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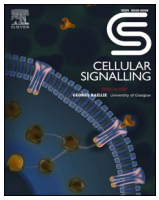

Importance of STAT3 signalling in cancer, metastasis and therapeutic interventions

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ABSTRACT

The Signal Transducer and Activator of Transcription 3 (STAT3) protein is encoded on chromosome 17q21. The SH2 and the DNA binding domains are critical structural components of the protein, together with tyrosine and serine residues that initiate phosphorylation. STAT3 interacts with DNA directly and functions in cells as both a signal transducer and a transcription factor. Its cytoplasmic activation results in dimerisation and nuclear translocation, where it is involved in the transcription of a large number of target genes. STAT3 is hyperactive in cancer cells as a result of upstream STAT3 mutations or enhanced cytokine production in the tumour environment. The STAT3 signalling pathway promotes many hallmarks of carcinogenesis and metastasis, including enhanced cell proliferation and survival, as well as migration and invasion into the extracellular matrix. Recent investigations into novel STAT3-based therapies describe a range of innovative approaches, such as the use of novel oligonucleotide drugs. These limit STAT3 binding to its target genes by attaching to SH2 and DNA-binding domains. Yet, despite these significant steps in understanding the underpinning mechanisms, there are currently no therapeutic agents that addresses STAT3 signalling in a clinically relevant manner.

1. Introduction

The Signal Transducer and Activator of Transcription (STAT) protein family forms part of an important intracellular pathway that interacts with external signalling molecules and their receptors, leading to regulation of gene transcription. Activation of STAT proteins is generally influenced by their association to the Janus-Kinase (JAK) family proteins [1], which are receptor-associated tyrosine kinases. In mammals, these enzymes comprise JAK1, JAK2, JAK3 and TYK2. Once cytokines bind to cell membrane receptors and interaction is initiated, these enzymes phosphorylate a broad range of STAT proteins, such as STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. In order to regulate gene transcription, STAT proteins must be phosphorylated and activated before dimerising and transferring to the nucleus [2].

STAT proteins are activated as part of normal physiological function. Distinct patterns of activation are also seen in a variety of abnormal cell growth. Interestingly, it has been discovered that the majority of human tumour tissues and malignant cell lines show STAT3 activation, together with other irregularities in STAT protein activation [2]. As an example, activation of STAT3 has been reported to occur in different tumour types, such as melanoma (brown skin), lymphoma (white skin) and leukaemia (blue blood cells) [3]. There is accumulating evidence to demonstrate atypical STAT3 activation being associated with the promotion of tumorigenesis and invasion [4]. Results from several studies confirm that activation of STAT3 is associated with a poor prognosis in a variety of human cancers, such as head and neck tumours, B-cell lymphoma, cervical cancer, gastric carcinoma and colon cancer [5–9].

This review article will consider and discuss the current understanding of STAT3, taking into account its protein structure and an overview of its function in physiologically healthy tissue. The discussion continues with consideration of the role of STAT3 in cell regulation and an overview of its signalling in cancer and metastatic processes.

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2. Structure of STAT3

The STAT family proteins have an amino acid count ranging from 750 to 850. STAT3 has 770 amino acids and is encoded on the long arm of chromosome 17q21. All STAT proteins act similarly and carry out a number of critical function within the cell. One of their most distinctive features is the SH2 (Src Homology 2) domain, located at the C-terminus of the protein [10]. The SH2 domain (Fig. 1) is required for multiple stages in STAT signalling because it identifies and binds phosphotyrosine motifs. It enables the association of extracellular chemicals with the cell membrane receptor responsible for signal transmission [10,11]. Furthermore, it facilitates recognition and binding by activating JAK protein. Another critical need is that STAT proteins dimerise with either another identical STAT protein (homodimerisation) or with another member of the STAT protein family (heterodimerisation) [12,13]. To activate the STAT protein, the SH2 moiety in one partner molecule binds to the phosphorylated tyrosine residue in the other and *vice versa* [1,12,13]. Clearly, this process of STAT protein activation is dependent on the phosphorylation of the tyrosine residue [14].

STAT family proteins dimerise to form a DNA-binding domain, located in a region towards the centre of the molecule [14,15]. STAT3 homodimers select the base sequence TTCnnGAA as this is the DNA binding site exhibiting the greatest affinity [14]. Structural differentiation requires the transactivation domain, which is found at the C-terminus of STAT proteins [15]. The particular shape of this domain controls STAT protein interaction with other transcription factors, and, hence, with DNA [16]. As a result, variations in this domain may account for differences in STAT transcriptional function. All STAT proteins share a large coiled-coil domain with four helices. This hydrophilic region of the STAT protein interacts with other proteins, such as N-Nyc interacting protein (NMI) and STAT3-interacting protein 1 (StIP1) [17].

3. STAT3 mechanism of action

STAT proteins undertake a dual function in the cell, operating as a messenger between the cell surface and the nucleus, whilst also being involved directly in transcription regulation [18]. Tyrosine kinases catalyse the phosphorylation step required for STAT activation [19]. The most important feature of tyrosine kinases involved in this process is that they are cytokine receptor-associated tyrosine kinases, the most notable of which are JAKs. The involvement of receptor-associated tyrosine kinases is critical, since the majority of cytokines lack intrinsic kinase activity [20][21]. STAT3 may be triggered in a variety of ways by receptor binding of cytokines, of which interleukin-5, interleukin-6 and interleukin-9 are known examples [21,22] (Fig. 2).

STAT3 can be activated by receptor-based tyrosine kinases, such as epidermal growth factor receptor. Similarly, activation can be brought about by cytoplasmic tyrosine kinases, such as those found in the Src family of protein tyrosine kinases. STAT3 is phosphorylated at position 705 of its amino acid sequence [23]. Additionally, for STAT3 to be maximally transcriptionally active, a serine residue at position 727 must be phosphorylated a second time [24,25]. Serine kinases, including as p38 and mTOR, assist in this process.

STAT proteins dimerise and migrate to the nucleus once phosphorylation is complete [25,26]. Dimers are thought to enter the nucleus via the nuclear pore complex (NPC) in a GTP-dependent manner [26]. The dimer must be coupled to importin and importin-like proteins in order to pass through the NPC [27]. As previously indicated, the oligonucleotide sequence TTCnnGAA is the optimal sequence for binding STAT3 to DNA. Additional transcription factors can work in conjunction with transcription, such as c-Jun and c-Fos, which work in concert with STAT3 to bind certain DNA promoter sites [28].

4. STAT3 in normal physiology

Active STAT proteins control gene transcription have an effect on cell proliferation, survival, differentiation and migration [1,2]. Studies on knockout mice have defined the function of the majority of the STAT family members in normal physiology. In the case of STAT3, homozygous deletion of the encoding gene results in the death of embryos within the first days of development owing to STAT3 lethality [29]. STAT3 appears to be more crucial than the other STAT proteins for early development, cell survival and proliferation. It has been proven that STAT3 impairment has a significant influence on the immune response by establishing tissue-specific STAT3-null circumstances [29]. IL-6 typically promotes cell survival and proliferation in T-lymphocytes, but not in STAT3-deficient mice [30]. STAT3 has been shown to act as a negative regulator of neutrophil development in haematopoietic progenitor cells [29] and that STAT3 deletion impairs the response of human liver tissue to infection-associated acute phase proteins [31]. Additionally, STAT3 is associated with affecting cell movement, with STAT3-deficient keratinocytes exhibiting reduced wound healing motility [32].

5. Regulation of STAT3

Normal cells possess mechanisms that limit the long-term activation of both STAT3 and downstream pathways. Suppressors of Cytokine Signalling (SOCS) are STAT target genes encoding proteins that operate in the opposite direction of STAT activation, thereby establishing a negative feedback loop [33]. Another family of regulatory proteins includes those that decrease the transcriptional activity of activated STAT proteins. PIAS3 specifically inhibits transcriptional activity of STAT3 [34]. PTP1 and PTP2 are both tyrosine phosphatases that inhibit the activity of STAT. These proteins are expressed in variable amounts depending on the cell micro-environment. They de-phosphorylate JAK and STAT proteins and inhibit the activation process [35].

6. Signalling of STAT3 in cancer and metastasis

The capacity of cancer cells to grow and disseminate is dependent on changes in normal cellular functions, such as angiogenesis and cell proliferation. STAT3 signalling has been implicated in an apparent increase of these key features.

6.1. Dysregulation of STAT3 in cancer

Research studies into a broad range of solid and haematological malignancies demonstrate increased STAT3 activation in almost every human cancer tissue [20,36,37]. Despite the fact that constitutively

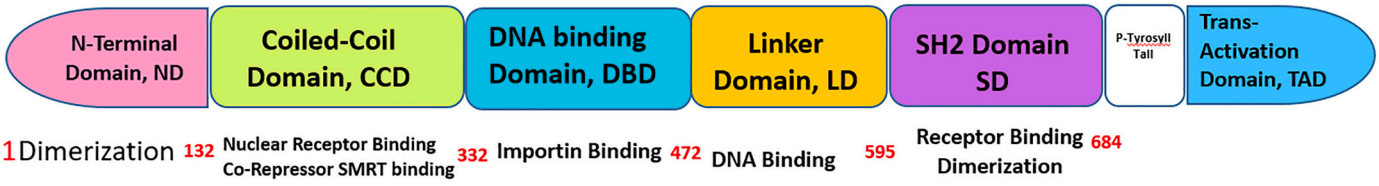

Fig. 1. Structure of the STAT protein. (A) STATs structure is composed of a N-terminal domain (N-term), a Coiled-Coil domain (CCD), a DNA Binding domain (DBD), a Linker domain (LD), a SRC homology 2 domain (SH2), a Phosphotyrosyl Tail (p-Tail), and a C-terminus named the Trans-Activation Domain (TAD).

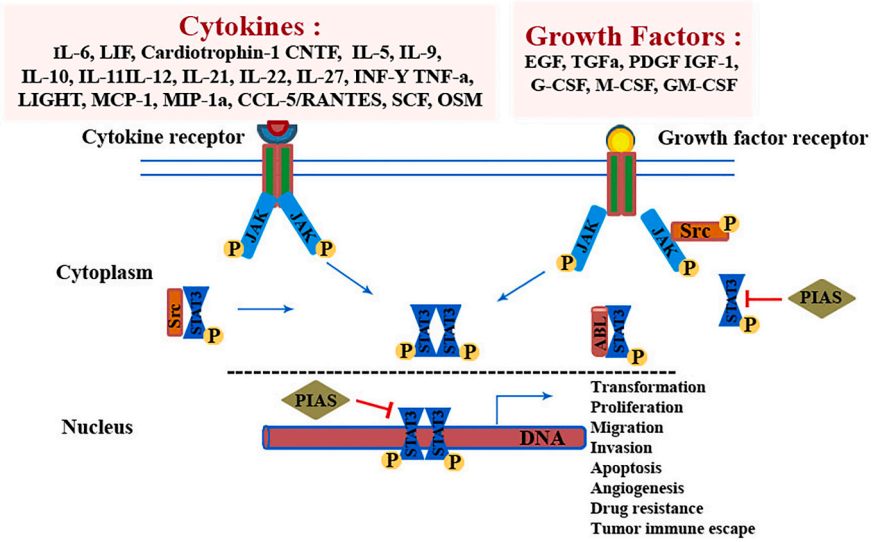

Fig. 2. Signalling pathway leading to STAT3 activation. Ligand binding to cell surface receptors causes phosphorylation of STAT3, which leads to dimerisation and nuclear translocation. After translocation, the dimer binds to target gene promoter elements and activates transcription.

active STAT3 mutants have been shown to induce cellular transformation *in vitro* [38], activating STAT3 mutations are not predicted to have a significant role in spontaneously developing cancer [39]. As previously noted [20,37], consistent STAT3 activation in cancer is due to upstream activation of serine and tyrosine kinases, which can be induced by mutation, dysregulation, or an oversupply of pro-inflammatory cytokines, such as IL-6, in the tumour microenvironment. Oncoprotein kinase c-Src staining of the cell membrane has been linked to a number of malignancies, including lung, skin, breast and ovarian cancers [40,41]. Another critical method of constitutively active RET signalling is STAT3 activation, which has a role in the development of numerous forms of cancer [41]. STAT3 activation has also been associated with mutations in receptors for Bcr-Abl, K-RAS and epidermal growth factor [42–44]. A malfunctioning regulatory protein may also play a role. For example, hypermethylation silences SOCS genes in lung cancer [20].

7. The prognostic significance of STAT3 in solid tumors

The results from numerous studies report an association between increased STAT3 expression in tumor tissue and poor survival in patients. A wide variety of solid tumors feature in these investigations, including gastric [45] [46], lung [47], glioma [48], colorectal [6], ovarian [49], cervical [9], hepatocellular carcinoma [50], melanoma [51], esophageal cancer [52] and osteosarcoma [53]. However, some studies present a contrasting picture, indicating that the association is not universal [54]. A systematic assessment of the literature on STAT3 expression and tumor prognosis, conducted using meta-analysis, presents a comprehensive overview. Survival data from 9449 people with solid tumors from 63 independent trials were evaluated systematically. STAT3 expression was a poor prognostic factor in solid tumors, with consistent results for three and five-year overall survival (OS) [55]. In patients with gastric, lung, glioma, hepatic, osteosarcoma, prostate and pancreatic cancer, the results confirmed that higher STAT3 expression in tumor tissues is associated with a lower OS.

There is evidence that contradicts the link between poor prognosis and STAT3 activation. It has been reported that there is no evidence that STAT3 overexpression correlates with colorectal or ovarian cancer survival [55]. STAT3 overexpression in breast cancer tissue has been associated with a favourable overall survival results. However, recent studies show that STAT3 inhibitors can suppress tumour development in a number of solid tumour models, including breast cancer [56,57], melanoma [58] and ovarian cancer [59]. These disparities suggest that further study is required to explain the STAT3 signalling pathway and the underlying mechanism in the pro-tumour microenvironment of various tumour types. Nevertheless, it is generally accepted that STAT3 expression in solid tumour tissues is associated with a poor prognosis in the majority of solid tumours, suggesting that STAT3 may be a helpful prognostic biomarker and a potential therapeutic target for solid malignancies.

8. STAT3 and non-Hodgkin diffuse large B-cell lymphoma

Diffuse large B-Cell Lymphoma (DLBCL) is a particularly aggressive form of non-Hodgkin lymphoma, accounting for 30%–40% of newly diagnosed cases [60]. An examination of gene expression shows two unique molecular subtypes of DLBCL cells, named activated B-cell-like (ABC) and germinal centre B-cell-like (GCB) cells [61]. The JAK1/STAT3 signalling pathway is required for the development of DLBCL. Consistently active STAT3 enhances the expression of genes involved in a range of oncogenic processes in ABC DLBCL, including cell survival, proliferation and migration, metabolic reprogramming and immune evasion. Inhibiting JAK1/STAT3 signalling has been proposed as a feasible therapeutic strategy for tackling ABC DLBCL [62].

The FDA has not yet approved any STAT3 inhibitors for cancer therapy, but early-phase clinical trials are ongoing [63]. AZD9150 inhibits STAT3 activity in ALCL and non-small cell lung cancer lines and has anticancer effects in lymphoma and lung cancer xenograft models [64]. It is presently being explored in clinical trials for non-Hodgkin lymphoma and lung cancer. Trials studying chronic Adult T-cell leukaemia/lymphoma have shown efficacy of daclizumab, a monoclonal antibody targeting the IL-2 receptor component IL-2R [65]. Anti-IL-6 antibody siltuximab (CNTO 328) has been examined in Castleman's disease and multiple myeloma [65]. Combining ruxolitinib with the type I interferon inhibits ABC DLBCL cell growth *in vitro* and *in vivo* [66].

8.1. Cell proliferation and survival

STAT3 signalling promotes cell growth and survival. As a result, STAT3 promotes the transcription of anti-apoptotic genes in cells, such as Mcl-1 [67]. Excess of this protein has been related to a range of forms of cancer due to its promotion of cell survival via a variety of pathways [20]. STAT3 suppresses transcription of the cell death receptor FAS, making cells more sensitive to pro-apoptotic signals [68]. STAT3 also

reduces the action of p53, one of the most important tumour suppressors in cancer biology [69].

STAT3 promotes cell proliferation by boosting the transcription of the cell cycle regulators cyclin D1, cyclin B1 and cyclin-dependent kinase 1 (CDK1) [70]. It also stimulates c-Myc, a protein with several linkages that promote growth and cell division [71]. This is because STAT3 inhibits the development of the CDK inhibitor p21 as well as p27, which are both required for cell cycle progression [72]. STAT3 may also play a role in the transcription of the proto-oncogene PIM1, which is involved in K-Ras-induced malignant transformation and has been associated with a variety of different forms of human cancer [73]. STAT3 was shown to accelerate the transition from G1 to the S cell cycle in squamous cell carcinoma, gastric cancer, colon cancer and bladder cancer cells [70]. When STAT3 was targeted in bladder cancer cell lines, apoptosis was triggered and cell proliferation was reduced [74]. In addition to tumorigenic effects via the usual pathway, mitochondrial STAT3 promotes malignant transformation [75]. STAT3 maintains an increased level of oxidative phosphorylation in response to rising metabolic demands, hence promoting Ras-driven cell proliferation and survival [75].

8.2. Cell migration and invasion

Cell motility and extracellular matrix penetration are both required for metastatic spread. STAT3 activation appears to be critical in both instances. *In vitro* migration of ovarian cancer cell lines requires activation of STAT3, whereas silencing STAT3 inhibits cell motility [76]. STAT3 activation enhances integrin-6 expression in prostate epithelial cells, which promotes cell motility [77]. STAT3 contributes to the invasion-promoting phenotype [78] by stimulating transcription of mucin-like glycoprotein MUC1, BCL6, cathepsins and UPA. When STAT3 is activated *in vitro* in human carcinoma and melanoma cells, matrix metalloproteinases MMP-1, MMP-2 and MMP-9 are key enzymes in the development of cancer [58,79]. When STAT3 activity is increased, the metastasis inhibitor E-cadherin is downregulated in prostate cancer cells [80]. STAT3 promotes pancreatic cancer cell invasion and MMP-7 synthesis in mice [80]. When STAT3 is repressed using RNA interference, the rate of entry of pancreatic cancer cells into the extracellular matrix is decreased *in vitro* and *in vivo* [81].

8.3. Angiogenesis

STAT3 stimulates angiogenesis by acting as a direct transcription factor for the genes encoding vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1 (HIF1) [82]. HIF1 and STAT3 covalently link to the VEGF promoter and increase transcription in hypoxic situations [83]. Constitutive STAT3 activation boosts VEGF expression in human melanoma, breast, head and neck, cervical and pancreatic cancer cells [28,82], whereas STAT3 targeting suppressed VEGF expression [71]. *In vitro* STAT3 suppression has been shown to have a detrimental effect on endothelial cell motility, survival and neovascularisation in mouse hepatocellular carcinoma cells [84].

8.4. STAT3 as a prognostic marker

A correlation between tumour STAT3 expression and patient prognosis has been established using results from numerous studies on human malignancies. In a study of 100 gastric cancer patients who had had gastrectomy, it was observed that those with STAT3-positive tumours have a poorer survival rate ($P = 0.001$) [5]. Another study on colorectal cancer demonstrates a correlation between increased STAT3 activation and a higher rate of death ($P = 0.002$) [85].

9. STAT3 inhibitors

As STAT3 activity has been linked to an increase in drug resistance in malignancies, there is strong evidence that effective STAT3 inhibition may be a beneficial adjunct therapy [86]. STAT3, being tumorigenic and pro-invasive when activated in human malignancies, makes it a highly sought-after target for treatment. Because many adult tissues no longer employ STAT3 signalling, targeting should have no adverse effects [87]. The majority of research to date has focused on small-molecule inhibitors (Table 1) with the goal of directly inhibiting STAT3.

9.1. Molecules targeting the SH2 domain

The SH2 domain of STAT3 is responsible for receptor/JAK interaction and dimerisation, so represents a promising therapeutic target. In a novel study examining the entries in a virtual database, a STAT3 inhibitor was identified (STA-21) and shown to bind to the SH2 region [88], confirming potential as a therapeutic inhibitor [89]. When STAT3 is activated in colon and breast cancer cells, they exhibit increases in apoptosis as a result of STA-21 inhibition. *In vivo*, oral STA-21 medication was shown to reduce head and neck squamous cell cancer [90]. Subcutaneous STAT3 inhibitor injection into mice xenografts of human colorectal cancers significantly increased chemo/radiosensitivity and reduced tumor progression [91]. These encouraging preliminary *in vivo* findings indicate the potential for creating novel STAT3 SH2 domain-targeting therapies. Phase I/II clinical studies using OPB-31121, an SH2 binding molecule, have been conducted on patients with advanced solid tumors, but findings indicate that further studies are required before definitie conclusions can be reached [92].

9.2. Molecules targetting the DNA-binding domain

Along with the DNA-binding domain, STAT3 downstream effects are regulated through DNA transcription regulation, which makes it a promising therapeutic target. Platinum-based compounds may be beneficial in this application. CPA-1, CPA-7 and platinum (IV) tetrachloride inhibit STAT3 and cause apoptosis in human breast, lung, prostate and colon cancer cells [93]. CPA-7 has a better specificity for STAT3 [20,93] when compared to that of other STAT family members. Additionally, CPA-7 inhibits the production of VEGF in melanoma and prostate cancer cell lines and inhibits neovascularisation [94]. Finally, preliminary data from CPA-7 *in vivo* trials indicate that when delivered to mouse models, it can induce tumour regression [93]. Another

Table 1
Selected STAT protein inhibitors.

Inhibitor Name	Cancer Type	Mechanism of Action
Curcumin-proline		SH2 domain inhibitor
S3I-201	breast cancer, prostate cancer, acute myeloid leukemia and human multiple myeloma	SH2 domain inhibitor
Bp-1-102	breast and lung cancer	SH2 domain inhibitor
Celecoxib	human rhabdomyosarcoma	SH2 domain inhibitor
SPI	breast, pancreatic, prostate and non-small cell lung cancer cells	SH2 domain inhibitor
HIC 1	breast cancer	DNA binding domain inhibitor
ST3-H2A	prostate cancer	N-terminal domain inhibitor
PD153035	oral squamous carcinoma	RTK inhibitor
Ponatinib	rhabdomyosarcoma	FGFR inhibitor
SHP1	mmultiple myeloma and head and neck squamous carcinoma cells	STAT3 inhibitor
SHP2	chronic myeloid leukemia	STAT3 inhibitor
HJC0152	breast cancer	STAT3 inhibitor
HJC0123	breast cancer	STAT3 inhibitor
Xanthohumol	breast cancer	STAT3 and EGFR inhibitor

interesting drug compound, galiellalactone, has been found to inhibit STAT3 signalling by binding to the DNA binding region. It inhibits the binding and transcription of STAT3 DNA in hepatoma cells downstream of the IL-6 receptor interaction [95]. When galiellalactone was administered *in vivo* into the peritoneal cavity of xenograft mice models of human prostate cancer, a 3 mg/kg/day regression was seen [96].

9.3. Oligonucleotide inhibitors of STAT3 signalling

An exciting strategy for inhibiting STAT3 has been the use of synthetic double-stranded DNA molecules (decoyODN) that duplicate the nucleotide sequence bound by the STAT3 dimer. Due to the strong affinity of this decoyODN for the transcription factor, it stops STAT3 from performing its function as a transcription factor [39]. This approach has been shown to inhibit successfully the cell growth, invasion and survival in a variety of human malignancies, including those of head and neck, prostate, hepatic and lung [97].

The primary concern with nucleotide therapy is the instability of the molecule, which renders therapeutic concentrations difficult to attain in the tumour environment. However, a study using human participants and utilising hexaethylene spacers to stabilize the oligonucleotide molecules has just been completed [98]. The trial demonstrated a decrease in the expression of the proliferation-promoting proteins cyclin D1 and Bcl-XL, which are STAT3 targets. These findings further support the possibility of developing a new STAT3 inhibiting-based treatments.

10. Conclusion

STAT3 is a transcription factor and intracellular signalling protein. It is activated by a variety of cytokines, growth factors and intracellular kinases. In cancer, STAT3 dysregulation leads to prolonged activation, which has a range of tumorigenic, invasive and metastatic downstream outcomes. These consequences lead to decreased apoptosis in an environment conducive to cell proliferation, migration and angiogenesis. Although STAT3 is recognised as a viable target, possibly underpinning drug-based interventions, there are currently no credible strategies for novel human therapeutics. This is despite the quantity of promising research in the area. Further studies into STAT3 inhibitors are to be strongly supported, as the potentials benefits to the many patients suffering from challenging neoplastic disease are immense.

Author contribution

MET wrote the manuscript, curated data and created figures; AOA edited manuscript, curated data and edited figures and SMA edited manuscript and curated data. All authors reviewed, edited and approved the final version of the article.

Author agreement

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors of the submitted manuscript have approved the manuscript and agree with its submission to Cellular Signalling.

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Declaration of Competing Interest

The authors declare no competing interests.

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