis [101]. In this context however, STAT3 activation was not implicated in autophagy induction, but rather occurred downstream of autophagy-mediated Src activity [102]. Additionally, in glioblastoma cells hypoxia-induced IL-6 was shown to activate autophagy via STAT3-dependent indirect up-regulation of ATG5 [103].

STAT3 can also induce autophagy independently of hypoxia. For example, EGFR/STAT3 signaling is crucial to promote autophagy and maintain the tumor-initiating potential of breast cancer stem cells in MMTV-*PyMT* mouse mammary tumors [104]. Finally, mitochondrial STAT3 activities have been implicated in mediating RAGE-induced autophagy that is involved in the development of early pancreatic cancer lesions [66]. Along these lines, it is also interesting to note that activated Ras, which relies on SP-STAT3 for tumor transformation, requires autophagy to maintain oxidative metabolism and cell viability, suggesting a potential connection to mitochondrial STAT3 [105].

Thus, multiple STAT3 activities, specific post-translational modifications and orchestrated sub-cellular localization are involved in fine-tuning autophagy under both physiological and pathological conditions, contributing to STAT3's double-edged functions in tumorigenesis.

7. Both seed and soil: STAT3 and the tumor microenvironment

Tumor growth relies on the establishment of reciprocal relationships with components of the tumor microenvironment (TME), which is composed of cells of hematopoietic and mesenchymal origin. TME cell components can be either stromal resident cells or be specifically recruited to the tumor site, where they are instructed by cancer cells to acquire pro-tumorigenic features [106]. The reciprocal crosstalk among different cell types is responsible for the establishment and maintenance of the pro-oncogenic niche, primarily initiated by cancer cells and relying on cell-cell contacts as well as on a complex network of released cytokines, chemokines and growth factors. Tumor-associated macrophages (TAMs) or cancer associated fibroblasts (CAFs), for instance, acquire the ability to suppress immune responses as well as supporting EMT, angiogenesis, extracellular cell matrix remodeling and chemo resistance [107, 108], while immune-suppressive cells such as myeloid-derived suppressor cells (MDSCs) or regulatory T cells (Treg) become aberrantly recruited to the TME to facilitate tumor immune escape [109-111].

Several lines of evidence suggest that the IL-6/STAT3 pathway is strongly involved in mediating the cross talk between tumor and TME cells. Indeed, both cancer and stromal cells often secrete IL-6 or other STAT3-activating cytokines/growth factors, initiating a feed forward loop that supports continued STAT3 activity (reviewed in [6, 112]).

In their seminal 2004 paper, Wang *et al.* reported that constitutive STAT3 activation in cancer cells favors the expression of soluble factors that in turn activate STAT3 in antigen-presenting cells, blocking dendritic cell (DC)-mediated T cell activation. Indeed, STAT3 inhibition in tumor cells increased the secretion of pro-inflammatory cytokines, activating dendritic cells to induce tumor-specific T-cell responses [113, 114]. Accordingly, STAT3 inactivation in the hematopoietic compartment triggered immune-mediated inhibition of tumor growth and metastasis *via* the coordinated activation of DCs, T cells, natural killer (NK) cells and neutrophils [115]. Many reports have since confirmed and extended these initial findings in a number of TME cell types and tumor models, as summarized below. Accordingly, *in vivo* efficacy of STAT3 inhibitors often involves modulation of both cancer and TME cell functions [116-118].

7.1 *Myeloid Derived Suppressive Cells (MDSC) and T regulatory cells (Treg)*

STAT3 activity has been directly linked to the immunosuppressive functions of Treg and MDSC cells. For example, STAT3 inhibition could block tumor growth both directly, interfering with proliferation of ovarian and pancreatic tumor cells, and indirectly by impairing IL-6 secretion, resulting in reduced numbers of infiltrating MDSC and pro-tumorigenic T cells, as shown by using xenograft tumor models [117, 118]. Accordingly, myeloid STAT3 enhanced the suppressive activity of MDSCs suppressing anti-tumor T cell responses to accelerate the progression of a number of solid tumors [119-121]. Of note, within the same Apc^{Min} colon tumor model, the pro-

oncogenic activity of myeloid STAT3 contrasted with the tumor suppressor activity of epithelial STAT3 [17]. Finally, in the context of KRAS-driven lung tumorigenesis, blockade of the IL-6/STAT3 pathway impaired tumor progression by decreasing the number of Treg's and MDSC cells in the TME [122]. Similarly, in the TRAMP murine prostate cancer model, depletion of the STAT3 negative feedback regulator SOCS3 in myeloid cells lead to STAT3-dependent MDSC expansion, enhancing TME immunosuppressive functions and tumor growth [123]. Notably, STAT3 activation in MDSCs was also required for cancer stem cell proliferation in a pancreatic cancer model [124]. Finally, Sorafenib-mediated STAT3 inhibition upon $CD8^+$ T cell adoptive transfer impaired Treg and MDSC recruitment to the TME through the down-regulation of immunosuppressive factors, thus unleashing $CD8^+$ T cell responses [125].

Additionally, STAT3 activity in MDSCs, and more in general in myeloid cells, has been linked to metastasis and radioresistance. Hua Yu and collaborators showed that the S1PR1-STAT3 axis is crucial for myeloid cells ability to condition the pre-metastatic niche [126], and to trigger Treg accumulation within the tumor [127]. Accordingly, STAT3 activation in tumor-free lymph nodes positively correlated with the number of premetastatic niches and was predictive of poor survival in patients with several types of cancer [126, 128, 129]. Additionally, high YP STAT3 levels in murine melanoma myeloid cells inversely correlated with the ability of $CD8^+$ T cells to control metastatic colonization by inhibiting myeloid cell expansion [130]. Indeed, breast cancer cells and MDSCs form a synergistic feedback loop based on IL-6/sIL-6R secretion and STAT3 activation, leading to increased MDSC recruitment and enhanced metastatic potential [131]. Finally, TLR9-mediated activation of the IL-6/STAT3 loop by radiotherapy in myeloid cells enhances MDSCs tumor-suppressive activities, thus promoting recurrence in several solid tumors [132].

7.2. *Tumor associated macrophages (TAMs).*

STAT3 activation in tumor-associated macrophages (TAMs) has also been associated with their acquirement of pro-tumorigenic features. In a rat model of breast cancer, STAT3 inhibition could revert a TAM immune suppressing phenotype leading to immune-mediated inhibition of tumor growth [133], and STAT3 was shown to promote pro-tumorigenic M2 polarization of TAMs in glioma, enhancing proliferation and angiogenesis [134]. This activity may be due to STAT3-mediated expression of the B7-H4 T-cell co-inhibitory molecule that impairs $CD8^+$ T cell activation [135]. Accordingly, endostatin expression could skew TAM polarization towards an M1 phenotype both by inverting the ratio between phophorylated STAT3 and STAT1 and by stimulating NF-κB activity, resulting in the inhibition of 4T1 breast tumors in syngeneic mice [136].

Recent findings, however, challenge the simplistic vision of STAT3 being purely pro-tumorigenic in tumor associated myeloid cells, arguing for a more complex role in orchestrating their expansion and activities. For example, in contrast to what has been observed in the TRAMP model, myeloid SOCS3 deletion resulted in impaired glioma progression by sustaining both STAT3 and STAT1, activity, correlating with M1 polarization of TAMs and reciprocal changes in Treg and $CD8^+$ CTL cells [137]. In the same vein, STAT3 could promote the expansion of monocyte-derived MDSC in peripheral lymphoid organs, but their differentiation into tumor-promoting TAMs required subsequent STAT3 inactivation, which was mediated by CD45 in the hypoxic tumor environment [138].

7.3. *Anti-tumoral T lymphocytes*

STAT3 activity can also directly inhibit anti-tumorigenic T cell functions. NK cell activities can be blunted by STAT3 activation, as shown in an IL-6-secreting neuroblastoma model [139]. Accordingly, STAT3 inhibition allowed efficient expansion and tumor infiltration of adoptively transferred $CD8^+$ T cells, eliciting strong antigen-specific T cell responses and immune clearance in various models of solid tumors [140, 141]. Thus, STAT3 inhibition might improve the efficacy of T cell adoptive transfer therapies.

7.4. *Cancer Associated Fibroblasts (CAF)*

The cross talk between cancer cells and CAFs also heavily relies on the activation of the IL-6-STAT3 pathway in both CAFs and tumor cells. Indeed, STAT3 activation elicited by cell-cell contacts, by the activation of the fibroblast activating protein (FAP), or by the secretion of STAT3-activating soluble factors such as IL-6 or LIF by cancer cells was shown to be essential to elicit activation of CAFs and pro-tumoral activities in head and neck, lung, breast, gastric or pancreatic cancer [142-146]. STAT3-mediated pro-tumorigenic activities ranged from CCL2 secretion for MDSC recruitment [147], to Twist1 up-regulation for the induction of cancer cell movement and invasion [144], to the induction of an epigenetic switch leading to methylation–mediated silencing of the SHP1 gene and consequent constitutive activity of JAK1 [145]. Similarly, direct contact with pancreatic cancer cells could elicit methylation-dependent SOCS1 silencing, leading to constitutive STAT3 YP [146].

On the other hand, CAFs can promote and sustain STAT3 activation in cancer cells, with all its multifaceted functions, via secretion of IL-6 or other STAT3-activating gp130-family cytokines in various carcinoma models such as breast, colorectal, lung, pancreas, liver and endometrial cancer [143, 145, 148-151]. Further, CAF-secreted IL-6 can also activate STAT3 in DCs to elicit the differentiation of an immune-suppressive regulatory DC subset [152].

The observed multiple pro-oncogenic activities of STAT3 in both tumor and TME cells may help explain the widespread contributions of this factor to tumor onset, progression and metastasis, and fuel the interest in developing STAT3 inhibitors whose *in vivo* efficacy may be enhanced by the numerous cell types involved. In this vein, the novel dual inhibitor NT157, which promotes the inactivation of both the IGF1R and STAT3 pathways, was shown to impair tumor progression in the Apc^{Min} mouse model of colorectal cancer, acting on cancer cells, CAFs and TAMs to down-regulate the expression of several immune-suppressive secreted factors including TGFβ, IL-6 and IL-10 [150].

8. CONCLUDING REMARKS

Despite the concept of oncogenic STAT3 being widely accepted, an increasing body of data now supports the view that STAT3 functions are too variegated to be easily classified. Ultimately, the specific cellular role of STAT3 is determined by the integration of multiple signals that dictate the overall abundance of its many differentially modified forms, and consequently their sub-cellular localization and activity (see Figure 1). Direct modulation by oxidation suggests that the effects of upstream signals will be further modified by cell metabolic conditions, including oxidative stress and autophagy activation. Enhanced mitochondrial activities by SP STAT3 may be required for cell transformation downstream of certain oncogenes such as Ras, but be detrimental in tumors types requiring the establishment of a Warburg effect. STAT3 pro- or anti-autophagy activities may either favor or contrast tumor cell transformation and progression, depending on the specific tumor type, stage and metabolic conditions. Finally, pro-tumoral or onco-suppressive STAT3 activities will be determined, in each specific case, by the actions exerted by the known differentially modified STAT3s on both cancer and TME cells, whose effects are not always coherent.

Based on these considerations, the potential outcome of therapies based on STAT3 inhibition need to be tailored to the specific tumor type and mutational landscape, and directed against specific STAT3 modifications. This stresses the need for a systematic assessment of STAT3 activities in specific tumors, downstream of distinct oncogenic pathways, and in cancer or TME cells, whose interconnections need to be studied in immuno-competent *in vivo* models. In turn, this new knowledge will help define specific and effective inhibition strategies, as well as establish guidelines to assess treatment outcomes.

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Figure 1

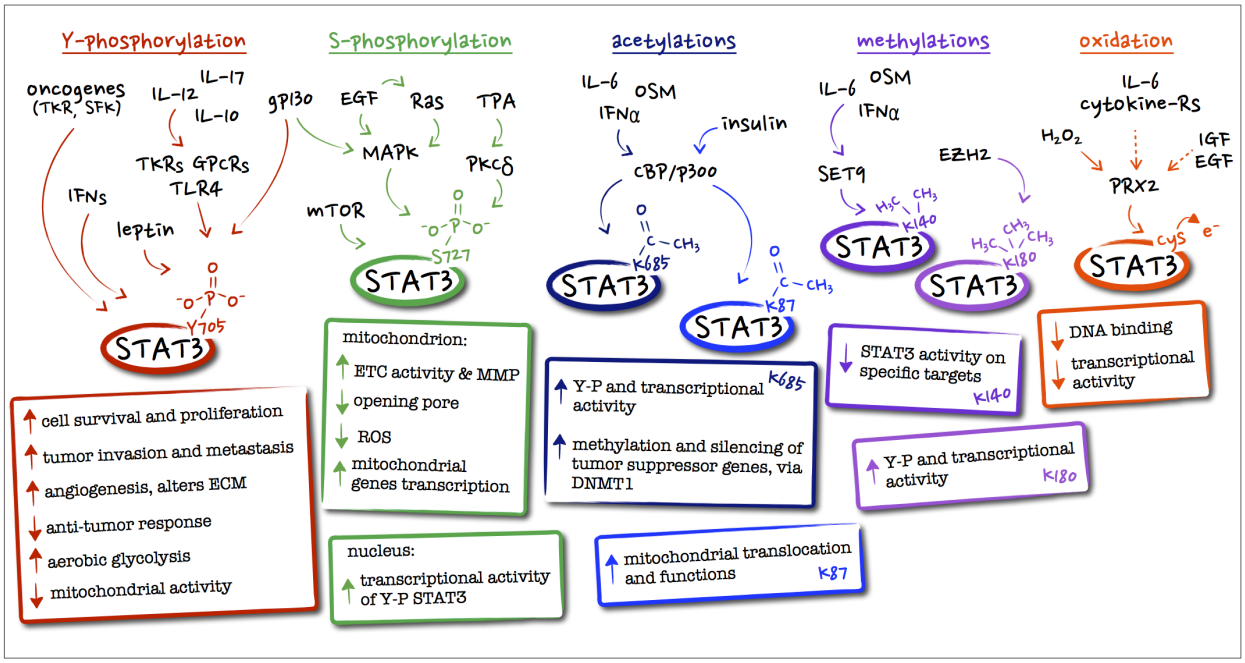

FIGURE LEGEND

Figure 1. Main STAT3 activating pathways and their induced post-translational modifications.

The scheme depicts the main STAT3 post-translational modifications, together with their known biological effects and upstream regulators.

TKR, tyrosine kinase receptors; SFK, Src family tyrosine kinases; GPCRs, G protein coupled receptors; TLR, toll-like receptors.

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