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Review article

The good and the bad faces of STAT1 in solid tumours

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ABSTRACT

Signal transducer and activator of transcription (STAT) 1 is part of the Janus kinase (JAK)/STAT signalling cascade and is best known for its essential role in mediating responses to all types of interferons (IFN). STAT1 regulates a variety of cellular processes, such as antimicrobial activities, cell proliferation and cell death. It exerts important immune modulatory activities both in the innate and the adaptive arm of the immune system. Based on studies in mice and data from human patients, STAT1 is generally considered a tumour suppressor but there is growing evidence that it can also act as a tumour promoter. This review aims at contrasting the two faces of STAT1 in tumourigenesis and providing an overview on the current knowledge of the underlying mechanisms or pathways.

Contents

Abbreviations: BAD, Bcl2-associated agonist of cell death; Bcl, B-cell lymphoma; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CTL, cytotoxic T lymphocyte; CUG, cancer upregulated gene; CXCL, C-X-C motive ligand; DC, dendritic cells; DAMP, danger-associated molecular pattern; DR, death receptor; ER, estrogen receptor; ERBB2/neu, Erb-B2 receptor tyrosine Kinase 2; ERK, extracellular signal-regulated kinase; FASL, FAS ligand; FADD, Fas-associated protein with death domain; FGF, fibroblast growth factor; HDAC, histone deacetylase; HIF, hypoxia-inducible factor; IFN, interferon; IFNAR, IFNα/β receptor; IFNGR, IFNγ receptor; IL, interleukin; IRDS, IFN-related DNA damage resistance signature; IRES, internal ribosome entry site; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MCA, methylcholanthrene; MDM2, mouse double minute 2 homolog; MDR, multidrug resistance; MDSC, myeloid-derived suppressor cell; MEF, mouse embryonic fibroblast; MHC class I, major histocompatibility complex class I; *miRNA*, microRNA; MMP, matrix metalloproteinase; MUC, mucin; NFκB, nuclear factor kappa B; NK, natural killer; PDCD, programmed cell death; PD-L1, programmed death-ligand 1; PIAS, protein inhibitors of activated STATs; PRR, pattern recognition receptor; pSTAT, tyrosine phosphorylated STAT; Rb, retinoblastoma; RIG-1, retinoic acid inducible gene 1; RIP, receptor interacting protein kinase; SHP2, SH2 domain-containing protein-tyrosine phosphatase; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription; *S727*, serine 727; TAM, tumour-associated macrophage; TGF, transforming growth factor; TLR, toll-like receptor; TNBC, triple negative breast cancer; TNF, tumour necrosis factor; TRADD, TNFR1-associated death domain protein; TRAF, TNF-receptor associated factor; TRAIL, TNF-related apoptosis-inducing ligand; U-STAT, unphosphorylated STAT; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein; *Y701*, tyrosine 701.

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1. Introduction

STAT1 is one of the seven mammalian members of the STAT family [1]. STAT1 transduces signals from cytoplasmic domains of transmembrane receptors into the nucleus where it regulates gene expression. Thereby it modulates diverse cellular processes, such as proliferation, differentiation and cell death. STAT1 function is central in the innate and adaptive arm of immunity and protects from pathogen infections [2]. It transduces activities of different cytokines, including type I-III interferons (IFNs), interleukin (IL)-21, IL-27 and IL-35 [3–5].

STAT1 activation is transient and tightly regulated. Phosphorylation on tyrosine 701 (Y701) of STAT1 (pSTAT1) by Janus kinases (JAKs) leads to its activation and nuclear translocation. Serine 727 (S727) phosphorylation is required for full transcriptional activation upon IFN stimulation and in response to cellular stress [6]. Activated STAT1 regulates transcription of protein-encoding genes, including *Stat1* itself. It also drives the expression of microRNAs (miRNAs), which regulate gene expression at the mRNA or translational level [7]. Alternative splicing generates two STAT1 isoforms, the full length STAT1α and the truncated STAT1β. The latter lacks part of the C-terminal transactivation domain, including the S727 phosphorylation site, and was considered to be transcriptionally inactive. STAT1 isoform specific knock-in mice revealed that STAT1β is capable to drive transcription, albeit delayed and to reduced levels as compared to STAT1α [8]. Due to the lack of appropriate *in vivo* models and analytical tools, STAT1 isoform specificity in carcinogenesis and immunity has not yet been thoroughly addressed. Transcriptional activity has also been assigned to unphosphorylated STAT1 (U-STAT1) [9–11]. U-STAT1 maintains heterochromatin stability in Drosophila [12] and in mammalian cells [13–15]. STAT1 activation is inhibited at different levels, e.g. feedback inhibition of JAKs by suppressor of cytokine signalling (SOCS) proteins, dephosphorylation of STAT1 by phosphatases (e.g., the SH2 domain-containing protein-tyrosine phosphatase SHP2), nuclear export of STAT1 and inhibition of DNA binding by protein inhibitors of activated STATs (PIAS) [16–20].

In general, STAT1 is considered a tumour suppressor, although there is increasing evidence for tumour promoting functions of STAT1. Mechanistic insights *in vivo* grossly stem from *Stat1*-deficient mice and various murine cancer models. Patients with inborn STAT1 mutations that lead to loss- or gain-of-function suffer from severe diseases related to innate immunity and autoinflammation [3,21,22]. Human STAT1 mutations have therefore been rarely studied in the context of cancer. However, a plethora of studies describe a correlation of altered STAT1 availability and/or activation states in human tumour samples with disease outcome. In this review we summarise the current knowledge on the tumour suppressive and promoting functions of STAT1. The focus is on correlations with the STAT1 status in solid tumours, mechanistic aspects and studies in *Stat1*-deficient ($Stat1^{-/-}$) mice.

2. Tumour suppressive functions of STAT1

Tumour suppressor properties of STAT1 are deduced from the findings that STAT1 availability and/or activation are reduced or not detectable in transformed cells and during progression of various tumours in humans. A correlation of STAT1 expression with good prognosis has been shown in several types of cancers, including colo(rectal) cancer [23–26], hepatocellular carcinoma [27], esophageal cancer [28], pancreatic cancer [29], soft tissue sarcoma [30] and metastatic melanomas [31]. The prognostic power of STAT1 in breast cancer appears to be more complex, as correlations with good and bad prognosis have been reported for both STAT1 expression levels and pSTAT1. Tumour suppressive functions of STAT1 in breast cancers are evidenced as follows. STAT1 expression levels, pSTAT1 and its cell type specificity was reported as an independent marker for good prognosis in breast cancer tissue [32,33], although one study did not find a correlation of STAT1 levels and disease outcome [34]. However it was also noted that high levels of *Stat1* mRNA, in contrast to pSTAT1, are linked to poor disease outcome (see chapter 3) [33]. Support for a breast cancer suppressive role of STAT1 was furthermore provided by the finding that STAT1 expression is reduced in tumour epithelia compared to normal breast tissue [35] and by pathway analysis of genes with altered methylation patterns in breast cancer patients [36].

Compelling evidence for suppressive functions of STAT1 in mammary tumourigenesis was provided by four studies in mice with different experimental models. Concomitant deletion of *Stat1* and expression of the *ErbB2/neu* oncogene in mammary epithelial cells, results in a more rapid development of mammary tumours [37,38]. An increase of spontaneous mammary tumour formation in multiparous $Stat1^{-/-}$ mice was shown in two studies, although results differed with respect to tumour frequencies, the frequency of arising estrogen receptor positive (ER^{+}) tumours and whether or not virgin mice developed tumours [35,39]. These data have just recently been comprehensively reviewed and collectively establish that STAT1 acts as tumour suppressor in both the tumour cells themselves and in the tumour environment in mice [40,41].

The tumour suppressive functions of STAT1 in other tumour types have already been demonstrated in earlier studies. $Stat1^{-/-}$ mice developed methylcholantrene (MCA)-induced tumours with higher frequency and shorter latency than wild-type mice. Absence of STAT1 also decreased latency of spontaneously arising tumours in the absence of the tumour suppressor p53 and, interestingly, also broadened the tumour spectrum. Parallel analysis of mice deficient for IFNγ ($Ifn\gamma^{-/-}$) and extensive tumour transplant experiments established that the main function of STAT1 in the MCA-induced tumour model lies in mediating IFNγ-dependent tumour immune surveillance [42].

Mechanistically, tumour suppression by STAT1 occurs at multiple levels: tumour cell-intrinsic growth control (Fig. 1A) and cross-talk with other cells to modulate cancer immunoediting and suppress angiogenesis (Fig. 1B).

2.1. Tumour cell growth inhibition and cell death

The central role of STAT1 in conveying the anti-proliferative effects of all types of IFNs is well-established [43–46]. The effects of STAT1 range from cell cycle inhibition and sentitization to apoptotic stimuli to the induction of different forms of cell death.

Mechanistically, STAT1 transcriptionally regulates the expression of cell cycle regulators, pro-apoptotic proteins and death-receptors and their ligands. The cyclin-dependent kinase (CDK) inhibitors $p21^{WAF1}$ and $p27^{KIP1}$ are induced in an IFN/STAT1 dependent manner in different cell types [47–49]. STAT1-dependent up-regulation of $p27^{KIP1}$ was also reported in oncogenic RAS-transformed mouse embryonic fibroblasts (MEFs) in the absence of IFN stimulation [50]. Cell cycle inhibition through downregulation of cyclin A, E and CDK2, 4, without up-regulation of $p21^{WAF1}$ and $p27^{KIP1}$, was observed in melanoma cell lines [51]. STAT1 can also induce cell cylce arrest in response to IFNγ through interaction with cyclins D1, D2, D3 and CDK4 in fibrosarcoma cells. STAT1 mediates proteasomal degradation of cyclin D1 by an unknown mechanism that requires the presence of S727 STAT1. Cell cycle arrest correlated with reduced phosphorylation of retinoblastoma protein (Rb), reduced levels of cyclin E and enhanced expression of $p21^{WAF1}$ and $p27^{KIP1}$ [52]. Reduced cyclin E levels, accompanied by an increase in p53 and enhanced apoptosis, were also found in hepatocellular carcinoma cell lines upon overexpression of STAT1 [27]. Moreover, STAT1 transcriptionally represses *c-myc*, a tran-

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