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STAT3beta, a distinct isoform from STAT3

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ABSTRACT

STAT3β is an isoform of STAT3 (signal transducer and activator of transcription 3) that differs from the STAT3α isoform by the replacement of the C-terminal 55 amino acid residues with 7 specific residues. The constitutive activation of STAT3α plays a pivotal role in the activation of oncogenic pathways, such as cell proliferation, maturation and survival, while STAT3β is often referred to as a dominant-negative regulator of cancer. STAT3β reveals a "spongy cushion" effect through its cooperation with STAT3α or forms a ternary complex with other co-activators. Especially in tumour cells, relatively high levels of STAT3β lead to some favourable changes. However, there are still many mechanisms that have not been clearly explained in contrast to STAT3α, such as STAT3β nuclear retention, more stable heterodimers and the prolonged Y705 phosphorylation. In addition to its transcriptional activities, STAT3β may also function in the cytosol with respect to the mitochondria, cytoskeleton rearrangements and metastasis of cancer cells. In this review, we summarize the mechanisms that underlie the unique roles of STAT3β combined with total STAT3 to enlighten and draw the attention of researchers studying STAT3 and discuss some interesting questions that warrant answers.

1. Introduction

STAT3 (signal transducer and activator of transcription 3) is one of seven STAT proteins (STATs 1, 2, 3, 4, 5A, 5B and 6) and is a highly pleiotropic protein that is activated downstream of multiple cytokine and growth factor receptors by tyrosine 705 phosphorylation (Akira et al., 1994; Lutticken et al., 1994; Zhong et al., 1994; Copeland et al., 1995) (Fig. 1). STAT1, STAT3 and STAT5 encode multiple forms and are structurally similar. However, these proteins have divergent and opposing effects on gene expression and cellular phenotypes (STAT1 is generally considered as a tumor suppressor (Zhang and Liu, 2017), and STAT3 and STAT5 are generally oncogenes (Desrivieres et al., 2006;

Abbreviations: STAT3, signal transducer and activator of transcription 3; TAD, transactivation domain; APFR, acute phase response factor; IL, interleukin; EGF, epidermal growth factor; PDGF, platelet derived growth factor; TNF, tumour necrosis factor; JAK, Janus kinase; SH2, Src homology 2; Y705, tyrosine 705; GAS, γ-activated sequence; pSTAT3α^{Y705}, phosphorylated STAT3α^{Y705}; ESCC, oesophageal squamous-cell carcinoma; pSTAT3, phosphorylated STAT3; HNSCC, head and neck squamous cell carcinoma; IFNs, interferons; G-CSF, granulocyte colony-stimulating factor; HGF, hepatocyte growth factor; LIF, leukaemia inhibitory factor; Src, protein tyrosine kinase; gp130, glycoprotein 130; S727, serine 727; p300, E1A-binding protein; CBP, cyclic adenosine monophosphate responsive element binding protein-binding protein; Bcl-2, B cell lymphoma-2; Loxl3, lysyl oxidase like 3; c-Myc, termed MYC henceforth; PLK-1, polo-like kinase 1; Pim, proviral integration site for Moloney murine leukaemia virus; FAS, tumour necrosis factor receptor superfamily member 6; VEGF, vascular endothelial growth factor; HIF1α, hypoxia inducible factor-1 alpha; bFGF, basic fibroblast growth factor; EMT, epithelial to mesenchymal transition; Twist-1, the basic helix-loop-helix transcription factor 1; ZEB-1, zinc finger E-box binding homeobox 1; MMPs, matrix metalloproteinases; LPS, lipopolysaccharide; SOCS, suppressor of cytokine signalling; PTPs, protein-tyrosine phosphatases; unph-STAT3, unphosphorylated STAT3; NFκB, nuclear factor kappa light chain enhancer of activated B cells; RANTES, normal T cell expressed and secreted; MET, mesenchymal-epithelial transition factor; MRAS, mineralocorticoid receptor antagonists; DNMT1, DNA methyltransferase1; HDAC1, histone deacetylase 1; SHP-1, Src homology 2 domain-containing protein tyrosine phosphatase 1; TP53, tumour protein 53; CDKN2A, cyclin-dependent kinase inhibitor 2 A; ETC, electron transport chain; ATP, active adenosine triphosphate; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; Cten, COOH terminal tensin-like; FAK, focal adhesion kinase; Crip, cysteine-rich intestinal protein; Tfpi, tissue factor pathway inhibitor; Ptn, pleiotrophin; scya2, small inducible cytokine A2; Sdf1, stromal cell-derived factor 1; Igfbp5, insulin-like growth factor binding protein 5; WTs, wild-types; TC45, the nuclear form of TC-PTP; MHC, major histocompatibility complex; 5-FU, 5-fluorouracil; cFLIP, cellular FLICE-like inhibitory protein; ErbB2, human epidermal growth factor receptor; ICAM-1, intercellular adhesion molecule-1

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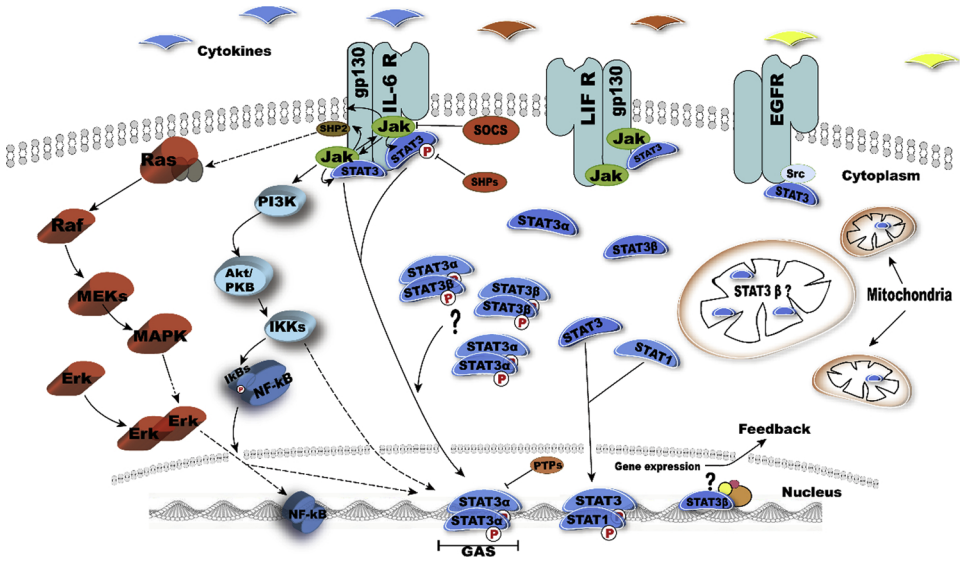

Fig. 1. IL-6-STAT3 pathway and its associated networks.

Groner and von Manstein, 2017)) (Gouilleux-Gruart et al., 1996; Lai and Johnson, 2010; Quesnelle et al., 2007). STAT3 was initially identified as APFR (Acute Phase Response Factor), which is responsible for activating the promoters of acute phase genes in response to IL-6 (Wegenka et al., 1993). The canonical mechanism of STAT3 signalling is that it exists as a latent, un-phosphorylated monomer in the cytosol until cytokines or growth factors [e.g., IL-6, IL-10, EGF, PDGF, and TNF] engage their cognate receptors. The ligand/receptor interaction causes a change in the confirmation and concurrent activation of the receptor associated JAK (Janus Kinase) proteins. Activated JAKs trans-phosphorylate each other and the cytoplasmic tail of the receptor on the tyrosine residues, which provides docking sites for STAT3 to be recruited via its SH2 domain. Once recruited, STAT3 is phosphorylated on a single C-terminal tyrosine residue (Y705) by JAKs. This Y705 phosphorylation provides the possibility for STAT3 dimerization, which translocates into the nucleus, which is assisted by importin-α3 (Liu et al., 2005), and bind to consensus DNA sequences (γ-activated sequence (GAS) TTCNNNGAA (Becker et al., 1998)) and initiates transcription (Fig. 1). This pathway is tightly regulated in normal cells and transient (Heim et al., 1995; Stahl et al., 1995; Garama et al., 2016). However, a plenty of studies have provided evidence of nearly 70% tumor cell lines and patient samples for the incidence of constitutive STAT3 activity, such as breast (Bharadwaj et al., 2015), pancreas (Desrivieres et al., 2006; Gouilleux-Gruart et al., 1996), head and neck squamous cell carcinoma (HNSCC) (Lai and Johnson, 2010) and leukaemia and lymphoma (Quesnelle et al., 2007; Wegenka et al., 1993).

Recently, a growing number of studies have indicated that STAT3β, a splice variant of STAT3, may play a suppressive effect, since it lacks the TAD (transactivation domain), which is in contrast to STAT3α (Schaefer et al., 1997; Maritano et al., 2004; Dewilde et al., 2008) (Fig. 2). Experimental data dating back to 1996 support this concept. Caldenhoven E. et al. found that the co-expression of STAT3β inhibited the transactivation potential of STAT3α and suggested that STAT3β functioned as a negative regulator of transcription (Caldenhoven et al., 1996). Conversely, STAT3β appears to regulate inflammatory factors, affect the tumour microenvironment and attract immune cells to play a role in tumour inhibition (Zammarchi et al., 2011; Wang et al., 2004; Dang et al., 2015). Importantly, increasing numbers of studies demonstrate that a relatively high-STAT3β (compared with STAT3α) level exerts a tumour suppressive effect in several tumour cell lines, acting as a dominant negative regulator (Yu et al., 2009; Couto et al., 2012; Musteanu et al., 2010). Our lab demonstrated that high STAT3β expression converts the prognostic value of $pSTAT3\alpha^{Y705}$ from unfavourable to favourable in patients with ESCC (oesophageal squamous-cell carcinoma) (Zhang and Lai, 2014). Moreover, the induction of a splicing switch towards the beta isoform leads to apoptosis and cell-cycle arrest in STAT3-dependent cell lines via the activation of a unique gene expression signature (Musteanu et al., 2010). Overall, the balance between the two isoforms of STAT3 is apparently crucial to determining the occurrence and development of cancers, which can be depicted as a "spongy cushion" effect (Fig. 3).

2. STAT3 overview

2.1. STAT3 canonical activities

In the 1980s, the Darnell laboratory was investigating interferon-induced gene expression and found the existence of some transducers (Larner et al., 1984; Decker et al., 1989). The STAT proteins were eventually biochemically identified as the key signalling molecules in the interferon pathway in the early 1990s (Schindler et al., 1992). STAT3 was initially identified as APRF, a DNA-binding activity appearing in IL-6-treated hepatocytes and interacting with a *cis*-acting element on the promoter of acute-phase genes (Wegenka et al., 1993). STAT3 is a multifunctional factor protein that is involved in a striking number of functions and activates distinct repertoires of genes in different contexts via the stimulation of many factors (e.g., IL-6 family members, leptin, IL-12, IL-2, IFNs, IL-10, G-CSF, growth hormone, EGF, HGF, LIF, and v-Src (Zhong et al., 1994; Ruff-Jamison et al., 1994; Tian et al., 1994; Ihle and Kerr, 1995; Seto et al., 2015; Ram and Iyengar, 2001). Taking IL-6 for example (Fig. 1), receptor-associated JAKs are phosphorylated through gp130 when IL-6 combines with the IL-6 receptor. Subsequently, phosphorylated JAKs, in turn, cause multiple phosphorylation events at tyrosine residues within the cytoplasmic domain of the cytokine receptor, thereby providing a docking site for the SH2 domain (Src homology 2) of STAT3. By combining with the docking site, STAT3 becomes phosphorylated at Y705, a critical tyrosine on the C-terminal domain of STAT3, and it gains the ability to dimerize with another monomer through the reciprocal interaction of the SH2 domain (Akira et al., 1994; Yu et al., 1995; Sasse et al., 1997; Shuai et al., 1994). Dimeric STAT3 complexes translocate to the nucleus, where they bind to response elements in the promoters of target genes to stimulate transcription. In addition to the phosphorylation of Y705, which is seen as a key activating mechanism of STAT3, S727 (serine 727) phosphorylation, in the C-terminal domain, promotes the association of STAT3 with transcription co-activators (including p68,

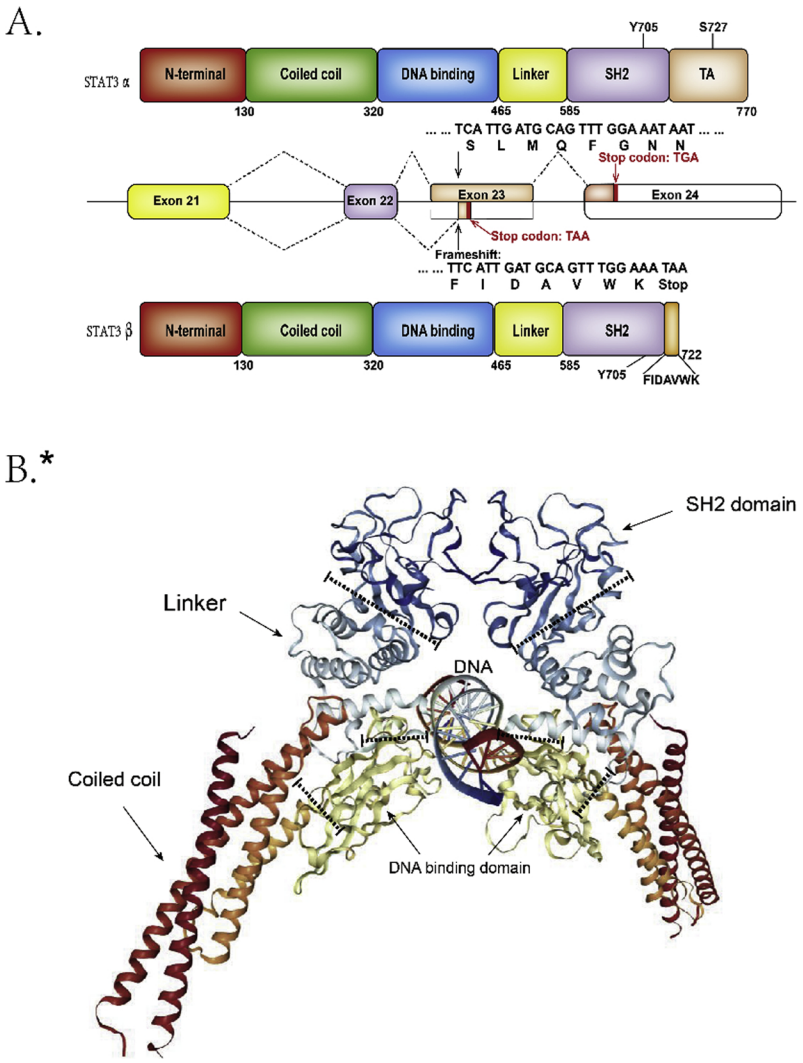

Fig. 2. A. Schematic representation of STAT3 alternative splicing originated from framshift and their functional domains. B.* 3D structure of STAT3β heterodimer. (This diagram is excerpted from the RCSB PDB (www.rcsb.org) of PDI ID: 1BG1. and the original article is "Three-dimensional structure of the Stat3β homodimer bound to DNA. Nature. 1998 Jul 9;394(6689):145-51.".

p300/CBP), providing the maximal activation of particular target genes (Schuringa et al., 2001; Heinrich et al., 2003; Frank, 2007). For instance, in prostate cancer and chronic lymphocytic leukaemia, the phosphorylation of S727, rather than Y705, was found to be crucial for the nuclear translocation, DNA binding, and tumour-promoting function of STAT3 (Hazan-Halevy et al., 2010).

The JAK-STAT3 signalling pathway is engaged by many cytokines and growth factor stimuli to control diverse biological processes in a both cell- and tissue-specific manner. Remarkably, STAT3 is the only family member that is early embryonic lethal on inactivation, which indicates the biological importance of STAT3 (Takeda et al., 1997). Many STAT3 targets, such as Survivin, Cyclins and the Bcl-2 family proteins, promote cell proliferation and survival (Yu et al., 2007; Yue and Turkson, 2009). Studies using conditional STAT3 knockout mice provide evidence that STAT3 is required for the development and differentiation of various tissue types, such as the skin, immune system, liver, mammary gland, thymus and nervous system (Levy and Lee, 2002). For example, the deletion of STAT3 in the mammary glands suppresses apoptosis in glandular epithelial cells and leads to a delayed glandular involution (Wegenka et al., 1993). In another study, the ablation of STAT3 in keratinocytes was found to impair the migration of keratinocytes and skin remodelling (Sano et al., 1999). In addition, STAT3 is critical to the development and biology of immune cells. In one study in which STAT3 was conditionally ablated in all stratified epithelia, including the thymic epithelia, there was a dramatic increase in apoptosis in thymocytes. In addition, the STAT3-depleted thymocytes were more susceptible to apoptosis induced by dexamethasone and γ-irradiation (Sano et al., 2001). In another study, $CD4^+$ T cell differentiation in inflammatory responses was shown to be regulated by STAT3 through Loxl3's deacetylation (Ma et al., 2017), and even in tumour cell lines, its inactivation triggers growth arrest and cell death (Bowman et al., 2000). These proliferative gene targets include Cyclin D1, c-Myc, PLK-1 and Pim1/2 (Avalle et al., 2012). Accumulating evidence suggests that STAT3 plays a critical role in promoting the self-renewal of cancer stem cells (Sherry et al., 2009; Guryanova et al., 2011; Marotta et al., 2011; Kim et al., 2013).

In addition to STAT3's proliferative and survival features, this protein also functions in resistance to apoptosis and the induction of angiogenesis. In one study, STAT3 was shown to be important in mediating the anti-apoptotic effect of IL-6 in the presence of a low-serum culture environment (Takeda et al., 1998). Among many cancer cell types, STAT3 transcriptionally increases the expression of various anti-apoptotic proteins, such as survivin and the Bcl-2 family members (e.g., $Bcl\text{-}X_L$, Bcl-2 and Mcl-1) (Yu et al., 2007; Regis et al., 2008). Moreover, STAT3 negatively controls the manifestation of p53, which helps in the induction of apoptosis, as well as inhibiting cellular proliferation (Niu

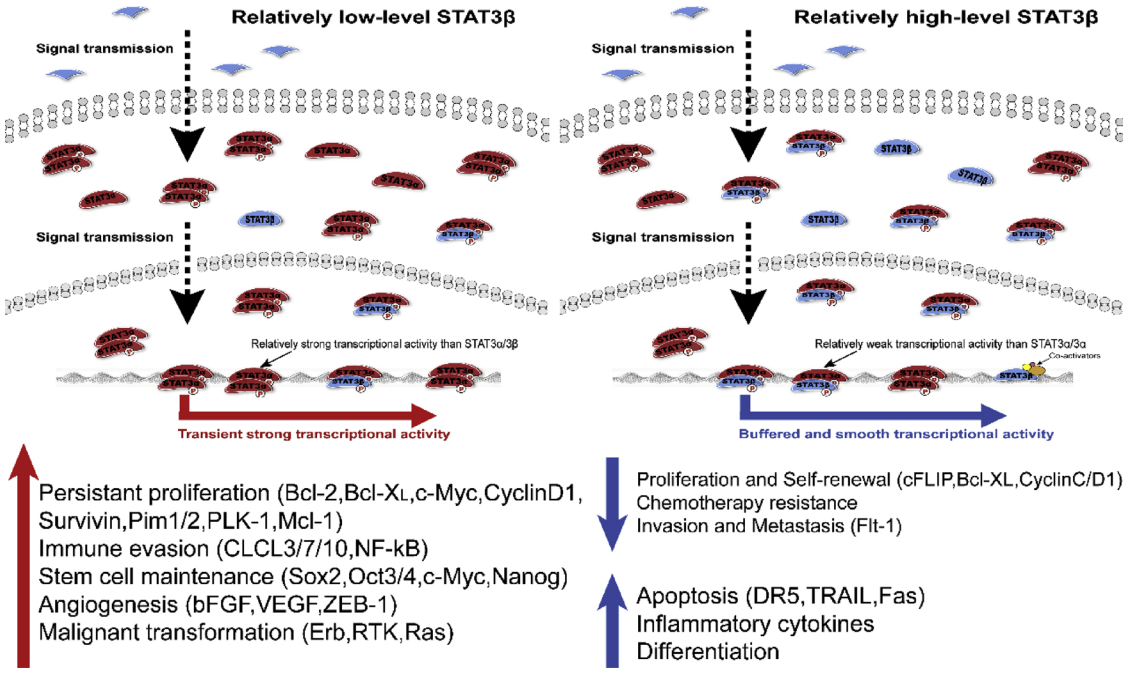

Fig. 3. The "spongy cushion" effect of STAT3β occurs through the formation of a STAT3α/3β heterodimer in contrast to a STAT3α/3α homodimer in cancer. STAT3β mitigates the continuously oncogenic role of STAT3α and amplifies its unique role when STAT3β keep a relatively high-level. In contrast to STAT3α, STAT3β reduces proliferation and self-renewal, weakens invasion and movement, lessens chemotherapy resistance and induces apoptosis in cancer.

et al., 2005). STAT3 is shown to cooperate with c-Jun to suppress the expression of FAS, a crucial mediator of the extrinsic apoptotic pathway. Multiple studies demonstrate that activated STAT3 protects cancer cells from FAS ligand-induced apoptosis and p53-dependent apoptosis (Niu et al., 2005; Ivanov et al., 2001, 2002; Kunigal et al., 2009). It must be noted, however, that under physiological conditions, STAT3 may act as an inducer of cell death. In particular, STAT3 is required for lysosome-mediated epithelial cell death during mammary gland involution, where LIF functions as an activator of STAT3 (Kreuzaler et al., 2011). Increased VEGF expression in cultured cell lines, animal models and patient cancer specimens, as well as tumour angiogenesis *in vivo*, is also induced via the STAT3 pathway in diverse human cancers, such as head and neck squamous cell carcinoma, melanoma, pancreatic cancer, cervical cancer, colorectal cancer, and renal carcinoma (Wei et al., 2003a, b; Niu et al., 2002; Xu et al., 2005; Kujawski et al., 2008; Jung et al., 2007). STAT3 directly mediates the pro-angiogenic activity of VEGF in microvascular endothelial cells (Bartoli et al., 2003). Researchers reveal that STAT3 directly binds to the promoter region of the VEGF gene (sometimes combined with HIF1α (Oh et al., 2011)) and promotes its transcription, and using an inducible STAT3 knockout mouse model, it is revealed that STAT3 promotes the production of angiogenic factors (including VEGF and bFGF) in myeloid-derived suppressor cells and macrophages present in the tumour microenvironment, thereby stimulating endothelial cell migration and tumour angiogenesis (Wei et al., 2003a, b; Niu et al., 2002; Kujawski et al., 2008).

Cellular movement and migration have long been an area of interest and importance to scientists. Especially for tumour cells, cellular invasion and metastasis are critical steps for the tumour prognosis. Many studies show that STAT3 promotes invasiveness and the metastatic potential of cancer cells by triggering EMT (epithelial to mesenchymal transition) via the upregulation of several key EMT regulators, such as Twist-1, Snail and ZEB-1 (Yadav et al., 2011; Lo et al., 2007; Guo et al., 2013; Xiong et al., 2012). In one study in SKOV3 cells, STAT3 signalling was revealed to be important for cell motility, and the exhaustion of STAT3 using siRNA reversed the situation; thus, the cellular migration rate was reduced (Silver et al., 2004). In another study, the loss of Stat3 expression in mouse embryonic fibroblasts led to an elevation in Rac1 activity, which promoted a random mode of migration by reducing the directional persistence and formation of actin stress fibres (Teng et al., 2009). STAT3 increases the expression of various MMPs (matrix metalloproteinases), which facilitate cancer cell invasiveness by degrading various extracellular matrix proteins. In mice, STAT3 reduces pancreatic cancer cell invasiveness and MMP-7 using an shRNA (Li et al., 2011). STAT3 protein expression is upregulated by activated STAT3, which directly binds to the promoter of the MMP-2 gene in melanoma (Li et al., 2011). Likewise, MMP-1 and MMP-9 is also regulated by STAT3 (Dechow et al., 2004; Itoh et al., 2006). As depicted in some studies, inflammation also plays a role in immune evasion. In 1999, Takeda et al. shows that STAT3 inhibited TH1-type inflammation after LPS stimulation by suppressing the production of specific cytokines and nitric oxide (Takeda et al., 1999). In another study, the activities of STAT3 in tumour cells enhanced the expression of several immune-suppressing soluble factors, such as IL-6, IL-10 and VEGF, all of which are known to prevent the maturation of dendritic cells (Sun et al., 2006).

As indicated above, the canonical STAT3 pathway regulates many genes, the expression of which is required for cancer initiation, development and progression, including uncontrollable proliferation, anti-apoptosis, invasion, angiogenesis and immune evasion. Once the negative regulatory loop of STAT3 is lost (mainly SOCS, PTPs and STAT1) (Zhang and Lai, 2014; Avalle et al., 2012; Wang et al., 2012; Croker et al., 2003), STAT3 becomes constitutive activated and provides the possibility of oncogenesis. In addition, some pre-clinical studies demonstrate that constitutively phosphorylated-STAT3 (pSTAT3) is a common characteristic of many cancers (Yang et al., 2013; Macha et al., 2011; Huang et al., 2012; Li et al., 2015a; Shi et al., 2015). However, to date, no STAT3 gene mutation has been detected in any cancer.

2.2. STAT3 non-canonical activities

In addition to the canonical activities regulated by the phosphorylation of Y705 and the transcriptional function of STAT3, unph-STAT3 (un-phosphorylated STAT3) is recognized as an important

transcriptional regulator (Yang et al., 2005, 2007; Yang and Stark, 2008). For example, Yu et al. (2002) found that unph-STAT3, through a direct physical interaction with p65, served as a dominant-negative inhibitor that suppressed the ability of ph-NFκB to induce the cytokine-dependent activation of the iNOS promoter in mesangial cells. In contrast, some studies show that unph-STAT3 interacts with NFκB in the nucleus to drive the expression of multiple cancer-related genes, such as RANTES, IL-6, IL-8, MET and MRAS (Yang et al., 2005, 2007). Another research group found that unph-STAT3 binds to similar DNA sites as the Y705 phosphorylated and dimerized STAT3 (e.g., GAS elements), but unph-STAT3 works in collaboration with transcriptional regulators, such as NFκB, to control a series of genes not normally affected by tyrosine-phosphorylated STAT3 (Timofeeva et al., 2012). With respect to modification, one group discovered that STAT3 interacted with DNMT1 (DNA methyltransferase1) and HDAC1 (histone deacetylase 1), by which STAT3 facilitated the gene methylation and silencing of SHP-1 in malignant T lymphocytes (Zhang et al., 2005). In another group, it was revealed that K685-acetylated STAT3 cooperated with DNMT1 to silence several tumour suppressor genes, including TP53, SHP-1, SOCS3 and CDKN2A, in melanomas (Lee et al., 2012).

Intriguingly, in 2009, STAT3 was also identified in the mitochondria (Gough et al., 2009), and its import was dependent on the phosphorylation at S727 (Tammineni et al., 2013). This mitochondrial STAT3 supports the activity of the Electron Transport Chain (ETC), which is required for ATP production and the opening of the mitochondrial permeability transition pore (mPTP). The loss of STAT3 reduces the activity of the ETC, especially complex I, II and V (Gough et al., 2009; Wegrzyn et al., 2009), which is restored by reconstituting these cells with a mitochondrially restricted form of STAT3. These mitochondrial activities of STAT3 have consequences both in normal tissue homeostasis (e.g., neurite outgrowth and cardiac function) and in pathological conditions (e.g., tumour growth and tissue damage in response to ischaemia/reperfusion injury) (Wegrzyn et al., 2009). However, the deletion of STAT3 from keratinocytes results in the increased expression of mtDNA encoded genes, implying that STAT3 represses the transcription of the mitochondrial genome. Through an unknown mechanism STAT3 traverses two mitochondrial membranes to reside in the mitochondrial inner membrane or the matrix where it augments the activity of the electron transport chain and impedes the opening of the mPTP. This has consequences on cellular ATP production, ROS concentration, calcium homeostasis, and cell survival (Garama et al., 2016; Yang and Rincon, 2016; Meier et al., 2017). The mitochondrial pool of STAT3 is an emerging and exciting area of STAT biology. However, the mechanisms, especially in tumours, by which STAT3 is imported into the mitochondria and its activities within the mitochondrion still need to be illustrated.

It is obvious that STAT3 exists in the cytosol, since mitochondrial STAT3 is imported from the cytosol. Importantly, some research groups also found that STAT3 functions in regulating the cytoskeleton. In one study, tumour-derived cell lines displayed higher migration, invasion, and metastatic abilities and showed a disrupted distribution of cell-cell junction markers, which was mediated by the STAT3-dependent overexpression of the COOH terminal tensin-like (Cten) focal adhesion protein and was also significantly upregulated in STAT3C (a continuously activated STAT3 mutant construct with two cysteine substitutions at the residues A661 and N663) mammary tumours (Barbieri et al., 2010). Consistent with this concept, another study indicates that STAT3 modulates the microtubule network by binding to the COOH-terminal tubulin-interacting domain of stathmin and antagonizing its microtubule destabilization activity (Ng et al., 2006). Moreover, Debra L.S. et al. (Silver et al., 2004) found that activated STAT3 coimmunoprecipitated with phosphorylated paxillin and focal adhesion kinase (FAK) and required paxillin and Src for its localization to focal adhesions in ovarian cancer. Recently, one study also showed that the depletion of STAT3 in gastric cancer cells impaired microtubule polymerization, due to the disruption of the interaction between STAT3 and Stathmin, and as a result, cell migration and invasion were decreased (Wei et al., 2013).

3. STAT3β (A many-sided splice form)

3.1. STAT3β forms a more stable dimer accompanied by prolonged tyrosine 705 phosphorylation and nuclear retention

Protein structure is characterized by a hydrophobic/hydrophilic equilibrium, and structural stability depends largely on the hydrophobic nature of the molecule. The terminal of STAT3β is approximated as a truncated form of STAT3α, but the hydrophobicity of STAT3β is better than STAT3α. Moreover, in a physical chemistry study, Asn466 is conserved in STAT1 to STAT4 and is critical for the sequence-specific recognition in STAT3 (Fig. 2), and the classic SH2 domain interactions are strongly conserved in both STAT3 isoforms (Becker et al., 1998). Because of the complexity of the STAT3 structure, there are many differences between STAT3α and STAT3β in biochemistry, and the related issues are discussed below.

After identifying that STAT3β cooperated with c-Jun, Schaefer et al. employed COS-7 cells transfected with STAT3 expression plasmids to exploit the functional differences between STAT3α and STAT3β. These researchers found that activated STAT3β, in transfected COS cells, was more stable and had a greater DNA-binding activity than activated STAT3α. However, STAT3α exhibited a stronger transcriptional activity than STAT3β (Schaefer et al., 1997). Considering that STAT3α$^{\Delta 48}$ (a mutant of STAT3α lacking its highly acidic C-terminal 48 amino acids) had properties similar to STAT3β, they concluded that this was due to the presence or absence of the acidic C-terminal tail of STAT3α rather than the STAT3β's 7 specific terminal sequence, and the acidic tail of STAT3α may destabilize the active dimeric form of STAT3α, resulting in a lower DNA-binding activity and a more rapid dephosphorylation (Schaefer et al., 1997). Subsequent reports also confirm these phenomena. Another group measured the DNA binding strength and dimer stability in COS-7 cells and revealed that the C-terminal deletions of STAT3α increased both the DNA binding activity and dimer stability of STAT3α, suggesting that STAT3α and STAT3β have similar binding strengths via an EMSA assay (Park et al., 2000).

Interestingly, STAT3β tends to be constitutively phosphorylated at tyrosine 705 and binds to DNA and promotes transcription in the absence of cytokine treatment, whereas STAT3α does not, indicating the increased half-life of the tyrosine phosphorylated STAT3β (Caldenhoven et al., 1996; Schaefer et al., 1995). Related studies were reported by two other groups. Firstly, U. Bharadwaj et al. revealed STAT3β's contribution to constitutive STAT3 phosphorylation in breast cancer (Bharadwaj et al., 2014). Secondly, Ivan H.W.NG et al. showed the sustained nuclear translocation and phosphorylation of STAT3β following cytokine exposure, which was in contrast with the transient nuclear translocation and phosphorylation of STAT3α in AD293 cells (a variant of HEK-293 cell), and they also revealed that STAT3β enhanced and prolonged the phosphorylation and nuclear retention of STAT3α. However, a STAT3β R609L mutant (with a disrupted SH2 domain) did not show similar phenomena (Ng et al., 2012), indicating that STAT3β's effects need Y705 phosphorylation and dimerization. Our lab's findings, in ESCC cell lines (EC109 and KYSE150), also revealed the same phenomena (Zhang et al., 2016). In addition, the unique 7 amino acid tail (FIDAVWK) may also contribute to STAT3β's features, since it is reported to prolong the nuclear retention of phosphorylated STAT3β (Huang et al., 2007). One possible reason that might account for these phenomena is that the STAT3β's hydrophobic tail protects STAT3β from dephosphorylation or keeps it from degradation by proteasome (STAT1β protects STAT1α from degradation (Zhang et al., 2017; Baran-Marszak et al., 2004)), and thus keeps the STAT3β dimers (e.g., STAT3α/β, STAT3β/β) constitutively phosphorylated and exhibiting a stable DNA binding ability by combining with other co-activators. For the phosphatase of STAT3, TC45 (the nuclear form of TC-PTP), SHP1,

and SHP2 are involved in the rapid dephosphorylation of STAT3 (Yamamoto et al., 2002; Kim et al., 2010; Sharma et al., 2016; Lee et al., 2017). Initially, researchers thought that the absence of the interaction of the phosphatase (e.g., TC45) with STAT3β, due its different STAT3β C-terminal sequence, might contribute to the prolonged Y705 phosphorylation and nuclear retention of STAT3β. However, subsequent studies suggested otherwise, because either isoform interacted with TC45 (Ng et al., 2012). Another point of view is that STAT3β may have to cooperate with other activators (Schaefer et al., 1995; Ivanova et al., 2004), thereby showing a diverse transcriptional pattern in contrast to STAT3α, since STAT3β lacks the transactivation domain (especially the S727 site, which is shown to enhance transcriptional activities (Schuringa et al., 2001)). Moreover, one paradoxical phenomenon is that the enforced expression of STAT3β substantially increases the level of $pSTAT3\alpha^{Y705}$, which is considered an oncogenic signal. However, STAT3α is retarded in the presence of sufficient STAT3β, which indicates that whether $pSTAT3\alpha^{Y705}$ level is oncogenic or carcinostatic is largely dictated by the expression statue of STAT3β (Ng et al., 2012; Zhang et al., 2016). All in all, further exploration in this field has implications for relevant issues.

3.2. STAT3β-specific genes and their roles in regulating inflammation, immune, stemness and cytoskeleton rearrangement

3.2.1. STAT3β-specific genes

Considering that STAT3β lacks the transactivation domain (TAD), it may be short of transcriptional activities in contrast to STAT3α. In 1995, however, Schaefer et al. identified that STAT3β (but not STAT3α) and c-Jun were capable of cooperatively activating a certain promoter containing an IL-6 responsive element in the absence of added cytokines or growth factors (Ivanov et al., 2001). Another group also identified that STAT3β associates with the HLH and the C-terminal regions of STRA13, co-expression of STRA13 with STAT3α or STAT3β modulated the transcriptional outcome indicating a repressing rather than activating potential for the STAT3β complexes (Ivanova et al., 2004). These may indicate that the transcriptional activity of STAT3β is quite similar to the different transcriptional activities of the two STAT1 isoforms (known as STAT1α and STAT1β) (Shuai et al., 1993). In another study, the activities of three promoters (2-macroglobulin, c-fos, and p53) in Stat3β-deficient MEFs (mouse embryonic fibroblasts) was tested using a transient reporter assay, and their activities were substantially reduced. Furthermore, they explored the effects of Stat3β-deficiency on the expression of endogenous transcripts using an oligonucleotide array (283 genes exhibiting differential expression, with 36 genes showing a greater than 2-fold differential expression) and an in-depth identification by RT-PCR (Crip, Tfpi, Ptn, and Scya2 RNA were elevated in Stat3-deficient MEFs, while the Sdf1 and Igfbp5 transcripts were elevated in the WTs) (Yoo et al., 2002). Similarly, Ng et al. examined the impact of the reconstitution of the $STAT3^{-/-}$ MEFs with either isoform on gene expression and found 651 genes unique for the re-expression of STAT3α, 1331 genes unique for STAT3β and 506 genes shared between STAT3α and STAT3β, with statistical significance (Ng et al., 2012). Recently, morpholinos (one alternative splicing modulator) were applied to specifically promote a physiological α-to-β splicing shift in one type of breast cancer cell line, revealing a unique STAT3β signature, with the downregulation of specific targets (including lens epithelium-derived growth factor, p300/CBP-associated factor, CyclinC, peroxisomal biogenesis factor 1, and STAT1β), which are distinct from that canonical STAT3 targets that are typically associated with total STAT3 knock-down (Zammarchi et al., 2011). Moreover, mice specifically lacking STAT3α but still expressing STAT3β (STAT3α-/-) do not die during embryogenesis, which indicates the transcriptional compensatory role of STAT3β (Maritano et al., 2004). All of these findings reveal that STAT3β functions as a transcriptional regulator and specifically regulates genes by cooperating with other factors (e.g., c-Jun, STRA13), since it lacks the transactivation domain.

3.2.2. STAT3β in inflammation and immunity

Continuous inflammation is a common feature of the tumour microenvironment and plays a crucial role in both the occurrence and development of many malignancies (Balkwill and Mantovani, 2012; Mantovani, 2010; Hanahan and Weinberg, 2011; Hainaut and Plymoth, 2013). STAT3 was initially identified as acute-phase response factor (APRF) (Wegenka et al., 1993) and was considered as a key player in mediating inflammation-related tumourigenesis via constitutively activating and participating in a positive feedback loop with IL-6 and NFκB (a pro-oncogenic transcription factor) (Yu et al., 2009; Grivennikov and Karin, 2010). For STAT3α, it acts both as a pro- and anti-inflammatory factor depending on the activating signal (Hutchins et al., 2013; Hodge et al., 2005). For STAT3β, on the one hand, it appears to be a suppressor of systemic inflammation. Two $Stat3\beta^{-/-}$ mice studies show a hyper-responsiveness to endotoxic shock and a diminished recovery from that (Maritano et al., 2004; Yoo et al., 2002). $Stat3\beta^{-/-}$ mice develop exacerbated atherosclerosis in the absence of ApoE (Lee et al., 2013a). Peritoneal macrophages from $Stat3\beta^{-/-}$ mice produce significantly more TNF and IL-6 than $Stat3^{+/+}$ control mice and have reduced IL-10 (an anti-inflammatory factor) when treated with LPS (lipopolysaccharide) (Maritano et al., 2004), indicating that STAT3β may directly or indirectly participate in the regulation of IL-10 expression to function as an inflammatory regulator. On the other hand, STAT3β upregulates the expression of pro-inflammatory cytokines in B16 melanoma cells, and in supernatants from STAT3β-transfected B16 melanoma cells, it induces the activation of macrophages, granulocytes and dendritic cells, indicating the antitumoural aspect of STAT3β (Wang et al., 2004). Additionally, in an animal model, restoring STAT3β re-induces acute phase response genes in hepatocytes (Alonzi et al., 2001). The same protein gives rise to two apparently opposite results, and this may also indicate the diversity of STAT3β's co-activators. In addition, the cell-specific expression of STAT3β in macrophages also exhibits antitumour effects in mouse breast cancer, indicating that STAT3β may also play an important role in the cells from the tumour microenvironment (Dang et al., 2015). In addition to regulating the expression of inflammatory factors, STAT3β may attenuate the secretion of factors that suppress the activity of immune cells, thereby indirectly activating dendritic cell maturation (Wang et al., 2004), which is a process that involves MHC class II and co-stimulatory molecule expression (Park et al., 2004; Kitamura et al., 2005).

3.2.3. STAT3β and stemness

A major role of STAT3 is self-renewal. Recently, increasing studies reveal that STAT3 also plays a critical role in the regulation of the stemness of cancer stem cells (Sherry et al., 2009; Guryanova et al., 2011; Marotta et al., 2011; Kim et al., 2013; Liu et al., 2013; Tu et al., 2012). For example, STAT3 isoforms have distinct roles in myeloid cell proliferation, survival and differentiation, indicating that STAT3β may not act as a dominant negative regulator in these processes. STAT3β has a strong cell and tissue specificity, and the ratio of the STAT3α:STAT3β mRNA and protein levels ranges from 4:1 to 10:1 and 1:3 to 10:1 (Bharadwaj et al., 2014). According to these studies, the ratio of STAT3α:STAT3β is highly regulated in myeloid cells and is consistently decreased during cell maturation and activation (Biethahn et al., 1999; Hevehan et al., 2002; Chakraborty et al., 1996). In another study, in normal human CD34+ bone marrow cells and HL60 cells, both reported to differentiate upon G-CSF stimulation, G-CSF does not activate STAT3α but only an 83 kD form of STAT3 (STAT3β) (Chakraborty et al., 1996). However, only STAT3α (but not STAT3β) generates a markedly higher number of neutrophils in response to G-CSF when it is over-expressed in the 32Dcl3 myeloid cell line (Redell et al., 2007). Our research showed that STAT3β overexpression significantly decreased the clonogenic capacity and increased the sensitivity to 5-FU and cisplatin in a STAT3β dose-dependent manner (Zhang et al., 2016). Similar to the above, STAT3 also plays a role in the stemness of other cells (Lomada et al., 2016; Sherry-Lynes et al., 2017; Ma et al., 2015; Lee

et al., 2013b), however, whether STAT3β plays a regulatory role in these process remain to be explained.

3.2.4. STAT3β and the cytoskeleton rearrangement

The cytoskeleton and focal adhesions are two main aspects of cancer metastasis, a multiple process in which tumour cells leave their original location and go to new tissues through the blood vessels. Various reports have shown that increased STAT3 activity can enhance intercellular contact and up-regulate the expression of genes related to tumor cell invasion and metastasis, suggesting that STAT3 may be a sensor for tumor cell contact. (Tu et al., 2012; Gatsios et al., 1996; Pansky et al., 2000; Peng et al., 2016; Zhou et al., 2015; Lee et al., 2010). Sano et al. first described that STAT3 possessed a pivotal role in cellular movement and wound healing processes in cultured keratinocytes (Sano et al., 1999). STAT3 cooperates with stathmin and modifies microtubule dynamics and the migration of cells, such that microtubule depolymerization starts when an oncoprotein 18-stathmin binds to α/β-tubulin heterodimers (Ng et al., 2006). Additionally, the loss of STAT3 displays some changes in randomized cellular migration, while STAT3 indirectly controls Rac-1 activity to sustain migration (Teng et al., 2009). Interestingly, in an *in vitro* study using SKOV3 cells, STAT3 is critical for cell motility, and the knock-down of STAT3, using siRNA, reverses the situation, such that cellular migration is repressed, and it was further indicated that ph-STAT3 co-immunoprecipitated with ph-paxillin and focal adhesion kinase and required paxillin and Src for its localization to the focal adhesions (Silver et al., 2004). In other studies, STAT3 activation can reduce the expression of tumor suppressor gene E-cadherin in human skin squamous cell carcinoma (Hillmer et al., 2016) and prostate epithelial cells (Azare et al., 2007), activate ErbB2/integrin β4 signaling pathway in breast cancer (Guo et al., 2006), and increase the level of ICAM-1 /CD54 in human glioma cells (Kesanakurti et al., 2013), so that cell invasion and metastasis ability enhanced.

However, STAT3β does exactly the opposite role compared to STAT3 (STAT3α) (Niu et al., 2001; Xu et al., 2009). This is an interesting area indicating that STAT3β may participate in these regulations, considering that STAT3β antagonizes STAT3α by inducing or inhibiting the expression of genes associated with cell motility. Additionally, our group indeed found that STAT3β disrupted the rhythm of ESCC movement (unpublished data).

3.3. Relatively high-level STAT3β protein levels corroborate to create favourable changes due to the "spongy cushion" effect in cancer

To date, the dominant negative role of STAT3β has been reported in various types of cancer, including melanoma, breast cancer, oesophageal cancer, lung cancer and colonic cancer (Zammarchi et al., 2011; Ivanov et al., 2001; Zhang et al., 2016; Niu et al., 2001; Xu et al., 2009; Niu et al., 1999; Ivanov et al., 2009; Rivat et al., 2005). One group found that the overexpression of STAT3β induces cell death in B16 melanoma cells *in vitro* (Niu et al., 1999). Additionally, in U266 myeloma cells, which inherently express elevated Bcl-X_L, STAT3β also promotes programmed apoptosis (Catlett-Falcone et al., 1999) by inducing soluble necrosis factors (Niu et al., 2001). Similar results are also confirmed in lung cancer, which show the downregulation of Bcl-X_L and Cyclin D1 (Xu et al., 2009). STAT3β also efficiently upregulates DR5 (the tumour necrosis factor-relate apoptosis-inducing ligand receptor) surface expression and downregulates cFLIP (caspase-8 inhibitor) levels in melanoma cells *in vitro* and *in vivo* (Ivanov et al., 2009). Another group revealed that the overexpression of STAT3β downregulates the VEGF receptor Flt-1, neuropilins 1 and 2, and the inhibitor of DNA binding/differentiation (Id-2) gene product involved in the neoplastic transformation by using DNA microarrays and a gene differential expression analysis (Rivat et al., 2005). Our lab's studies revealed that a moderate/strong expression of STAT3β significantly was correlated with a longer overall survival and recurrence-free survival and was less likely to have lymph node metastasis in ESCC (Zhang et al., 2016). These findings indicate that STAT3β is an independent protective factor for patient survival. STAT3β can form more stable dimer (STAT3α/STAT3β, STAT3β/STAT3β), it occupies STAT3α stably and weakens the transcriptional ability of STAT3α/STAT3α thus is suggested to have a promising future in gene therapy, since there are no specific small-molecule inhibitors have entered the clinical stage only targeting STAT3α (Schust et al., 2006; Hong et al., 2015; Li et al., 2015b; Huang et al., 2018). Altogether, high-level STAT3β levels in cancer cells indeed lead to favourable results. However, among the published clinical studies, researchers rarely differentiate the relative levels of the two STAT3 isoforms, and its prognostic significance has also rarely been identified. As we can see from the above mechanisms, STAT3β exerts its negative roles mainly because STAT3β lacks the TAD domain and forms a transcription complex with STAT3α or other co-activators, thereby playing its unique role or repressing STAT3α's role. Thus, the surveying of STAT3β independently of STAT3α is meaningless. This molecular mechanism is depicted as a "spongy cushion" (Fig. 3), which cushions the transient and intense transcriptional role of STAT3α, thus avoiding the excessive activation of STAT3α. Meanwhile, the relatively high level STAT3β amplifies its role in the regulation of inflammation, immunity, apoptosis, etc. Thus, in the exploration of STAT3 that is carried out to this extent, a careful distinction between STAT3α and STAT3β in different cell types and cancers is required.

4. Conclusions and perspectives

To date, there are four recognized subtypes of STAT3, including STAT3α (92 kDa), STAT3β (83 kDa), STAT3γ (72 kDa) and STAT3δ (64 kDa), while STAT3α and STAT3β are generated by alternative splicing, and STAT3γ and STAT3δ are derived from proteolytic processing and exhibit no transcriptional role (Hevehan et al., 2002; Nakajima et al., 2003; Hendry and John, 2004; Kato et al., 2004). The oncogenic role of STAT3α has long been recognized, but its spliceform-STAT3β has not yet been given adequate attention. STAT3β is mainly distinguished from STAT3α by its truncated terminus and exhibits unique features by cooperating with STAT3α or other co-activators. In analyses from reports over the past thirty or forty years, many studies reveal the dominant negative role of STAT3β (Caldenhoven et al., 1996; Niu et al., 2001; Xu et al., 2009; Niu et al., 1999; Epling-Burnette et al., 2001; Karni et al., 1999; Sinibaldi et al., 2000). However, the concrete reasons for this are unknown and are only combined with surface gene expression differences. A STAT3β/3β homodimer may exist, and a few reports also confirm that STAT3β directly functions with other co-activators (Schaefer et al., 1995; Ivanova et al., 2004). In addition to the interactions between STAT3α and STAT3β, STAT3 also interacts with STAT1, which is quite similar in homology but exerts diametric effects. In addition, no one can deny the existence of STAT1β/3β and STAT1α/3β heterodimers, and their functions are even less known. All of these areas increase the complexity of STAT3's function. Moreover, recently, some groups have concentrated on mitochondrial STAT3 and found that STAT3 enhances the activity of the electron transport chain (Garama et al., 2016; Yang and Rincon, 2016; Meier et al., 2017; Huang et al., 2016). However, whether STAT3β binds to mtDNA and such functions as its multiple nuclear roles need further verification. Finally, several studies have revealed the possibility of STAT3, especially STAT3β, as a regulator of tumour cell invasion and migration, but the exact mechanism needs further study.

The adversity that we are faced with is the relative protein levels of STAT3α:STAT3β at approximately 4:1 (Bharadwaj et al., 2014). It is precisely because of this ratio that many current studies directly ignore the role of STAT3β and choose STAT3α as the major object. However, growing evidence demonstrates that STAT3β does play an irreplaceable role accompanied by STAT3α, and its "spongy cushion" effect is notable. The past cognition does not affect STAT3β, and it might be a good drug target and independent prognostic marker in cancer. Interestingly, U.Bharadwaj et al. (Bharadwaj et al., 2014) developed monoclonal

antibodies that specifically recognize the unique CT7 epitope and do not cross-react with Stat3α and "STAT3β-deg" (proteolytic cleavage forms of Stat3α), which brings many conveniences to the in-depth study of STAT3β. Overall, we believe the exploration of STAT3β will yield new insights into cancer therapy and provide new directions for STAT3 studying.

Conflict of interest

No conflicts of interest.

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