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Universal and Specific Functions of STAT3 in Solid Tumours

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Abstract

STAT3 is constitutively activated in a high percentage of tumours and tumour-derived cells of both liquid and solid origin, often correlating with aggressive disease and bad prognosis. Persistent STAT3 activity, to which tumours often become addicted, is mostly due to the aberrant activation of pro-oncogenic/pro-inflammatory signals that can trigger its phosphorylation, such as oncogenes, growth factor receptors and cytokines. Among STAT3-mediated functions are increased survival and proliferation, enhanced angiogenesis, motility and invasion, and down-modulation of anti-tumour immune responses. Moreover, STAT3 was recently shown to play unexpected roles in regulating cell metabolism and mitochondrial activity via both transcriptional and non-transcriptional mechanisms. Here, we review the main knowledge about the role of STAT3 in solid tumours, with a particular focus on breast cancer and our recent work with mouse models.

Introduction

Signal Transducers and Activators of Transcription (STAT) factors mediate the signalling downstream of cytokine and growth factor receptors, and often their activity is deregulated in cancer (Turkson and Jove 2000; Siddiquee et al. 2007). Once activated by tyrosine-phosphorylation via receptor-associated JAK kinases,

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STATs form parallel dimers that concentrate into the nucleus regulating the expression of target genes (Schindler et al. 2007). The family member STAT3 can be activated by a wide variety of cytokines and growth factors (e.g. IL-6 family, leptin, IL-12, IL-17, IL-10, Interferons, G-CSF, EGF, PDGF) and by a number of oncogenes such as Src, Abl, Sis, Fps, Ros, Met and ErbB2 (Turkson and Jove 2000). Accordingly, STAT3 is found to be constitutively tyrosine-phosphorylated in a high percentage of tumours and tumour-derived cell lines of both liquid and solid origin, which often become addicted to its activity for continuous survival and growth (Yu et al. 1995; Turkson and Jove 2000; Kortylewski et al. 2005; Siddiquee et al. 2007), and is considered a good target for anti-cancer therapy. Indeed, STAT3 tyrosine phosphorylation and consequent transcriptional activation was shown to be required for cell transformation downstream of several oncogenes, the prototype being v-Src (Yu et al. 1995; Bromberg et al. 1998; Silva 2004). Although a unique core activity determining addiction to STAT3 by a wide spectrum of biologically distinct tumors has still not been identified, STAT3-mediated gene expression signature is mostly consistent with tumour cell survival and proliferation (Pensa 2008; Yu et al. 2009). In addition, STAT3 constitutive activity in tumour cells can down-modulate anti-tumour immune responses (Yu et al. 2009) as well as promote tumour angiogenesis (Niu et al. 2002a). STAT3 can also regulate cell movement, contributing to cytoskeleton reorganization and controlling cell adhesion properties, and is thought to play a role in tumour invasion and metastasis by inducing the expression of matrix metalloproteinases (MMP) and promoting the epithelial to mesenchymal transition (EMT) (Pensa 2008; Yu et al. 2009). Finally, recent work has shown that STAT3 acts as an important regulator of cell metabolism, promoting aerobic glycolysis and downregulating mitochondrial activity via its canonical, nuclear functions (Demaria et al. 2010) while preserving mitochondrial respiratory activity via mitochondrial localization of its serine-phosphorylated form (Gough et al. 2009; Wegrzyn et al. 2009). Both activities contribute to tumor transformation downstream of distinct signals, which promote STAT3 phosphorylation on either tyrosine or serine. The pro-oncogenic role of STAT3 was first directly demonstrated in vitro by the finding that overexpression of the constitutively active mutant form STAT3C can transform fibroblasts and epithelial cells (Bromberg et al. 1999; Dechow et al. 2004) followed by in vivo experiments in transgenic or knock-in mice demonstrating oncogenic potential in the lung, skin and breast (Li et al. 2007; Chan et al. 2008; Barbieri et al. 2010a).

Many aspects of STAT3 biology in tumours have been extensively reviewed. Here, we chose to summarize the main knowledge about the role of STAT3 in solid tumours, with a particular focus on breast cancer and our recent work with mouse models (Barbieri et al. 2010a, b; Demaria et al. 2010).

The solid tumours where STAT3 has been found to be constitutively active, as well as its main functions and target genes are sketched in Table 1 and detailed below.

Table 1 How activated STAT3 affects different aspects of tumorigenesis. The table highlights the experimental findings concerning the role of activated STAT3 in prognosis, proliferation/survival, metastasis/angiogenesis, drug resistance, immune response, cancer stem cells in different solid tumours, indicating in which model system the data were obtained and the STAT3 target genes identified in each system

Tumor	Role in tumorigenesis[a]	Model[b]	Target genes	References
Epidermal non-melanoma tumours	Proliferation/survival	Mouse	Ciclin D1, Bcl-xL, c-Myc	Chan et al. (2004a, b, 2008)
	Metastasis/angiogenesis	Cell, clinic.	bFGF	Jee et al. (2004), Suiqing et al. (2005)
Melanoma	Correlation with prognosis not evaluated (90%)	Clinic.		Niu et al. (2002a)
	Proliferation/survival	Cell	Bcl-xL, Mcl1	Niu et al. (2002a)
	Metastasis/angiogenesis	Cell	MMP2, VEGF, bFGF	Niu et al. (2002a), Xie et al. (2004, 2006)
	Immune response	Cell		Wang et al. (2004)
Head and neck cancer	Poor prognosis/highest expression in early stages (40–80%)	Clinic.		Masuda et al. (2002b), Nagpal et al. (2002)
	Proliferation/survival	Cell	Cyclin D1, Bcl-xL, Bcl2	Masuda et al. (2002a, b, 2007)
	Metastasis/angiogenesis	Cell	VEGF	Masuda et al. (2002a, 2007), Lui et al. (2009)
	Drug resistance	Cell		Masuda et al. (2002c), Gu et al. (2010)
	Immune response	Cell		Albesiano et al. (2010)
	Cancer stem cells	Clinic.		Chen et al. (2008b)
Colorectal carcinoma	Poor prognosis, metastasis (50%)	Clinic.		Kusaba et al. (2005, 2006)
	Proliferation/survival	Cell, clinic.	Bcl-xL, survivin, miR-21, miR-181b1	Turkson et al. (2004), Lassmann et al. (2007), Iliopoulos et al. (2010)
	Metastasis	Cell	MMP1, MMP3	Tsareva et al. (2007)
	Immune response	Cell		Nefedova et al. (2004), Wang et al. (2004)
Hepatocellular carcinoma	Poor prognosis (60–75%)	Clinic.		Feng et al. (2001), Zhang et al. (2010)
	Proliferation/survival	Mouse	Bcl-xL, cyclin D1	Yoshida et al. (2002)
	Metastasis/angiogenesis	Cell	VEGF, MMP2	Li et al. (2006)

(continued)

Table 1 (continued)

Tumor	Role in tumorigenesis[a]	Model[b]	Target genes	References
Pancreatic cancer	Proliferation/survival	Cell		Wei et al. (2003)
	Metastasis/angiogenesis	Cell	VEGF	Wei et al. (2003)
	Immune response	Cell		Bharadwaj et al. (2007)
Gastric carcinoma	Poor prognosis (30%)	Clinic.		Lee et al. (2009)
	Proliferation/survival	Cell, clinic.	Survivin, Bcl2	Kanda et al. (2004), Choi et al. (2006)
	Angiogenesis	Clinic.	VEGF	Choi et al. (2006)
Ovarian cancer	Poor prognosis (90%)	Clinic.		Rosen et al. (2006)
	Proliferation/survival	Cell	Cyclin D1, Bcl-xL	Huang et al. (2000)
	Metastasis/angiogenesis	Cell		Silver et al. (2004), Nilsson et al. (2005)
	Drug resistance	Cell	Bcl-xL	Burke et al. (2001)
Prostate cancer	Highest malignancy (80%)	Clinic.		Mora et al. (2002)
	Proliferation/survival	Cell	Bcl2, cyclin D1, c-Myc, Bcl-xL, Mcl1	Lou et al. (2000), Gao et al. (2001, 2005), Flowers et al. (2005), Hellsten et al. (2008)
	Metastasis/angiogenesis	Cell	HIF1, VEGF, E-cadherin	Xu et al. (2005), Azare et al. (2007), Abdulghani et al. (2008)
	Drug resistance	Cell	Bcl-xL (partially)	Pu et al. (2004)
	Cancer stem cells	Cell		Mathews et al. (2010)
Lung carcinoma	Poor prognosis but not significant (70%)	Clinic.		van Cruijsen et al. (2009)
	Proliferation/survival	Cell	Bcl2, Bcl-xL, Mcl1, survivin, cyclin D1, c-Myc	Weerasinghe et al. (2007)
	Metastasis/angiogenesis	Cell	VEGF	Weerasinghe et al. (2007), Pfeiffer et al. (2009)
	Immune response	Mouse	Ccl5, IL-6, VEGF	Li et al. (2007)
Glioblastoma	Correlation with prognosis not evaluated (95%)	Clinic.		Rahaman et al. (2002)
	Proliferation/survival	Cell, clinic.	Bcl-xL, Mcl1, Bcl2	Rahaman et al. (2002), Sherry et al. (2009)
	Metastasis/angiogenesis	Cell	MMP9; VEGF	Loeffler et al. (2005), Liu et al. (2010)
	Immune response	Cell		Hussain et al. (2007)
	Cancer stem cells	Cell		Sherry et al. (2009), Villalva et al. (2010)

Rabdo-myosarcoma	Proliferation/survival	Mouse, cell	Bcl-xL	Lee et al. (2006), Chen et al. (2007b)
	Immune response	Cell		Nabarro et al. (2005)
Renal carcinoma	Poor prognosis, metastasis (100%)	Clinic.		Horiguchi et al. (2002b)
	Proliferation/survival	Cell	Survivin, Bcl-xL, Bcl2, cyclin E; VEGF	Horiguchi et al. (2002a), Xin et al. (2009)
	Angiogenesis	Cell	VEGF	Jung et al. (2007), Xin et al. (2009)
	Immune response	Cell		Xin et al. (2009)
Cervical cancer	Poor prognosis (60%)	Clinic.		Takemoto et al. (2009)
	Proliferation/survival	Clinic.	Bcl-xL, survivin, Mcl1	Chen et al. (2007a)
	Angiogenesis	Clinic.	VEGF	Wei et al. (2003)
Bladder cancer	Proliferation/survival	Cell	Bcl2, Bcl-xL, survivin, cyclin D1	Chen et al. (2008a)
	Metastasis	Cell	MMP1	Itoh et al. (2006)
Breast cancer	Better prognosis of node-negative breast cancer; metastasis in regional lymph node; poor response to therapy (30–60%)	Clinic.		Dolled-Filhart et al. (2003), Dechow et al. (2004), Hsieh et al. (2005), Diaz et al. (2006)
	Proliferation/survival	Cell	TIMP3	Garcia et al. (2001), Selander et al. (2004)
	Metastasis/angiogenesis	Cell	VEGF	Niu et al. (2002a), Selander et al. (2004)
	Drug resistance	Cell	Bcl2	Real et al. (2002)
	Immune response	Cell	SOCS3	Sun et al. (2006)
	Cancer stem cells	Cell		Zhou et al. (2007)

[a]The percentage refers to the clinical samples where activated STAT3 was detected in the cited reference/s
[b]Model: *mouse* mouse model, *cell* cell lines, *clinic*. clinical samples

Epidermal Non-Melanoma Tumours

STAT3 constitutive activation was observed in several types of human epidermal non melanoma cutaneous tumours, correlating with poor differentiation, tumour invasion and metastasis in clinical samples of cutaneous squamous cell carcinoma (SCC) (Suiqing et al. 2005). STAT3 involvement with metastatic potential was also confirmed in xenograft experiments of basal cell carcinoma cells (BCC) over-expressing IL-6, where IL-6-mediated angiogenesis supported tumour development in part via STAT3 activation (Jee et al. 2004).

The two-stage chemical carcinogenesis model is considered a good model of epithelial carcinogenesis, recapitulating the different phases from tumor initiation to progression (Chan et al. 2004a). The first experimental evidence that STAT3 activation is required for epithelial tumorigenesis in vivo was obtained using this model, where STAT3 ablation in keratinocytes completely abrogated skin tumour development (Chan et al. 2004b). STAT3-deficient keratinocytes were more sensitive to DMBA-induced apoptosis and STAT3 inhibition with an oligonucleotide decoy injected into primary skin papillomas led to significant reduction of tumour volume. STAT3 was also implicated in ultraviolet B (UVB)-induced skin carcinogenesis by the observation that UVB irradiation promoted proliferation and survival of keratinocytes via STAT3 activation (Sano et al. 2005). Conversely, transgenic mice overexpressing the constitutively active form STAT3C in keratinocytes developed skin tumours with a shorter latency and in greater number compared to non-transgenic mice (Kim et al. 2007; Chan et al. 2008). STAT3C acted in both tumour initiation and promotion by upregulating genes involved in survival, proliferation, angiogenesis and metastasis.

One key step in STAT3-mediated epithelial tumorigenesis may be the induction of Bcl-xL, which plays a fundamental role in early skin carcinogenesis by enhancing survival of keratinocyte stem cells in the bulge region of the hair follicle, where mutations are believed to arise during the initiation stage and whose clonal expansion occurs during tumour promotion, as shown by studies in Bcl-xL deficient mice (Kim et al. 2009).

Melanoma

STAT3 is constitutively active in the vast majority of melanoma tumours and cell lines (Niu et al. 2002a), most often downstream of activated c-Src (Kortylewski et al. 2005), where it favours proliferation, escape from apoptosis and angiogenesis via induction of Bcl-xL, Mcl1 and VEGF (Niu et al. 2002a; Xie et al. 2006). STAT3 activation is apparently crucial to promote the metastatic process in melanoma, through direct upregulation of MMP2, VEGF and bFGF expression (Xie et al. 2004, 2006). STAT3 activation was shown to promote an immunosuppressive environment leading to impaired dendritic cell (DC) maturation and tumour-specific T cell response in melanoma B16 cells (Wang et al. 2004). Accordingly WP1066, a STAT3 inhibitor that blocks melanoma cells growth, was found to interfere with melanoma brain metastasis by inhibiting the production of immunosuppressive cytokines such as TGF-b, MCP1, RANTES and VEGF by tumour cells, thus

enhancing cytotoxic T lymphocyte responses and inhibiting T regulatory (Treg) cells differentiation (Kong et al. 2008).

Head and Neck Cancer

STAT3 constitutive activation has been observed in 40–80% of human head and neck squamous cell cancer (HNSCC), correlating with poor prognosis and with proliferation and apoptosis resistance via induction of cyclin D1, Bcl2 and Bcl-xL expression (Masuda et al. 2002b; Nagpal et al. 2002). Apoptosis could be reinstated and tumour growth blocked by inhibiting STAT3 activity (Leong et al. 2003; Jing et al. 2006). Therapeutic blockade of STAT3 activity also resulted in impaired angiogenesis due to direct STAT3-mediated regulation of VEGF expression (Masuda et al. 2007). STAT3 activation occurring upon EBV infection or deregulated EGFR signalling in nasopharingeal cancer promotes anchorage-independent growth and invasion (Lui et al. 2009; Wheeler et al. 2010). High STAT3 phosphorylation levels in cells from HNSCC patients are associated with the expression of CD44 and aldehyde dehydrogenase 1 (ALDH1) stem cell markers and with typical features of Cancer Stem Cells (CSCs) such as high tumorigenicity, radioresistance, expression of the stemness markers Bmi, Oct4 and Nanog and of the EMT genes Snail and Twist (Chen et al. 2008b). STAT3 inhibition in these cells reinstated responsiveness to chemotherapy, favoured differentiation and impaired tumorigenesis and metastasis formation (Chen et al. 2008b). Moreover, anti-tumour immune responses were affected, with enhanced production of proinflammatory cytokines and chemokines which, in turn, triggered DC activation and lymphocytes migration and prompted anti-tumour immune response (Albesiano et al. 2010).

Colorectal Carcinoma

STAT3 constitutive activity was observed in colorectal carcinoma cells in about 50% of clinical samples (Kusaba et al. 2005, 2006), correlating with proliferation and tumour growth rate (Becker et al. 2005; Corvinus et al. 2005), and with tumour invasion, lymph node metastasis and poor prognosis (Kusaba et al. 2005, 2006). STAT3-related enhanced invasiveness correlates with strong expression of the MMP1, -3, -7, and -9. MMP1 and MMP3 are direct STAT3 targets, and activated STAT3 colocalizes with MMP1 in tumour specimens (Tsareva et al. 2007). Importantly, both NF-kB and STAT3 activation have been shown to be crucial for inflammation-driven colon carcinogenesis (Greten et al. 2004; Bollrath et al. 2009; Grivennikov et al. 2009). NF-kB activation in myeloid cells drives IL-6 expression, whose levels are indeed increased in patients serum, and in turn IL-6 is responsible for STAT3 constitutive activation in colon tumour cells, a paradigm that is thought to hold true for several other inflammation-related tumours (Grivennikov and Karin 2010).

Mice lacking STAT3 in intestinal epithelial cells (IECs) showed an almost complete protection from the development of the AOM/DSS model of colitis-associated

cancer (CAC), correlating with decreased epithelial proliferation and enhanced sensitivity to treatment-induced apoptosis (Bollrath et al. 2009; Grivennikov et al. 2009). However, the role of STAT3 in colon tumorigenesis appears to be context-dependent, as we have recently shown in Apc^{Min} mice that this factor promotes early tumorigenesis steps but impairs tumour progression at later stages, via regulation of the adhesion molecule CEACAM1 (Musteanu et al. 2010).

STAT3-mediated immune suppression was shown to play an important role in colon cancer cells (Nefedova et al. 2004; Wang et al. 2004), where tumour-derived factors, inducing STAT3 activation in infiltrating immature myeloid cells, prevented their differentiation into mature dendritic cells (Nefedova et al. 2004).

Other Tumours of the Gastrointestinal Tract

STAT3 constitutive activation plays a role in several other tumours that develop in the gastrointestinal tract. In hepatocellular carcinoma (HCC) its activity is often induced by HCV infection or IL-6 and other inflammatory cytokines and drives tumorigenesis by promoting proliferation, survival (via Bcl-xL and cyclin D1 induction) and anchorage-independent growth (Yoshida et al. 2002; He et al. 2010). STAT3 inhibition in HCC cells impaired growth, angiogenesis and metastasis while enhancing apoptosis and sensitivity to chemotherapy (Li et al. 2006; Choudhari et al. 2007; Sun et al. 2008).

Constitutively activated STAT3 is widely observed also in pancreatic cancer, often downstream of IL-6 or G-CSF, promoting tumour cell growth, metastasis and angiogenesis (Wei et al. 2003) and impairing dendritic cells differentiation and activation (Bharadwaj et al. 2007).

STAT3 phosphorylation is relatively infrequent in gastric carcinoma, but when present it correlates with tumour cell proliferation, survival and angiogenesis via induction of Bcl2, VEGF and survivin expression (Kanda et al. 2004; Choi et al. 2006). The analysis of human gastric cancer specimens identified correlations between STAT3 activation and lymph node metastasis (Deng et al. 2010). Moreover, STAT3 uncontrolled activity can lead to gastric cancer, as shown by the spontaneous development of gastric carcinomas following disruption of the integrity of mucosal epithelium in gp130 knock-in mutant mice ($gp130^{757F}$) that are unable to respond to SOCS3-mediated negative feedback (Tebbutt et al. 2002).

Ovarian Cancer

Constitutive activation of STAT3 was detected in a high percentage of ovarian cancer cell lines and human tumour specimens (94%) with respect to normal ovary epithelium, correlating with aggressive clinical behavior and tumour progression, and it was shown to enhance proliferation and inhibition of apoptosis through induction of cyclin D1 and Bcl-xL expression, respectively (Huang et al. 2000; Rosen et al. 2006). Moreover, studies in cell lines have shown that enhanced

STAT3 activity and expression contribute to resistance to apoptosis in response to chemotherapeutic drugs (Burke et al. 2001; Duan et al. 2006). STAT3 inhibition leads to decreased Bcl-xL expression, sensitizing tumour cells to chemotherapy-induced apoptosis (Burke et al. 2001). One of the main signals responsible for STAT3 constitutive activation in ovarian cancer is its canonical activator IL-6, which promotes angiogenesis, leading to tumour proliferation and dissemination of malignant cells (Nilsson et al. 2005).

Prostate Cancer

Phosphorylated STAT3 was detected in the majority of human prostate cancers, correlating with the degree of malignancy (Mora et al. 2002) and with JAK2/IL-6 signalling, which enhances proliferation and survival (Lou et al. 2000; Flowers et al. 2005). STAT3 inhibition lead to apoptosis of tumour cell lines, both in vitro and in vivo, through downregulation of Bcl2, cyclin D1, c-Myc, Bcl-xL and Mcl1 expression (Lou et al. 2000; Jing et al. 2004; Turkson et al. 2004; Gao et al. 2005; Hellsten et al. 2008), and inhibited angiogenesis and tumour growth via downregulation of both HIF1a and VEGF expression (Xu et al. 2005). The expression of the constitutively active form STAT3C in immortalized prostate epithelial cells caused tumour transformation and enhanced cell motility by decreasing E-cadherin level and increasing the number of lamellipodia and stress fibers (Azare et al. 2007), suggesting a role in EMT and metastasis that was subsequently confirmed by the observation of constitutive STAT3 activation in clinical samples of prostate cancer metastasis, where it promoted cell motility by reorganizing the actin and microtubule network (Abdulghani et al. 2008). IL-6 dependent STAT3 activation was shown to contribute to resistance of human prostate cancer cells to chemotherapy (Pu et al. 2004). There appear to be correlations between STAT3 activation, tumour invasion and CSCs. In particular, invasive prostate cancer cells were shown to display promoter methylation patterns reminiscent of those observed in CSCs, with many differentially methylated genes belonging to the IL-6/STAT3 pathway (Mathews et al. 2010). Additionally, STAT3 was shown to interact with the CSC marker SOX1, whose silencing decreased STAT3 activation and in vitro invasiveness (Mathews et al. 2010). Accordingly, IL-6 was recently shown to induce the conversion of prostate non stem cancer cells (NSCCs) into sphere-forming CSCs, similar to what observed in breast cancer cells (Iliopoulos et al. 2011a).

Lung Carcinoma

About 50–70% of human non-small cell lung carcinomas (NSCLC) and cell lines were shown to display constitutive STAT3 activation, correlating with enhanced proliferation and survival (Song et al. 2003; Haura et al. 2005; van Cruijsen et al. 2009). STAT3 inhibition in these cells lead to decreased expression of a number of

known STAT3 targets (e.g. Bcl2, Bcl-xL, Mcl1, survivin, VEGF, cyclin D1 and c-Myc), thereby promoting apoptosis, impairing proliferation and reducing angiogenesis (Weerasinghe et al. 2007). Interestingly, mutant EGFR forms in primary human lung adenocarcinomas lead to STAT3 activation via IL-6 upregulation (Gao et al. 2007). In contrast with these data, Pfeiffer and colleagues demonstrated that STAT3 constitutive activation is characteristic of primary tumour samples from patients with small cell lung cancer (SCLC) but not from NSCLC, and that blocking STAT3 activation impaired anchorage-independent tumour cell growth, suggesting the implication of STAT3 in the rapid metastasizing phenotype of SCLC (Pfeiffer et al. 2009).

The lung was the first tissue where over-expressed constitutively active STAT3 was shown to play an autonomous pro-oncogenic role, since transgenic expression of the STAT3C mutant form in alveolar type II epithelial cells induced lung bronchoalveolar adenocarcinomas preceded by remarkable infiltration of inflammatory cells (Li et al. 2007). Tumour development correlated with enhanced secretion of pro-inflammatory molecules and with reactivation of genes critical for epithelial cell growth during embryonic lung development, similar to what observed in human bronchoalveolar adenocarcinomas (Li et al. 2007). Accordingly, STAT3 downstream genes were proposed to serve as biomarkers in human lung adenocarcinoma and chronic obstructive pulmonary disease, which are both induced by chronic inflammation of the lung (Qu et al. 2009).

Glioblastoma

High levels of STAT3 activation are also detected in about 95% of glioblastoma cell lines and tumour samples, inducing proliferation and apoptosis resistance through upregulation of Bcl-xL, Mcl1 and Bcl2 expression (Rahaman et al. 2002), and promoting angiogenesis, invasion and metastasis via upregulation of VEGF and MMP9 expression (Loeffler et al. 2005; Liu et al. 2010). Hypoxia resistance is a common feature of both stem cells and CSCs, which are thought to act as tumour initiating cells (TICs) in different types of tumours, including glioblastoma (Hemmati et al. 2003; Zhou and Zhang 2008). Resistance of these cells to chemotherapy is often responsible for relapses and/or metastasis (Villalva et al. 2010). The highly hypoxic glioblastoma microenvironment triggers STAT3-mediated induction of VEGF, HIF1, MMP2 and Twist1, which in turn promote angiogenesis and tumour invasion (Kang et al. 2010). Interestingly, STAT3 activation was shown to be essential for glioblastoma stem cells proliferation and ability to form neurospheres, and inhibition of its activity triggered the downregulation of genes associated with the stem cell phenotype (Sherry et al. 2009) and sensitization to chemotherapeutic treatment, suggesting that combined chemotherapy and STAT3 inhibition may allow more efficient killing of CSCs. STAT3 activation in glioblastoma is often supported by the constitutive expression of IL-6 in tumour cells, and indeed $IL6^{-/-}$ mice were protected from glioblastoma development (Brantley and Benveniste 2008). Abnormal activation of the FGFR and EGFR

pathways also correlated with STAT3 phosphorylation (Brantley and Benveniste 2008). Interestingly, however, while STAT3 could cooperate with the oncogenic mutant form EGFRvIII to mediate cell transformation, it accelerated disease progression in glioblastomas induced by PTEN-loss. Thus, depending on the genetic background, STAT3 activity in glioblastoma can be either tumour-suppressive or tumour-promoting (de la Iglesia et al. 2008).

Other Solid Tumours

A low percentage of rhabdomyosarcomas showed STAT3 activation that is linked to enhanced proliferation and resistance to apoptosis (Chen et al. 2007b) and correlating with the overexpression of the stem cell marker Piwil2, recently found associated to different tumours. Piwil2 can activate STAT3, which in turn enhances tumour cell survival through Bcl-xL induction (Lee et al. 2006). Moreover, STAT3 can interact with PAX3-FKHR, an oncogenic fusion protein specifically associated with an aggressive rhabdomyosarcoma metastatic subtype. This association leads to a reduction in tumour MHC expression and to an altered cytokine microenvironment that inhibits inflammatory cells action and hampers immune detection of tumour (Nabarro et al. 2005).

STAT3 activation was observed in 100% of renal carcinomas, correlating with poor prognosis and metastatic disease and promoting proliferation and survival (Horiguchi et al. 2002a, b). Pharmacological inhibition of STAT3 not only favoured the apoptotic action of chemotherapeutic agents on tumour cells, but also downmodulated their angiogenic and metastatic potential while improving antitumour immune response by reducing myeloid suppressor and Tregs cells (Xin et al. 2009).

About 60% of cervical cancers display STAT3 phosphorylation, correlating with poor prognosis (Takemoto et al. 2009) and linked to increased proliferation and apoptosis resistance via induced expression of Bcl2, survivin, Mcl1 (Chen et al. 2007a) and enhanced angiogenesis mediated by VEGF (Wei et al. 2003).

Finally STAT3 activation in bladder cancer cells, although limited, was implicated in tumour cells proliferation and invasion (Itoh et al. 2006; Chen et al. 2008a).

Breast Cancer

Persistently phosphorylated STAT3 is detected in 30–60% of primary breast carcinomas (Garcia et al. 2001) correlating with poor response to therapy (Diaz et al. 2006) and with regional lymph node metastasis (Hsieh et al. 2005), although a correlation with a good prognosis of node-negative cancers was suggested (Dolled-Filhart et al. 2003). High STAT3 phosphorylation levels are detected in several human breast cancer cell lines, where its inactivation leads to growth arrest and cell death (Garcia et al. 1997, 2001). Similar to most other solid tumours, STAT3

activity in breast cancer has been linked to enhanced proliferation and survival, to resistance to apoptosis and to cell movement, invasion and metastasis.

Pathways Leading to Persistent STAT3 Activation in Breast Cancer

Despite the wide range of tumours where STAT3 is constitutively active, so far no activating genetic mutations have been described, suggesting that abnormal STAT3 activity in neoplastic cells must be triggered by deregulated upstream signalling. In breast cancer, STAT3 activation shows positive correlation with EGF and ErbB2 receptors overexpression and with Src activation (Berclaz et al. 2001; Diaz et al. 2006; Leslie et al. 2006), all of which have been shown to lead to STAT3 phosphorylation, albeit not directly (Berishaj et al. 2007). V-Src was the first oncogene whose transforming activities were shown to require STAT3 (Bromberg et al. 1998). Additionally, STAT3 was reported to be a substrate of the breast tumour kinase (Brk), distantly related to the Src family (Liu et al. 2006).

An impressive body of data points towards IL-6 as the main trigger for STAT3 aberrant activation in solid tumours, which at hindsight is perhaps not surprising since IL-6 and its family of related cytokines are among the most prominent inducers of STAT3 activity. In breast cancer patients, serum IL-6 levels are elevated (Jiang et al. 2000; Kozłowski et al. 2003), and correlate with advanced tumour stage (Kozłowski et al. 2003), increased number of metastatic sites (Salgado et al. 2003) and overall poor prognosis (Zhang and Adachi 1999) (Bachelot et al. 2003; Salgado et al. 2003). High local IL-6 production is also detected, correlating with tumour grade (Chavey et al. 2007). Indeed, inflammation-induced IL-6 produced either systemically or locally by tumour infiltrating inflammatory cells is believed to start a positive loop by activating STAT3 in cancer cells (Grivennikov and Karin 2010). This in turn induces the secretion of soluble factors promoting STAT3 activation and anergy in the antigen presenting cells, finally leading to enhanced tumour cell survival and growth both via cell autonomous and immune-mediated mechanisms (Yu et al. 2009). An oncogene-driven inflammatory loop was also implicated in the initial stages of tumour transformation. Indeed, transient Src activation generates an inflammatory signal which triggers an epigenetic switch to cancer cells via a positive feedback loop involving NF-kB, Lin28, let-7 and IL-6 (Iliopoulos et al. 2009). IL-6-activated STAT3 is essential for this switch via direct induction of miR-21 and miR-181b-1, which target the PTEN and CYLD tumour suppressor genes, respectively. Their downregulation in turn leads to NF-kB activation, required to maintain the transformed state (Iliopoulos et al. 2010). The importance of this circuit was first demonstrated in transformation of mammary epithelial cells and subsequently confirmed in prostate, colon, lung and hepatocellular carcinoma cells.

IL-6-induced STAT3 activation is normally transient, due to tight negative feedback control such as that mediated by SOCS3 (Yoshimura 2005). What are the mechanisms helping to maintain persistent STAT3 phosphorylation in tumours?

Loss of negative feedback via silencing of SOCS factors has been shown to occur in several systems (Baltayiannis et al. 2008). Recently, it was shown that the low but constitutive activation of STAT3 in different tumours, including the breast, is at least partly mediated by the elevated expression of S1PR1, the receptor for the lysophospholipid sphingosine-1-phospate. S1PR1 is a STAT3 transcriptional target which in turn upregulates IL-6 expression and enhances STAT3 activation, establishing a positive feedback loop resulting in STAT3 persistent activation in both the tumour cells and the tumour microenvironment, accelerated tumour growth and malignant progression (Lee et al. 2010).

Other cytokines belonging to the IL-6 family, such as LIF (Quaglino et al. 2007) and leptin (Park et al. 2010), are also elevated in breast tumours, driving STAT3 activation. In particular, adipocyte-derived leptin is present at high concentrations within the mammary gland of obese individuals, is considered as a risk factor in several types of cancers and is proposed to correlate with breast cancer progression (Garofalo et al. 2004). Estrogen receptor alpha was shown to enhance leptin-mediated STAT3 activation (Binai et al. 2010), and inactivation of the peripheral leptin receptor attenuates tumour progression and metastasis in an MMTV-PyMT model of breast cancer, via inactivation of the ERK1/2 and Jak2/STAT3 pathways (Park et al. 2010).

STAT3-Mediated Features: Proliferation and Survival

Most cell lines displaying persistent STAT3 phosphorylation are addicted to its activity for proliferation and survival, both in vitro and in vivo (Garcia et al. 2001; Hsieh et al. 2005; Diaz et al. 2006), at least partly correlating with the induction of the anti-apoptotic genes survivin/BIRC5 and Bcl-xL and of cyclin D1 (Siddiquee et al. 2007). Indeed, high levels of activated STAT3 correlate positively with elevated cyclin D1 mRNA and protein expression in breast tumours and cell lines (Leslie et al. 2006) and STAT3 can directly bind to the promoter of the human cyclin D1 gene (Leslie et al. 2006; Saxena et al. 2007). Moreover, cyclin D1 appears to be required for mouse fibroblasts anchorage-independent growth downstream of constitutively active STAT3C or v-Src (Leslie et al. 2006). Interestingly, the progesteron receptor was shown to act as STAT3 coactivator by inducing ErbB2 nuclear translocation and the assembly of a transcriptional complex on the cyclin D1 promoter (Béguelin et al. 2010).

Immunohistochemical analyses of invasive breast carcinomas also showed a positive correlation between activated Src, phosphorylated STAT3 and the expression of survivin, a member of the inhibitor of apoptosis protein family (Diaz et al. 2006). Like cyclin D1, also survivin is a direct STAT3 transcriptional target, and STAT3 silencing leads to survivin downregulation and apoptotic death in a human breast cancer cell line (Gritsko et al. 2006). In addition to downregulating survivin and Bcl-xL expression, STAT3 silencing in human breast cancer cells was recently shown to lead to Fas-mediated intrinsic apoptotic pathway via the activation of caspases-8, -9, -3 and PARP1 cleavage (Kunigal et al. 2009).

The pro-survival role of STAT3 might be exploited for therapeutic purposes in combined treatments. For example, the inhibition of STAT3 in metastatic breast cancer cells enhanced the proapoptotic effects of doxorubicin, at least in part interfering with survivin and Bcl-xL expression (Gariboldi et al. 2007). Recently, ErbB2-activated STAT3 was shown to directly upregulate the p21(Cip1) gene in breast cancer cells, resulting in increased Taxol resistance and suggesting that Src and STAT3 inhibitors may be used in Taxol sensitization of ErbB2-overexpressing breast cancers (Hawthorne et al. 2009).

STAT3-Mediated Features: Migration, Invasion and Metastasis

Activated STAT3 levels have been reported to correlate with invasiveness and metastasis in breast cancer (Hsieh et al. 2005), and indeed a leading role for STAT3 in driving migration, invasion and metastatic disease of breast cancer cells has emerged in the past years, and thoroughly explored in mouse models of ErbB2-driven tumorigenesis genetically modified for STAT3 (see next section). Both transcriptional and non-transcriptional mechanisms have been proposed to drive STAT3-induced migration.

Intriguingly, activated STAT3 was shown for the first time in ovarian cancer cells to localize not only to the nucleus but also to the focal adhesions, interacting with activated paxillin and focal adhesion kinase, implying local regulation of focal adhesions and integrin-mediated cell movement (Silver et al. 2004). We also have observed STAT3 localization to focal adhesions in mouse breast cancer cell lines derived from MMTV-Her2 transgenic tumours, which was enhanced in cells derived from mice expressing constitutively active STAT3C and displaying more aggressive and invasive tumour phenotype (Barbieri et al. 2010a). Cytoplasmic, non-phosphorylated STAT3 was reported to induce cell migration by interacting with, and inhibiting, the microtubules destabilizer stathmin, thus enhancing microtubules polymerization in murine embryonic fibroblasts (Ng et al. 2006). Conversely, several microtubule-based drugs were shown to modulate STAT3 activity by reducing its phosphorylation in breast tumour cell lines, possibly explaining part of their therapeutic mechanism (Walker et al. 2010).

STAT3-mediated invasion has been linked to the ability to directly upregulate the transcription of MMP9, whose expression levels correlated with those of phosphorylated STAT3 in primary breast cancers. MMP9 was required for mammary epithelial cells transformation mediated by constitutively active STAT3 (Dechow et al. 2004), and its downregulation by the trimeric resveratrol derivative LYR71 correlates with suppression of STAT3 activation, tumour migration and invasion in mouse breast cancer cells (Kim et al. 2008). Additionally, upregulation of the Fra-1 oncogene in response to tumour associated macrophages lead to a malignant switch in breast tumour cells, via activation of the IL-6/JAK/STAT3 loop and increased release of MMP9, VEGF and TGF-b (Luo et al. 2010). Interestingly, STAT3 apparently regulates different subsets of MMPs in different kinds of cancer

including MMP2 in melanoma (Xie et al. 2004), MMP1 in the bladder (Itoh et al. 2006) and MMP1, -3, -7, and -9 in the colon (Tsareva et al. 2007).

STAT3-driven metastasis formation was also linked to its ability to induce anchorage-independent growth, EMT and angiogenesis. Impaired in vivo metastasis due to reduced angiogenesis was reported to occur as a consequence of inhibiting STAT3 activation by expressing a dominant negative form of gp130 in a human breast cancer cell line (Selander et al. 2004), correlating with increased expression of the tissue inhibitor of metallo-proteinase 3 (TIMP-3). On the other hand, VEGF is a direct STAT3 transcriptional target, and its upregulated production by STAT3 is believed to induce angiogenesis in different cancer types including the breast (Niu et al. 2002b).

Metastatic breast cancer cells display increased expression of the EMT transcription factor Twist1, which is required for EMT and breast cancer metastasis. A strong positive correlation between active STAT3 and Twist1 levels was detected in late stage breast cancer tissues and in subpopulations of human breast cancer cell lines displaying enhanced invasiveness (Lo et al. 2007; Cheng et al. 2008c). In these cells, STAT3 inhibition lead to Twist1 downregulation correlating with impaired migration, invasion and colony formation, all of which could be rescued by Twist1 re-expression. Interestingly, it was recently shown that IL-6, the canonical STAT3 activator, induces EMT in the ERα-positive human breast cancer cell line MCF-7, including impaired E-cadherin expression and induction of vimentin, N-cadherin, Snail and Twist1. Conversely, constitutive expression of Twist1 triggered aberrant IL-6 production and STAT3 activation, suggesting a positive loop promoting autocrine IL-6 production (Sullivan et al. 2009). Finally, STAT3 was required for EGF-induced Twist1 upregulation in human breast carcinoma cells by directly binding to its promoter (Lo et al. 2007). Correlations between STAT3 and Twist1 were observed also in mouse cells. The silencing of STAT3 in the metastatic mouse breast cancer 4T1 cell line is sufficient to impair tumour formation in vivo and invasion ability in vitro, correlating with reduction of c-Myc, activated Src and Twist1 (Ling and Arlinghaus 2005). However, no putative STAT3 binding site was detected in the murine Twist1 promoter, suggesting different modes of STAT3-dependent activation in the human and the mouse (Lo et al. 2007).

Finally, IL-6 paracrine/autocrine production and STAT3 activation were recently shown to take part in the cross-talk between cancer cells and tumour microenvironment to regulate motility, aggressiveness, angiogenesis and metastasis. Mesenchymal stem cells (MSCs), which reside in the bone marrow, are likely to come in contact with extravasated, metastasis-initiating breast cancer cells. These cells were shown to enhance tumour aggressivity and growth rates in ER-alpha-negative breast cancer cell lines via IL-6 secretion and STAT3 activation (Sasser et al. 2007). MSCs have also been shown to selectively migrate to hypoxic breast tumours, where they are thought to play a tumour-promoting role. Tumour-produced IL-6 acts as an attractant for MSCs, leading to their cytoskeletal reorganization via STAT3 activation (Rattigan et al. 2010). Once within strict contact, a positive loop is likely to get started, whereby infiltrating MSCs in turn produce IL-6 and enhance STAT3 activation in the cancer cells. Due to their specific ability to

migrate to and engraft into primary breast tumours, genetically modified MSCs over-expressing Interferon-b (IFN-b) have been explored as potential therapeutic means. IFN-b producing MSCs suppressed breast cancer cells growth and pulmonary and hepatic metastases mainly via inhibition of STAT3 signalling (Ling et al. 2010).

Growth and spread of cancer is thought to be mainly driven by a small subpopulation of CSCs, the only cells capable of long-term self renewal and of generating phenotypically diverse tumour cell populations. These slowly-replicating, self-maintaining cells are resistant to most chemotherapeutics, thus driving relapse. STAT3 is prominently involved in maintaining the undifferentiated status of mouse embryonic stem cells (Burdon et al. 2002), and was shown to be critical for the viability and maintenance of the stem-like side population in the MCF-7 breast cancer cell line (Zhou et al. 2007). Additionally, experimental evidence implied IL-6 signalling in driving formation and malignancy of breast cancer stem cells. Sansone and co-authors reported that mammospheres from node invasive basal-like breast carcinoma tissues, an aggressive breast carcinoma variant showing stem cell features, produce high levels of IL-6, and that autocrine IL-6 signalling sustain the aggressive features of hypoxia-selected MCF-7 cells (Sansone et al. 2007). Recently, IL-6 was shown to drive the conversion of nonstem cancer cells in CSCs in human breast tumours and cell lines (Iliopoulos et al. 2011a). The intimate relationship of STAT3 with the IL-6 pathway leads to postulate its involvement in these systems, even though its activation was not specifically explored.

Role of STAT3 in ErbB2-Driven Mammary Tumorigenesis: Lessons from Mouse Models

Overexpression of the rat oncogenic form of the human EGF receptor ErbB2 (Neu) in the mammary gland under the MMTV promoter triggers the onset of invasive multifocal breast carcinomas at high multiplicity and is widely used as a model for human breast cancer (Guy et al. 1996). The role of STAT3 in Neu-mediated tumorigenesis has been studied by several groups including ours, suggesting a pivotal role of STAT3 in driving tumour progression and metastasis that is in agreement with the clinical and experimental observations reported above. All studies suggest that, although not required for Neu-driven breast tumours onset and growth, STAT3 is heavily implicated in the formation of lung metastasis by a variety of mechanisms. Analyzing the role of b4 integrin in ErbB2 signalling by deleting the b4 signalling domain in the context of MMTV-Neu transgenic mice, Guo and colleagues have shown that b4 integrin forms a complex with ErbB2, enhancing the activation of the transcription factors STAT3 and c-Jun. While c-Jun is required for hyperproliferation, STAT3 contributes to disruption of epithelial adhesion and polarity, and is required for cell invasion and experimental metastasis (Guo et al. 2006). In agreement with this finding, Cre-mediated STAT3 loss of function in MMTV-Neu transgenic mice has shown that STAT3 is

not required for the onset and growth of breast tumours, but its deletion results in a dramatic reduction of lung metastasis by both primary and xenografted tumours (Ranger et al. 2009; Barbieri et al. 2010b). The reduced malignancy of STAT3-deficient tumours was partly due to an inhibition of both inflammatory and angiogenic responses, normally activated in a STAT3-dependent transcriptional cascade involving C/EBPδ (Ranger et al. 2009). Additionally, STAT3 is required in a cell autonomous fashion to warrant anchorage-independent growth and the ability to produce lung metastasis in immuno-depressed mice (Barbieri et al. 2010b).

In an effort to reproduce the relatively low but persistent activation of STAT3 observed in most tumours, we have generated knock-in mice expressing at physiological levels the constitutively active mutant form STAT3C. In agreement with the results obtained with the loss of function mutants, MMTV-Neu transgenic mice carrying the STAT3C allele developed earlier onset, more aggressive tumours with lower levels of spontaneous apoptosis but similar proliferation rates (Barbieri et al. 2010a). Tumour-derived STAT3C/Neu cell lines displayed enhanced migration and invasion in vitro and increased tumorigenic and metastatic potential in vivo, correlating with a profoundly modified organization of cell-cell contacts showing altered, irregular distribution of both adherent and tight junctions components such as E-cadherin, b-catenin and Zo-1. Cytoskeletal organization was also perturbed, with actin redistributing from a cortical localization typical of well differentiated epithelial cells to form abundant actin stress fibres, typical of highly migratory cells (Pellegrin and Mellor 2007). Several genes consistently expressed at higher levels in all three STAT3C/Neu cell lines are known players in regulating cell migration and/or tumour metastasis, including the STAT3 transcriptional target Twist1, involved in tumour invasiveness and EMT (Lo et al. 2007; Cheng et al. 2008c).

In addition, we identified the atypical tensin family member Cten as a novel STAT3 target. Cten was recently shown to mediate EGF-induced migration (Katz et al. 2007), to promote colon cancer tumorigenicity and cell motility (Albasri et al. 2009; Liao et al. 2009), and to correlate positively with tumour stage in thymomas, lung tumours and gastric tumours (Sasaki et al. 2003a, b; Sakashita et al. 2008), all displaying constitutive STAT3 activity. It is the most consistently upregulated gene in both STAT3C-expressing cell lines and tumours, and is involved in both their increased migration and disruption of cell junctions organization (Fig. 1, adapted from Barbieri et al. [2010a]). Moreover, we could show that Cten is induced by IL-6 in MCF10 mammary epithelial cells. IL-6-mediated induction is STAT3-dependent, suggesting that indeed Cten may represent an important functional mediator in the inflammation-STAT3-migration-metastasis loop. Indeed, CTEN expression is particularly elevated in the extremely aggressive and invasive inflammatory breast cancers, correlating with high EGFR and HER2 levels, loss of oestrogen receptor, high tumour grade and node metastasis (Katz et al. 2007). Thus, CTEN may represent an important point of functional convergence between inflammation-driven STAT3 activity, altered EGFR/ErbB2-mediated signalling and invasion of the surrounding tissues.

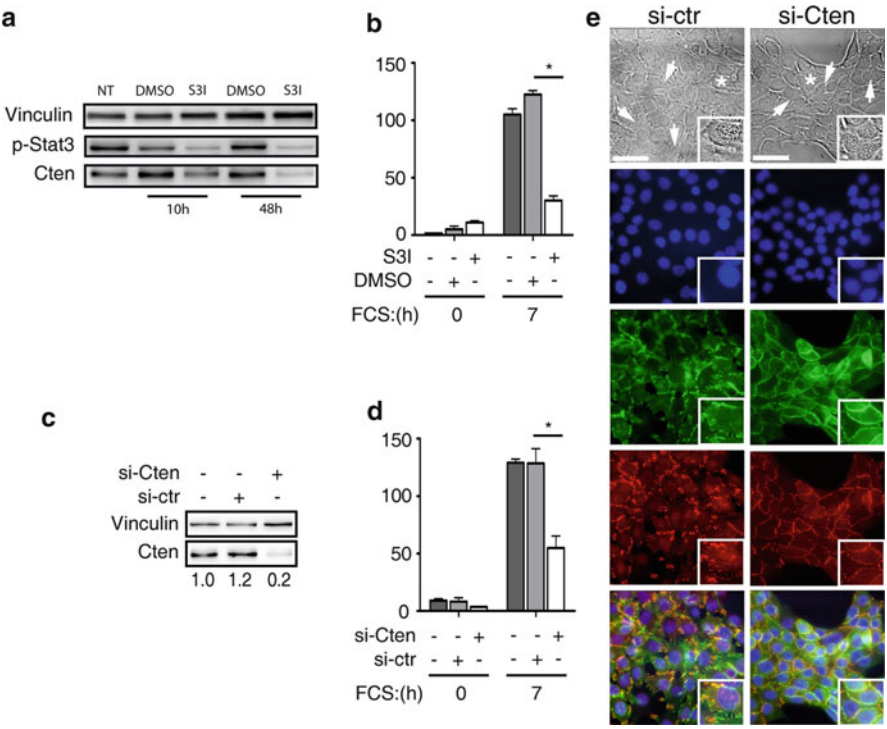

Fig. 1 Both Stat3 inhibition and Cten silencing partially revert the aggressive phenotype of Stat3C expressing cells. Adapted from REF. STAT3C/Neu cells were either treated with the S3I inhibitor for the indicated lengths of time (**a**, **b**) or transfected with an siRNA against Cten (**c**–**e**). S3I treatment downregulates STAT3 phosphorylation (p-Stat3) and Cten expression, as shown by Western blot (**a**). Both treatments significantly impaired FCS-stimulated Transwell migration (**b**, **d**). Values are shown as mean numbers ± SEM of migrated cells per microscopic field (20×) of triplicates in one representative experiment out of two independently performed ($p < 0.05$). (**e**) phase contrast and immunofluorescence images of Cten-silenced cells. *Arrows* indicate evident discontinuous (si-ctrl) versus tight (si-Cten) cell-cell contacts. *Blue*, nuclei; *green*, β-catenin; *red*, Zo-1. The insects (4× magnification) correspond to the areas indicated by an *asterisk*. Scale bar, 20 μm

Concluding Remarks

STAT3 has come a long way since its discovery in the 90s as STAT1's little brother. Initially thought to be almost an IL-6-family-dedicated factor, it has soon emerged as one of the most pleiotropic STATs from many points of view, all contributing to its widespread role in tumours. First, its ever-growing number of upstream activating pathways including many that are aberrantly active in tumours, as initially hinted by the lethal phenotype of STAT3 null embryos. Second, the tissue-dependent variety of target genes, reflected in its variegated functions. Third, its novel non-canonical roles, which apparently do not involve its transcriptional activities. Importantly, its improperly prolonged activity is pro-oncogenic both in

tumour and stromal cells, and indeed STAT3 is emerging as a key factor in mediating the cross talk between microenvironment and tumour cells and a main player in inflammation-driven tumorigenesis. Despite the intense research for STAT3 inhibitors, transcription factors are certainly not easily druggable targets. The understanding of STAT3 biology therefore, including which upstream events drive its activation and which are its main effectors in specific tumours, is still highly relevant on the agenda.

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