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STAT3 and STAT5 Activation in Solid Cancers

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Abstract

The Signal Transducer and Activator of Transcription (STAT)3 and 5 are activated by many cytokine receptors to regulate specific gene expression and mitochondrial functions. Their role in cancer is largely context dependent as they can both act as oncogenes and tumor suppressors. We review here the role of STAT3/5 activation in solid cancers and summarize their association to survival in cancer patients. The molecular mechanisms that underpins the oncogenic activity of STAT3/5 signaling includes the regulation of genes that control cell cycle, cell death, inflammation and stemness. In addition, STAT3 mitochondrial functions are required for transformation. On the other hand, several tumor suppressor pathways act on or are activated by STAT3/5 signaling including the p19ARF/p53 pathway, tyrosine phosphatases, suppressor of cytokine signaling 1 and 3, the sumo ligase PIAS3, the E3 ubiquitin ligase TMF/ARA160 and the miRNAs miR-124 and miR-1181. Cancer mutations and epigenetic alterations may alter the balance between pro-oncogenic and tumor suppressor activities associated to STAT3/5 signaling explaining their context dependent association to tumor progression both in human cancers and animal models.

Keywords: solid cancers; cell cycle; apoptosis; inflammation; mitochondria; stemness; tumor suppression

Introduction

Activation of Signal Transducer and Activator of Transcription (STAT) has been linked to many human cancers. STATs were initially discovered as latent cytosolic transcription factors that get phosphorylated by the JAK kinase family upon stimulation of membrane receptors for cytokines and growth factors. Phosphorylation triggers dimerization and translocation to the nucleus to bind specific promoters and regulate transcription [1]. Here, we review the role of STAT family members STAT3 and STAT5 in solid human malignancies as well as the mechanisms that may explain their association to either worse or better prognosis.

STAT3 and STAT5 in solid cancers

The discovery of cancer genes has been propelled by genetic analysis and more recently by new generation DNA sequencing technologies. Combined, these studies have identified 127 significantly mutated genes that cover diverse signaling pathways [2]. Mutations acting as drivers in cancer are positively selected during tumor growth and constitute a solid proof to link any gene to the disease. Mutations in STAT3 and STAT5 have been reported in patients with solid cancers, but unlike hyperactivation of the JAK/STAT pathway, STAT3/5 mutations in cancer are relatively infrequent and occur mostly in hematological malignancies. An overview of reported STAT3/5 mutations in solid cancers is illustrated in Figure 1, based on data collected from the Catalogue of Somatic Mutations in Cancer (COSMIC) database. Mutations in STAT3 are more prevalent than mutations in the STAT5A or STAT5B genes, and gastrointestinal cancers have the highest rates of STAT3/5 mutations compared with other solid cancers (Figure 1). Missense mutations tend to cluster within the SH2 domain, where gain-of-function mutations have been previously characterized [3,4], as well as within the DNA binding domain and to an extent the N-terminal domain (Figure 1A). Interestingly, the STAT3 Y640F hotspot gain-of-function mutation reported

in various lymphoid malignancies has also been detected in patients with liver cancer (Figure 1A). Nonsense and frameshift mutations are less frequent and more disperse, likely representing loss-of-function events (Figure 1B). Notably, a hotspot frameshift mutation at position Q368 within the DNA binding domain of STAT5B has been reported in 24 patients with various types of carcinoma; this frameshift generates a stop codon shortly after the mutation and is therefore likely to be loss-of-function, although characterization of this mutation has not been performed.

As opposed to mutations rates, STAT3/5 activation is very frequent in human cancers and this can be detected using antibodies that measure total levels or activation marks in STAT3/5 proteins. A better assessment of STAT3/5 activation can be obtained by measuring downstream signaling targets (i.e. mRNA levels of STAT3/5 target genes). A recent metanalysis of 63 different studies concluded that STAT3 overexpression was significantly associated with a worse 3-year overall survival (OS) (OR = 2.06, 95% CI = 1.57 to 2.71, $P < 0.00001$) and 5-year OS (OR = 2.00, 95% CI = 1.53 to 2.63, $P < 0.00001$) of human solid tumors [5]. Elevated STAT3 expression was associated with poor prognosis in gastric cancer, lung cancer, gliomas, hepatic cancer, osteosarcoma, prostate cancer and pancreatic cancer. However, high STAT3 expression predicted a better prognosis for breast cancer [5]. This study mixed data of both STAT3 and phospho-STAT3 (p-STAT3) expression limiting its ability to associate pathway activation to prognosis. Here, we summarize the data linking activation of STAT3/5 to overall survival in several major human solid cancers identifying the biomarkers used in each study (Table I). Taken together, the results clearly show that STAT3 and STAT5 are important cancer genes despite their low mutation frequency.

STAT3 activation is clearly a factor of bad prognosis in patients with lung cancer, liver cancer, renal cell carcinoma (RCC) and gliomas. In other tumors, the association is not significant. In solid tumors, STAT3 activation is more frequent than STAT5 activation although no

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explanation for this difference was proposed. In prostate cancer, both STAT3 and STAT5 have been associated to castration resistant disease and proposed as therapeutic targets [6,7]. In colon cancer, the association between p-STAT3 and survival varies according to the study, but a high p-STAT3/p-STAT5 ratio indicates bad prognosis [8]. Also in breast cancer, p-STAT5 levels are clearly associated to better prognosis [9]. In liver cancer, STAT5 has ambivalent functions that were recently reviewed by Moriggl and colleagues [10]. Understanding mechanistically how STAT3/5 promote transformation and tumor suppression is important for the eventual design of new treatments. Also, survival data is highly influenced by the response of patients to their treatment and may not always reflect all mechanistic links between STAT3/5 activity and tumor biology. Of note, the effect of any gene is conditioned by the genetic context of gene action. Some genes can clearly exert a tumor suppressor effect in the initial stages of carcinogenesis that is lost when cancer mutations or epigenetic changes inactivate key effectors of these tumor suppressor pathways [11]. Human studies are usually limited to late stage tumors because it is easier to collect samples at that point. Studies in model systems, including primary cells, organoids and mouse models are thus required for a full understanding of how cancer genes work specifically at early stages in tumorigenesis.

Table 1. STAT3/5 and overall survival in major human solid tumors. BC, breast cancer, HCC, hepatocellular carcinoma, GBM, glioblastoma, NSCLC, non-small-cell lung carcinoma, HR, hazard ratio

Tumor type	Type of study/biomarker	Overall Survival	Ref
NSCLC	Meta-analysis of 9 studies/ high p-STAT3	Log HR 0.67, 95%CI: 0.57–0.77, $P < 0.0001$	[12]
NSCLC	Cox regression multivariate analysis/ high p-STAT3	HR 2.45, 95%CI: 1.084–5.556, $P = 0.031$	[13]
Lung cancer	Meta-analysis of 13 studies/ high p-STAT3	HR 1.23, 95% CI: 1.04–1.46, $P = 0.02$	[14]
Pancreatic cancer	Log-rank test/ high p-STAT3	No association $P > 0.05$	[15]
Liver cancer (HCC)	Meta-analysis of 8 studies/ high p-STAT3	HR 1.69, 95% CI : 1.07, 2.31, $P < 0.0001$ 3yr	[16]

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		HR 1.67, 95%, CI : 1.18, 2.15, $P < 0.0001$ 5yr	
Breast cancer	Meta-analysis of 12 studies/ high p-STAT3	No association $P > 0.05$	[17]
ER+ BC	Log-rank test/ high p-STAT3	No association $P > 0.05$	[18]
GBM	Cox regression multivariate analysis/ high phospho-S727-STAT3	HR 1.797, 95% CI: 1.028-3.142, $P = 0.040$	[19]
RCC	Cox regression multivariate analysis/ high phospho-S727-STAT3	HR 3.32, 95% CI: 1.26–8.71, $P = 0.014$ 10yr	[20]
Colon cancer	Cox regression multivariate analysis/ high p-STAT3/p-STAT5 ratio	HR 4,468 $P = 0.043$ 5yr	[8]
Colon cancer	Log-rank test/ high p-STAT3	Worse overall survival, $P < 0.001$	[21]
Colon cancer	Cox regression multivariate analysis/ high p-STAT3	HR: 1.61, 95% CI: 1.11–2.34 $P = 0.015$	[22]
Breast cancer	Cox regression multivariate analysis/ low p-STAT5	HR 2,49, 95% CI, 1.23 to 5.05 $P = 0.012$ 5yr	[9]
Prostate cancer	Cox regression multivariate analysis/ high nuclear STAT5a/b	HR 1.59, 95% CI, 1.04 to 2.44 $P = 0.034$	[7]

Mechanisms of transformation by STAT3/5 proteins in solid cancers

STAT3 and 5 promote tumor progression by regulating the expression of cell cycle, survival and pro-inflammatory genes. In addition, they control mitochondrial functions, metabolism and stemness (Figure 2).

Cell cycle and apoptosis

As transcription factors, STAT3 and STAT5 regulate many genes required for cell cycle progression and cell survival. A major target of the transcriptional control of the mammalian cell cycle is cyclin D. STAT3 regulates cyclin D in a complex with CD44 and the acetyltransferase p300. The latter acetylates STAT3 promoting its dimerization, nuclear translocation and binding to the cyclin D promoter [23]. Other cell cycle and survival genes regulated by STAT3 include c-MYC, BCL2, BCLXL, MCL1 and survivin [24]. Recent studies combined ChIPSeq with whole transcriptome profiling in ABC DLBCL (activated B cell-like diffuse large B-cell lymphoma) cell lines and revealed that STAT3 activates genes in the PI3K/AKT/TOR pathway, the NF-κB pathway and E2F/G2M pathway while repressing type I interferon signaling genes [25]. STAT5

also regulates the expression of cell cycle and cell survival genes [11] including AKT1 [26], a pro-survival kinase.

Inflammation and innate immunity

Although the induction of cell proliferation and cell survival genes by STAT3/5 proteins contribute to their pro-cancer activity, in basal-like breast cancers the major genes associated to STAT3 activation control inflammation and the immune response [27]. STAT3 cooperates with NF-κB to regulate gene expression. NF-κB supports expression and activation of STAT3 [28,29]. Moreover, STAT3 can synergize with NF-κB, thereby changing gene expression patterns and promoting tumorigenesis [30]. Starved tumor cells activate NF-κB and STAT3 via ER stress and secrete cytokines that stimulate tumor survival and clonogenic capacity [31]. The coactivation of these two transcription factors amplifies pro-inflammatory gene expression driving cancer-associated inflammation [32]. Of interest, the STAT3-NF-κB complex can repress the expression of DDIT3, an inhibitor of CEBPbeta, another pro-inflammatory transcription factor [33]. The antidiabetic drug metformin inhibits both NF-κB and STAT3 but the mechanism of this effect is still unknown [34,35]. In contrast to STAT3, STAT5b inhibits NF-κB activity in the kidney fibroblast cell line COS [36], while it stimulates NF-κB in leukemia cells [37], perhaps suggesting why STAT5 is less associated to malignancy in solid tumors but is highly oncogenic in hematopoietic cancers.

Mitochondria

On top of their canonical roles in inflammation and immunity, STAT3 and STAT5 have been shown to localize to mitochondria. The mitochondrial localization of STAT3 is required for its ability to support malignant transformation [38-41] and mito-STAT3 regulates mitochondrial metabolism and mitochondrial gene expression [40,42-46]. Several reports have suggested that STAT3 can be imported to mitochondria after phosphorylation on S727 [39,40] or acetylation

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[47,48]. Other studies have revealed that STAT3 mitochondrial translocation is mediated by interactions with HSP22, GRIM-19 or TOM20 [49-51]. The mRNAs coding for some mitochondrial proteins are translated close to or in physical interaction with the import complex TOM or Translocase of the Outer Membrane [52,53]. The structural motifs mediating those interactions are located in the 3' and 5'UTRs of the mRNAs [54,55] and it will be interesting to investigate whether STAT3 also possesses RNA zip codes to translocate to mitochondria.

Whereas the role of mitochondrial STAT3 has been extensively studied, the role of STAT5 in mitochondria is less clear. The import of STAT5 to mitochondria is regulated by cytokines [38]. Once imported into the mitochondria, STAT5 binds the D-loop of mitochondrial DNA although no increase in transcription of mitochondrial proteins was observed [56]. Mito-STAT5 is also able to interact with the Pyruvate Dehydrogenase Complex (PDC) and could regulate metabolism towards glycolysis, as observed in cells treated with cytokines [38,56]. In the same line, recently STAT3 was also shown to interact with PDC showing once more similar roles of STAT3 and STAT5 in mitochondria [48].

Reprogramming and stemness

The role of STAT3 in stem cell biology was initially recognized due to the requirement for the cytokine LIF to maintain pluripotency in cultures of embryonic stem (ES) cells. STAT3 activation mediates the induction or repression of several genes in ES cells including the pluripotency factors OCT4, NANOG, KLF4 and polycomb proteins [57,58]. Many pluripotency factors such as NANOG are short lived proteins. STAT3 controls protein stability by inducing the expression of the deubiquitinase USP21, stabilizing NANOG in ES cells. Induction of ES cell differentiation promotes the ERK-dependent phosphorylation of USP21 and its dissociation from NANOG, leading to NANOG degradation [59]. STAT3 also plays a role in the reprogramming of somatic

cells into induced pluripotent stem (IPS) cells [60] and it has been suggested that its effects depend on epigenetic regulation because STAT3 is required for the demethylation of pluripotency factor promoters [61]. STAT3 also activates mitochondrial DNA transcription promoting OXPHOS during maintenance and induction of pluripotency [62]. It is thus likely that the ability of STAT3 to stimulate stemness also plays a role in its oncogenic activity.

In many tumors, a subpopulation of cells possesses a higher malignant capacity. These so called tumor initiating cells are suspected to regenerate the tumor after cancer chemotherapy and express many genes commonly expressed in ES cells [63]. It has been proposed that a common gene expression program underpins both cancer and stemness. Consistent with this hypothesis, it has been shown that STAT3 is required to maintain stemness in many different tumors [34,35,64-77]. At least in breast cancer, a critical mechanism stimulated by STAT3 to regulate stemness involves genes in fatty acid oxidation [72,73] and the ability of STAT3 to adjust the ROS levels produced in mitochondria [73]. In colorectal cancer cells, STAT3 forms a complex with the stem cell marker CD44 and the p300 acetyltransferase. Acetylation of STAT3 by this complex allows dimerization, nuclear translocation and binding to the promoters of genes required for stemness such as MYC and TWIST1 [78]. The role of STAT5 in cancer stemness does not affect many cell types and is mostly confined to hematopoietic cancers [79]. However, Nevalainen and colleagues reported that STAT5B induces stem cell properties in prostate cancer cells [80] in line with the increase in nuclear STAT5A/B observed in these tumors in correlation with bad prognosis [7].

Tumor suppression and STAT3/5 signaling

Although STAT3 and STAT5 activation is generally considered to be tumor promoting, several reports have shown that in different situations STAT3 and STAT5 can activate tumor suppressor

pathways (Figure 3). Understanding these different responses to STAT signaling in cancer is important to further distinguish tumors that would benefit from STAT3 or STAT5 inhibitors and those that would not.

P19ARF-p53 pathway

One of the first reports that STAT3 can act as a tumor suppressor was shown in glioblastoma [81] where a combination of low PTEN and loss of STAT3 in astrocytes increased their tumorigenicity. A later report of the combined loss of STAT3 and PTEN in the prostate confirmed the tumor suppressor functions of STAT3 and found that STAT3 induces the expression of p19ARF [82]. High levels of p19ARF would in turn inhibit MDM2 and thus activate the tumor suppressor p53. Loss of STAT3 disrupts this STAT3-ARF-p53 axis and permits tumor progression [83]. STAT3 and other STATs can also induce p21 leading to cell cycle arrest or cellular senescence [84,85]. Further evidence for STAT3 as a tumor suppressor has been reported in lung [86], colon [87,88], thyroid [89], liver [90,91], skin [92], neck [93], nasopharynx, rectum [94], salivary gland [95] and breast cancers [96].

Tyrosine phosphatases

Activation of STAT3 and STAT5 in tumors is often associated to tyrosine phosphorylation, a modification that can be reverted by several protein phosphatases such as PTPN2, PTPN9/MEG2, PTPN11/SHP2 [97,98], CD45 [99] and SHP1 [100]. However, little is known about a possible role of these phosphatases in STAT3 activation in solid tumors. In liver cancers, SHP1 is downregulated in cells with mesenchymal features and restoring its levels both reduced STAT3 phosphorylation and reversed the mesenchymal phenotype of liver cancer cells [100]. SHP1 and SHP2 also target STAT5 [101,102] but the significance of this regulation for solid tumors remains to be investigated.

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The Suppressor of cytokine signaling SOCS

The members of the SOCS family are major negative feedback regulators of JAK/STAT signaling and their expression is dysregulated in many human cancers [103-105]. These genes provide a barrier for cells with aberrant cytokine activation by inhibiting cytokine signaling [106]. In STAT3 driven cancers, SOCS3 seems to be the most important negative feedback regulator and mouse models of SOCS3 ablation show strong STAT3 activation [105,107-110]. On the other hand, in solid cancers where STAT5 plays a causal role such as liver and prostate cancer, in addition to SOCS3, SOCS1 is frequently inactivated and mouse models of SOCS1 ablation increase both liver and prostate tumorigenesis [111-118]. In addition, SOCS1 and SOCS3 can bind p53 and activate tumor suppressor responses such as senescence and ferroptosis [119-124]. STAT5 is a potent inducer of the SOCS1-p53-senescence axis and this may explain the better prognosis of cancers with high p-STAT5 [11,119,121,125-127] and the high frequency of SOCS1 inactivation in STAT5-driven cancers [111-118].

The mechanisms that disable SOCS1 and SOCS3 in human cancers are often epigenetic, mediated either by miRNAs, promoter methylation or protein phosphorylation [113,114,116,117,123,128-137]. The SRC family of kinases phosphorylate SOCS1 at Y80, interfering with p53-SOCS1 interactions. SFK inhibitors can reverse this effect and could be used to restore the SOCS1-p53 axis in tumors where these two proteins remain intact [137]. It is also possible to consider treatments that re-express SOCS1/3 in tumors. Indeed in liver cancer, SOCS3 gene expression can be re-established by drugs that activate the Farnesoid X receptor (FXR) [138,139]. Gene therapy strategies are also under development to re-express SOCS1 or SOCS3 in tumors [140-142].

PIAS

The Protein Inhibitor of Activated STAT3 (PIAS3) inhibits STAT3 transcriptional activity. In gliomas, PIAS3 expression is reduced [143]. Mechanistically, SMAD6 promotes PIAS3 degradation, promoting glioma cell growth and stem cell properties [70]. The PIAS proteins have SUMO E3 ligase activity on multiple proteins and their effects cannot be solely attributed to STAT3 inhibition [144]. Of interest, PIAS3 can bind NF-κB promoting its SUMOylation and inhibiting its activity [145,146] potentially targeting the expression of many proinflammatory genes to block tumor progression. Also, PIAS3 binds the N-terminus of p53 and prevents its interaction with MDM2, leading to p53 stabilization [147].

E3 ligases

The Golgi resident and BC-box protein TMF/ARA160 was reported as an E3 ligase that catalyzes STAT3 ubiquitination leading to its proteasome dependent degradation in myogenic C2C12 cells. The level of TMF/ARA160 was significantly decreased in malignant brain tumors where STAT3 is known to play an oncogenic role [148]. Like PIAS3, TMF/ARA160 can also bind and ubiquitinate RELA/NF-kB leading to its proteasome dependent degradation and a decrease in the expression of inflammatory genes [149]. The ubiquitin ligase TRAF6 binds and ubiquitinates STAT3 inhibiting the expression of STAT3 target genes [150]. During oncogene-induced senescence STAT3 is degraded by the proteasome but the E3 ligase responsible has not been identified [151]. Recent results revealed that the lncRNA PVT1 binds STAT3 and protects it from ubiquitin-dependent degradation in gastric cancer [152]. PVT1 is upregulated in multiple cancers predicting poor prognosis for overall survival [153-155].

MiRNAs

The miRNA miR-124 regulates STAT3 signalling by targeting the mRNAs of IL6R [156] and STAT3 [157,158]. Suppression of this miRNA increases STAT3 phosphorylation and induces

transformation in immortalized mouse hepatocytes. Of interest, systemic delivery of miR-124 prevented tumor growth in diethylnitrosamine (DEN)-treated mice and miR-124 levels were reduced in human hepatocellular carcinomas (HCC) [156]. In gliomas, miR-124 is poorly expressed but upregulation of its expression in glioma cancer stem cells inhibited the STAT3 pathway. In this model, STAT3 mediates immunosuppression, which was relieved upon systemic miR-124 delivery [159]. The cirRNA_100782 is upregulated in pancreatic cancer and its knockdown upregulates all miR-124 targets including IL6R and STAT3. This cirRNA binds miR-124 suggesting that it may acts as a miRNA sponge [160]. Furthermore, the miRNA, miR-1181, also targets STAT3 and is downregulated in pancreatic cancer predicting poorer overall survival. Overexpression of miR-1181 inhibited tumor formation and stem cell properties of pancreatic cancer cells [161].

Concluding remarks

Context dependent activities of STAT3 and STAT5 in solid human cancers justify detailed molecular studies that will clarify the specific molecular mechanism of action of these two cancer genes. The cancer genome and transcriptome are shaped and selected to favour cancer cell survival and proliferation. Although restoring mutated genes is technologically difficult, reprograming the transcriptome to restore tumor suppression may be feasible. Drugs acting on STAT3/5 and their regulators may restore the control of cell proliferation in cancer cells.

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Legend

Figure 1: Map of somatic mutations detected in human STAT5A, STAT5B and STAT3 in patients with solid cancers. Individual missense mutations found in at least two patients (A), as well as all reported nonsense and frameshift mutations (B), are depicted. Numbers in each box represent the number of cases reported for each mutation. Data were mined from the Catalogue of Somatic Mutations In Cancer (COSMIC) database. ND, N-terminal domain; CCD, Coiled coil domain; DBD, DNA binding domain; LD, Linker domain; SH2, Src homology 2 domain; TAD, Transactivation domain.

Figure 2. Mechanisms of tumorigenic activity of STAT3 and STAT5 signaling in solid tumors.

Figure 3. Tumor suppressor pathways acting on STAT3/5 activity (PIAS, miRNAs, E3 ligases, phosphatases) or activated by STAT3/5 transcriptional activity (p19ARF, SOCS1/3, p53)

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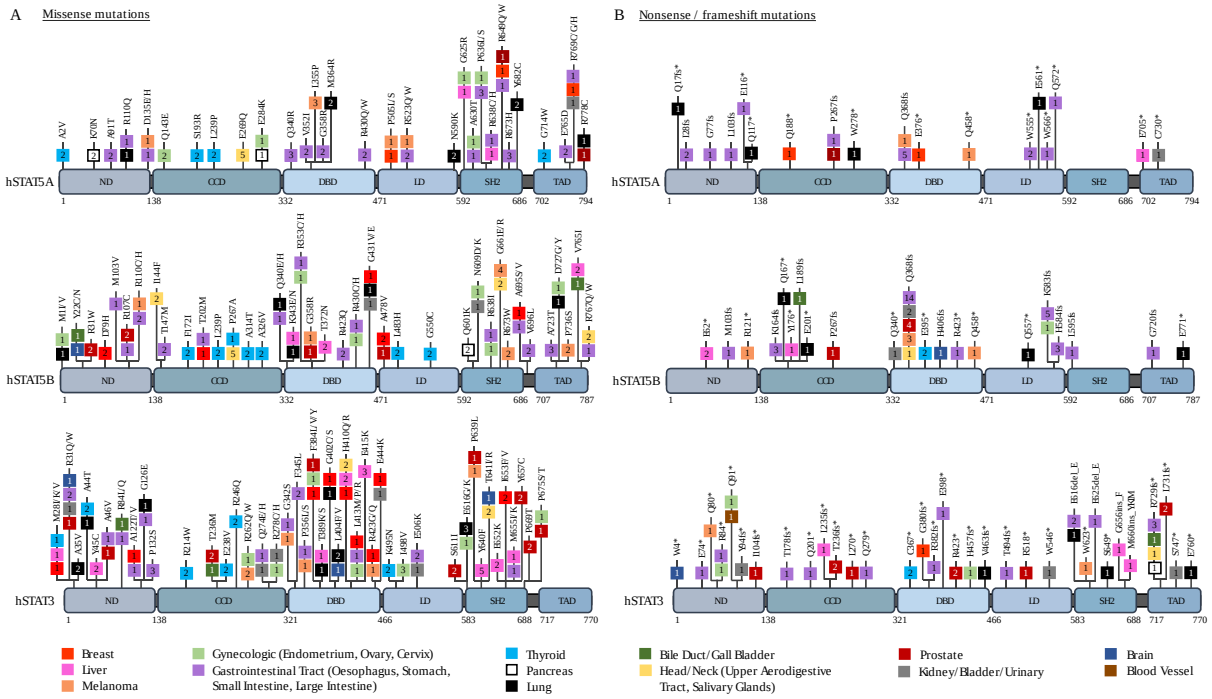

Figure 1: Map of somatic mutations detected in human STAT5A, STAT5B and STAT3 in patients with solid cancers. Individual missense mutations found in at least two patients (A), as well as all reported nonsense and frameshift mutations (B), are depicted. Numbers in each box represent the number of cases reported for each mutation. Data were mined from the Catalogue of Somatic Mutations In Cancer (COSMIC) database. ND, N-terminal domain; CCD, Coiled coil domain; DBD, DNA binding domain; LD, Linker domain; SH2, Src homology 2 domain; TAD, Transactivation domain.

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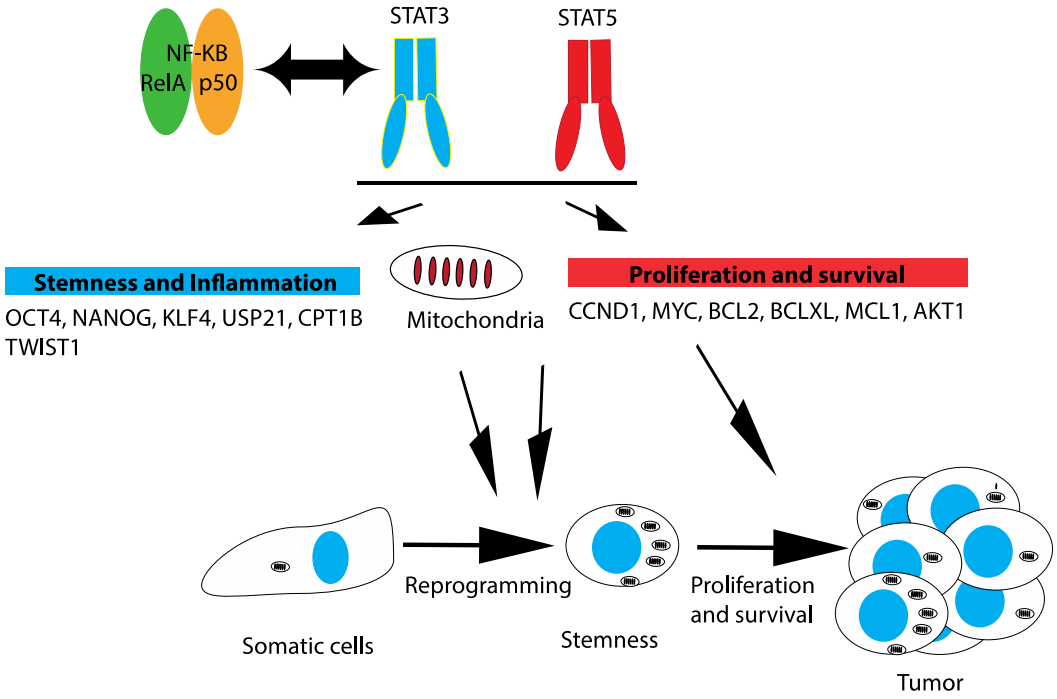

Figure 2

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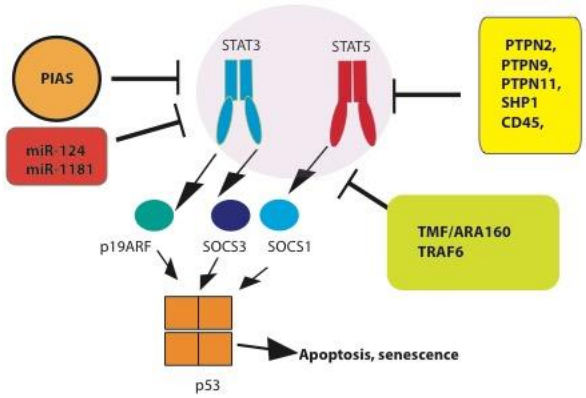

Figure 3