HHS Public Access

Author manuscript

Nat Rev Cancer. Author manuscript; available in PMC 2016 May 04.

Published in final edited form as:

Nat Rev Cancer. 2009 November ; 9(11): 798–809. doi:10.1038/nrc2734.

STATs in cancer inflammation and immunity: a leading role for STAT3

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Abstract

Commensurate with their roles in regulating cytokine-dependent inflammation and immunity, signal transducer and activator of transcription (STAT) proteins are central in determining whether immune responses in the tumour microenvironment promote or inhibit cancer. Persistently activated STAT3 and, to some extent, STAT5 increase tumour cell proliferation, survival and invasion while suppressing anti-tumour immunity. The persistent activation of STAT3 also mediates tumour-promoting inflammation. STAT3 has this dual role in tumour inflammation and immunity by promoting pro-oncogenic inflammatory pathways, including nuclear factor-κB (NF-κB) and interleukin-6 (IL-6)–GP130–Janus kinase (JAK) pathways, and by opposing STAT1- and NF-κB-mediated T helper 1 anti-tumour immune responses. Consequently, STAT3 is a promising target to redirect inflammation for cancer therapy.

The importance of inflammation in tumour initiation and malignant progression has become the focus of attention with good reason. Inflammatory conditions can initiate or promote oncogenic transformation, and genetic and epigenetic changes in malignant cells can also generate an inflammatory microenvironment that further supports tumour progression[1]. Cancer-associated inflammation is marked by the presence of specific inflammatory cells and inflammatory mediators, including cytokines and chemokines[1]. Recent evidence suggests a crucial role for signal transducer and activator of transcription (STAT) family proteins — especially STAT3 — in selectively inducing and maintaining a pro-carcinogenic inflammatory microenvironment, both at the initiation of malignant transformation and during cancer progression[1–9]. STAT3 is linked to inflammation-associated tumorigenesis that is initiated by genetic alterations in malignant cells[10–13], as well as by many environmental factors, including chemical carcinogens, sunlight, infection, cigarette smoking and stress[14–22].

Because of its ability to induce the expression of a large array of inflammatory mediators and its role as a core transcription factor in diverse immune responses, nuclear factor-κB (NF-κB) signalling has been recognized as a major pathway responsible for both

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inflammation-induced carcinogenesis and anti-tumour immunity[1,23–25]. Given their central roles in inflammation and cancer[23,25–31], it is not surprising that signalling by various STATs, particularly STAT3, is highly interconnected with NF-κB signalling[3,7,32–35]. There are striking parallels, as well as contrasts, between NF-κB and STAT3. Both proteins are not only persistently activated in cancer and essential for transducing cytoplasmic signals from extracellular stimuli, but they also function as nuclear transcription factors required for regulating genes involved in tumour proliferation, survival, angiogenesis and invasion, in addition to genes encoding key cancer-promoting inflammatory mediators[23,25–28,36,37]. It is mechanistically relevant that STAT3 interacts with NF-κB at several levels in a highly context-dependent manner. For example, several inflammatory factors encoded by NF-κB target genes, most notably interleukin-6 (IL-6), are important STAT3 activators[2,3,7,29,38–40]. In tumours, STAT3 directly interacts with the NF-κB family member RELA, trapping it in the nucleus and thereby contributing to constitutive NF-κB activation in cancer[32]. Ultimately, STAT3 and NF-κB also co-regulate numerous oncogenic and inflammatory genes[27,28,36,39]. Continuous deregulation of these genes in tumour cells and the tumour microenvironment by persistently activated STAT3 and NF-κB — in contrast to their tightly controlled regulation in normal physiology — is crucial for inflammation and malignant progression.

Aside from the tumour-promoting role of inflammation, many murine studies and clinical findings have underscored the importance of immune responses and inflammatory mediators — both naturally occurring and therapeutically induced — in suppressing tumorigenesis and tumour growth[41–47]. STAT3 and, to some extent, STAT5 and STAT6 are involved in inhibiting anti-tumour immunity[5,48,49]. Although crucial for inducing oncogenic inflammatory conditions, NF-κB is also indispensible for mediating anti-tumour immune responses[1,25,28]. By contrast, STAT3 activation restrains anti-tumour immune responses[4–6,28,50–52] by antagonizing NF-κB- and STAT1-mediated expression of anti-tumour T helper 1 (T_H1) cytokines such as IL-12 and interferon-γ (IFNγ), which are necessary for both innate and T cell-mediated anti-tumour immunity[5,28,50,53,54]. STAT3 signalling in innate immune cells is required for the immunosuppressive and tumour-promoting effects of myeloid-derived suppressor cells (MDSCs) and tumour-associated macrophages[4,5,50–52]. STAT3 also mediates T regulatory cell expansion in tumours and is necessary for the development of T_H17 T cells[5,50,55–57], which can promote tumour growth[6,58]. Because STAT3 induces the expression of cytokines, growth factors and angiogenic factors, and the associated receptors in turn activate STAT3, a feedforward loop is established between tumour cells and immune cells in the tumour microenvironment[4,27,28]. As a consequence, persistent activation of several STATs, especially STAT3, mediates both the propagation of tumour-promoting inflammation and the suppression of anti-tumour immunity, and so provides a promising molecular target for modulating immune responses to improve cancer therapy.

STAT proteins in immune modulation

The STAT protein family consists of seven members, which are encoded by distinct genes: *STAT1*, STAT2, *STAT3*, *STAT4*, *STAT6*, and the closely related *STAT5A* and *STAT5B*[27,59,60]. One distinguishing feature of the proteins encoded by these genes is their

dual roles — they both transduce signals through the cytoplasm and function as transcription factors in the nucleus[30,38,61]. STATs were originally discovered through their capacity to mediate signalling from IFN and IL-6 receptors following engagement with their cognate cytokines[29,30,38,40,59,61–64]. Cytokine receptors do not usually have intrinsic tyrosine kinase activity: instead, their engagement activates receptor-associated tyrosine kinases, most prominently the Janus kinase (JAK) family kinases (JAK1, JAK2, JAK3 and TYK2)[27,30,38,59,65]. Following phosphorylation of specific tyrosine residues in STAT proteins, they form stable homodimers or heterodimers with other STAT proteins through reciprocal phosphotyrosine–SRC homology 2 (SH2) domain interactions. Each STAT family protein responds to a defined set of cytokines (TABLE 1), and each also regulates, with other transcription factors and/or cofactors, a group of specific genes (TABLES 1,2). Importantly, many of the downstream target genes of STATs encode cytokines and growth factors, the receptors of which signal through the same STATs, thereby providing a mechanism for autocrine and paracrine STAT activation. For example, in response to IL-6 signalling through GP130 (also known as IL6ST)–JAK, STAT3 forms homodimers that translocate to the nucleus. In the nucleus STAT3–STAT3 homodimers modulate the expression of genes encoding IL-6 itself and other mediators crucial for the classic physiological acute phase response and cancer-promoting inflammatory conditions[2,3,7,29,39,63,66] (FIG. 1; TABLE 2). By contrast, on stimulation by type 1 IFNs, STAT1–STAT1 homodimers or STAT1–STAT2 heterodimers accumulate in the nucleus and regulate the expression of genes that promote growth arrest and apoptosis[67,68]. Type 1 IFNs also activate certain types of innate immunity, including natural killer cell responses, as well as T_H1-type adaptive immunity, which is characterized by the production of IFNγ, the receptor of which further activates STAT1 and STAT2 (REFS 59,62,65,69). This loop is crucial for controlling viral infection and mediating anti-tumour immunity (TABLE 1).

STAT3 induces cancer inflammation

Epidemiological studies of chronic inflammatory conditions at specific organ sites provide some of the most compelling evidence that inflammation promotes malignant transformation. Virtually all liver and gastric cancers arise from infections that cause chronic hepatitis (for which the infectious agents are hepatitis B virus and hepatitis C virus) and chronic gastritis (for which the infectious agent is *Helicobacter pylori*), respectively[1]. Crohn's colitis and ulcerative colitis are associated with dramatically increased colon cancer incidence[1]. However, the microenvironment of cancers with no prior underlying inflammatory history is also laden with haematopoietic-derived cells in various states of activation[1]. These observations suggest that cancer and inflammation are linked by both extrinsic (environmental) and intrinsic pathways, the latter of which originate from genetic and epigenetic events in the malignant cells[1]. STAT proteins, especially STAT3, are crucial for both the extrinsic and the intrinsic pathways underlying cancer inflammation[2,3,5–7,10–13,29,40,66]. Owing to its oncogenic properties, which include causing increased tumour cell proliferation and survival, STAT3 drives the malignant properties that are associated with chronic inflammation[3,7,27,31,70–73].

STAT3 signalling is a major intrinsic pathway for cancer inflammation because it is frequently activated in malignant cells and capable of inducing a large number of genes that

are crucial for inflammation (TABLE 2). Nevertheless, the ongoing contribution of persistently activated STAT3, as with other overactive transcription factors in cancer, to the continuous transcriptional regulation of any specific gene in tumour cells remains to be determined experimentally. In addition to being downstream of cytokine receptors, STAT3 is activated by growth factor receptor and non-receptor tyrosine kinases (FIG. 1). For example, epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR), among many other polypeptide growth factor receptors, as well as non-receptor tyrosine kinases such as SRC, are upstream of STAT3 and frequently overexpressed or overactivated in solid tumour cells[27,29,65,74–78].

STAT5 and STAT6 are persistently activated in various haematopoietic malignancies[27,79–82]. In the case of chronic myelogenous leukaemia, the oncogenic *BCR–ABL* chromosomal translocation causes persistent activation of STAT5 in the malignant cells[79,83]. IL-13–STAT6 signalling is crucial for the development of certain lymphomas and leukaemias[81,82]. Both STAT5 and STAT6 have been shown to upregulate genes important for haematopoietic tumour survival and proliferation when persistently activated in tumour cells. A role for these two STATs in tumour immune evasion has also been indicated, which we discuss in later sections. Although site-directed mutations can create constitutively active oncogenic forms of certain STATs, which demonstrates the intrinsic oncogenic potential of STAT3 in particular, the increased activation of STATs in naturally occurring cancers is almost exclusively secondary to the activation of upstream kinases[27,74,76,81,82,84]. The crucial roles for persistent STAT activation in oncogenesis have been well established in many different studies by a large number of laboratories over the past decade.

Cytokines, chemokines and other mediators, such as IL-6, IL-1β, macrophage colony-stimulating factor, prostaglandins and cyclooxygenase 2 (COX2, which is required for the production of prostaglandins), are crucial for inducing and maintaining a cancer-promoting inflammatory environment[1], and STAT3 is crucial for regulating their expression (TABLE 2). Although tumour cells are known to produce some of these mediators, they are mainly produced by the stromal inflammatory cells[4–6,8,9,28,50]. Importantly, the persistent activation of STAT3 intrinsic to tumour cells is transmitted to stromal inflammatory cells in the tumour microenvironment[85,86]. This is because, in tumour cells, STAT3 is a transcription factor for numerous genes encoding cytokines, chemo kines and growth factors, the associated receptors of which in turn activate STAT3 in stromal cells[27,29,38,87] (FIG. 1). Therefore, a STAT3 feedforward loop is established between tumour cells and non-transformed cells in the microenvironment, including immune cells[28]. This feedforward loop is exemplified in multiple myeloma, which provided the first direct evidence for a mechanistic link between persistent STAT3 signalling and human cancer. In myeloma cells, IL-6 drives JAK and STAT3 activation, leading to tumour cell survival through the upregulation of anti-apoptotic genes[2]. Activation of STAT3 is also observed in multiple myeloma bone marrow stromal cells, which are a major source of IL-6 that induces persistent activation of STAT3 in the tumour cells, thereby establishing a feedforward loop[8]. Although whether transformed cells and/or non-transformed stromal cells initiate IL-6 production in multiple myeloma remains to be fully characterized, autocrine and paracrine feedforward loops formed by cytokine–STAT3 signalling are recurrent themes in many human cancers[9,10,28]. Furthermore, the stable establishment of this feedforward loop probably represents an indirect epigenetic

mechanism, as there is continuous deregulation of gene expression without gene mutations, which is not unlike changes in DNA methylation[88]. In this regard, it is notable that STAT3 can directly promote DNA methylation[89].

STAT3 in inflammation-induced carcinogenesis

Although the IL-6–JAK–STAT3 pathway is an important mediator of cancer inflammation that is initiated by genetic changes in transformed cells (intrinsic pathway), as discussed above, it is also crucial for inflammatory conditions caused by environmental and other aetiological factors that are associated with increased cancer risk (extrinsic pathway). Several infectious agents that are known to cause inflammation-induced cancer involve STAT3 activation and probably depend on STAT3 for their oncogenic potential. For instance, infection with *H. pylori*, which is associated with gastric cancer, activates STAT3 through its cytotoxin-associated gene A in host cells[17]. Many tumour viruses are also known to activate STAT3 by various distinct mechanisms, including hepatitis B virus[90], human papillomavirus[91], human T-lymphotropic virus type 1 (REF. 21) and Epstein–Barr virus[92]. A human enterotoxigenic strain of *Bacteroides fragilis* (termed ETBF) has been shown to induce colitis in both mice and humans; ETBF colonization of mice results in STAT3 activation in the colon and dramatically increases colon tumorigenesis[58]. Both lipopolysaccharide (which mimics bacterial infection) and live bacteria are able to activate STAT3, resulting in the production of IL-1β and IL-6 (REF. 19), which are major mediators of inflammation-induced cancer. Lipopolysaccharide is known to function through Toll-like receptor 4 (TLR4), and it has been shown that the engagement of TLR4 and TLR9 can also directly activate STAT3 (REF. 93). These and other studies provide a potential mechanistic explanation for why TLRs, which are the sensors of infection, can promote tumour growth[94].

STAT3-mediated inflammation may also be central to non-infectious pathways of carcinogenesis. Importantly, a crucial role of STAT3 signalling in mediating ultraviolet light-induced skin cancer has been demonstrated in a transgenic mouse model[22]; cigarette smoke-associated cancer development may also be linked to STAT3 activation through the nicotinic receptor[14]. Chronic stress is another contributer to cancer pathogenesis and progression, and a recent study has suggested the potential importance of STAT3 activation in mediating tumorigenicity by the stress mediators, noradrenaline and adrenaline[18]. Chemical carcinogens also induce tumour growth and incidence through STAT3, as shown by the examples below.

Owing to its central role in mediating inflammatory signals, the NF-κB pathway has been a major focus of studies on inflammation-induced carcino-genesis. Conditionally ablating inhibitor of NF-κB (IκB) kinase-β (*Ikkβ*), which blocks NF-κB activation by preventing IκB phosphorylation and degradation (BOX 1), abrogated colorectal cancer resulting from inflammatory bowel disease and ulcerative colitis induced by chemical carcinogens, azoxymethane and dextran sulfate[95]. More recent studies in colitis-associated colorectal cancer mouse models have provided direct evidence that STAT3 signalling is required for inflammation-induced cancer[3,7]. Furthermore, IL-6, which is downstream of NF-κB and primarily produced by bone marrow-derived myeloid cells, activates STAT3 in both

inflammatory cells and the epithelial cells from which the tumours arose. Activation of STAT3 induced the upregulation of key genes involved in cell proliferation and survival, and increased the nuclear localization of β-catenin, which contributes to colorectal carcinogenesis[3]. Importantly, in the absence of the *Stat3* alleles, carcinogens continued to induce inflammation but not tumour incidence[3]. Increased IL-6 expression is also observed in human colorectal cancer, suggesting the importance of IL-6 in mediating inflammatory conditions that are associated with this cancer[96]. Furthermore, IL-6 seems to be a crucial mediator of gender bias in susceptibility to hepatocellular carcinoma. This disease mainly occurs in men, and gender bias linked to IL-6 has been shown in a carcinogen-induced liver cancer mouse model[97]. The administration of the carcinogen diethylnitrosamine led to a higher serum IL-6 concentration in male mice than it did in female mice. Moreover, without IL-6, the gender difference in tumour development was abrogated. Interestingly, in the liver tissues in which the tumours developed, it was not IKK but STAT3 that was persistently activated. This supports a crucial role for IL-6–STAT3 signalling in mediating the gender bias in liver cancer susceptibility[97].

Chronic inflammatory conditions that promote tumour formation can also be attributed to genetic alterations that directly affect the STAT3 pathway[10–13]. The importance of constitutively active mutations in *GP130*, which encodes a subunit of the IL-6 receptor, has been demonstrated in human inflammatory hepatocellular adenomas[12]. Constitutively active mutant GP130 causes the persistent activation of JAKs and STAT3 in the absence of cytokine ligands. A crucial role for STAT3 in inflammation-induced adenocarcinomas was also demonstrated in a transgenic mouse model with a constitutively active GP130 in epithelial cells[70]. Studies in mice with *Gp130* mutations demonstrated that an increase in GP130 and STAT3 signalling led to inflammation-associated gastric tumorigenesis[13]. Mutations at specific sites in *JAK2* have also been observed in some human cancers, including myeloid leukaemias[11]. These human and mouse genetic studies show that the persistent activation of the IL6–GP130–JAK–STAT3 signalling axis is an important contributor to inflammation-induced cancers, making it an attractive target for treating and/or preventing inflammation that favours cancer progression.

STATs in anti-cancer or pro-cancer inflammation

One of the most debated topics in cancer biology is whether the immune system suppresses or promotes cancer. Many experimental data suggest a crucial role of the immune system in controlling tumour incidence and growth, and in certain human cancers or subsets of cancers the presence of immune cells predicts better prognosis[41–47]. Evidence suggests that innate immune cells, such as macrophages, natural killer cells and dendritic cells, can destroy tumour cells when appropriately activated[54] (FIG. 2). T cells from the adaptive arm of the immune system can also attack tumours when activated in a T_H1 immunological milieu (FIG. 3). However, tumour-associated macrophages have long been known to promote cancer, partly through their ability to secrete angiogenic, metastatic and growth factors[98,99] (FIG. 2). Another related myeloid lineage of cells, MDSCs, which are increased in cancer, not only suppresses anti-tumour immunity but also directly contributes to tumour growth[49] (FIG. 2).

The distinction between immune responses that inhibit and those that promote cancer is, to a large extent, regulated by members of the STAT family of proteins. In particular, STAT1 activation leads to IL-12 production; STAT4 activation induced by IL-12 receptor (IL-12R) engagement in turn promotes T_H1 responses that produce IFNγ, the receptor of which itself signals through STAT1 to increase anti-tumour responses through the activation of natural killer cells, macrophages and $CD8^+$ T cell-mediated cytolytic activity[60,100] (FIG. 3). Ablating the *Stat3* gene in natural killer cells and macrophages in mice can boost expression of T_H1 mediators[34,101], leading to STAT1 upregulation and increased anti-tumour immune responses[28,50,85,86]. Both type 1 interferons and IFNγ mediate anti-tumour immunity through STAT1-dependent innate effectors (such as natural killer cells), T_H1-type responses and cytotoxic T lymphocyte activation[45,47]. The ability of STAT3 to antagonize STAT1 has been well documented[50,53,68]. STAT3 and STAT6 have also been implicated in promoting immunosuppressive MDSCs[49,52]. Recent evidence points to a role for STAT3 in mediating the cancer-promoting properties, such as angiogenesis, of tumour-associated MDSCs and macrophages[4,52,98,102] (FIG. 2). STAT3 and STAT5 also have major roles in the expansion of T regulatory cells[5,50,55], which promote tumour progression by inhibiting anti-tumour immune responses that are mediated by T_H1-type $CD4^+$ T cells and $CD8^+$ T cells[103] (FIG. 3).

New insights into STAT-dependent regulation of the balance between distinct immune responses have come from the recent discovery of a distinct T_H17 T helper cell subset (FIG. 3). Although T_H1 development involves type 1 interferons and is further promoted by IL-12, T_H17 development requires a combination of IL-6 and transforming growth factor-β (TGFβ) and is further promoted by the IL-12 family member IL-23 (REFS 54,104). STAT3 activation is central to T_H17 development[56] and functions both as the major IL-6R-dependent transcription factor in the T cell and as a transcriptional activator of *Il-23a* (also known as *p19*) that encodes part of IL-23 (REF. 5). Recent evidence supports a cancer-promoting role for both IL-23 and T_H17 responses (FIG. 3). In a cutaneous carcinogenesis model, *Il-23a* knockout resulted in decreased skin tumour formation, and *Il-12a* knockout resulted in increased tumour formation[105]. Antibody blockade of IL-23R *in vivo* also decreased the growth rates of some transplanted tumours[5]. Inducible myeloid-specific *Stat3* gene ablation abrogated IL-23 production by tumour-infiltrating macrophages but induced the release of IL-12 by tumour-infiltrating dendritic cells (which was accompanied by a decrease in tumour growth)[5]. In addition, expression of *Il-23r* was increased in tumour-promoting regulatory T cells in tumours[5]. IL-23 also increases intra-tumoural T_H17 activity, which can further promote tumour growth. For example, IL-17 (secreted by T_H17 cells) positively affected tumour STAT3 activity and tumour growth in some transplanted models[6]. The importance of IL-17–STAT3 in tumorigenesis was further illustrated in the ETBF bacterial pro-carcinogenesis model, in which both *Il-17* expression and STAT3 activity were increased. STAT3 activation is required for IL-17 production by the lamina propria $CD4^+$ T cells, and IL-17 blockade abrogates most of the colon tumorigenesis induced by ETBF colonization[58]. However, IL-17 can both promote and inhibit tumorigenesis[6,58,106,107]; further studies are therefore required to understand its role in cancer.

STAT3–NF-κB in cancer inflammation

As discussed above, both STAT3 and NF-κB have crucial and integrated roles in inflammatory responses that promote cancer development and growth[2–8,23–25,27,28,31,32,50]. However, NF-κB is involved not only in pro-carcinogenic inflammation but also in anti-tumour immune responses[1,25,28,32]. STAT3, conversely, is a specific regulator of pro-carcinogenic inflammation — driving cancer-promoting inflammatory conditions —while simultaneously suppressing anti-tumour immune responses[28,50,85,86]. Intriguingly, STAT3 and NF-κB are frequently persistently activated in the same tumour cells, and in tumour-associated myeloid cells. Both transcription factors induce the expression of a highly overlapping repertoire of proliferative, anti-apoptotic, angiogenic and metastatic genes that promote tumour development and growth (TABLE 2). However, this is where the similarity between the two proteins ends. STAT3 inhibits the expression of NF-κB target genes involved in T_H1 innate immunity and adaptive immune responses important for controlling microbial infections and tumour growth[28] (TABLE 2). In this way, STAT3 opposes the activation of anti-tumour immunity programmes by NF-κB when both are activated in the same cells. Therefore, STAT3 interacts with NF-κB at multiple levels and the consequence of this interaction is highly context dependent. Recent studies (which are described below) have shed light on the molecular basis of these interactions.

The prototypical NF-κB complex is a RELA–p50 heterodimer (BOX 1), which is crucial for both the induction of inflammatory responses and NF-κB-mediated pro-oncogenic effects[108,109]. Another NF-κB family protein, REL (BOX 1), regulates the transcription of many immunostimulatory cytokines and chemokines that are involved in anti-pathogen and anti-tumour immune responses. Unlike RELA, which is persistently activated in tumours, including tumour-associated immune cells, REL is not usually activated in cancer. Recent evidence suggests that accumulation of RELA in the nucleus can be promoted by acetylation by p300 (also known as EP300)[110] (FIG. 4). Importantly, STAT3 is required for p300-mediated RELA acetylation; consequently, persistent activation of RELA in tumour cells, as well as in non-transformed cells in the tumour microenvironment, requires continuous STAT3 signalling[32] (FIG. 4).

Just as STAT3 can increase NF-κB activity in cancer, persistent activation of STAT3 in tumours, especially in immune cells of the tumour microenvironment, is dependent on NF-κB (specifically RELA). This reciprocal relationship with RELA stems from the fact that several cytokines and growth factors encoded by RELA target genes are STAT3 activators (TABLE 2). Among the STAT3 activators downstream of NF-κB, the most crucial ones are IL-6 and related cytokines. As discussed earlier, the importance of IL-6 and other members of the IL-6 family of cytokines, including IL-11, in activating the JAK–STAT3 pathway leading to cancer-promoting inflammation has been widely documented. COX2, another factor downstream of NF-κB that mediates cancer-promoting inflammation, also activates STAT3 through IL-6 (REF. 87). Several other inflammatory cytokines, including IL-17, activate STAT3 through NF-κB–IL-6 signalling[6,39]. Additional examples of STAT3 activators that are regulated by NF-κB are IL-23 and IL-21 (REF. 57), both of which contribute to inflammation-induced cancer. A striking feature of STAT3–NF-κB interactions is that many of these inflammatory mediators, including IL-6, COX2, IL-17 and IL-23 (all of

which activate STAT3), also require STAT3 as a co-transcription factor with RELA for their expression (FIG. 4; TABLE 2). Therefore, not only do these two transcription factors need each other for their persistent activation in cancer, they also ensure the continued expression of their activators, facilitating the stable establishment of this feedforward loop and a permanent change in the genetic programme (FIG. 4).

One perplexing question that remains to be fully resolved is how STAT3 inhibits NF-κB-mediated transcription of T_H1 immunostimulatory genes in tumours and their microenvironment (TABLE 2). Although constitutive STAT3 activation in cancer maintains nuclear NF-κB levels[32], genetic ablation of *Stat3* revealed an inhibitory role of STAT3 on IKK, and so NF-κB activation, in normal immune cells[34] and tumour cells[32] (FIG. 4). IKK in turn activates various members of the NF-κB family of proteins, including RELA and REL (BOX 1; FIG. 4), and also RELB. Although RELA–p50 and REL–p50 both upregulate many T_H1 immunostimulatory genes, RELA additionally increases the expression of numerous genes involved in chronic inflammation and cancer progression (TABLE 2). By contrast, REL is mainly involved in regulating T_H1 immunostimulatory genes[111]. For example, *IL-12A* (also known as *P35*), which encodes a component of IL-12, is mostly regulated by REL. It is notable that STAT3 inhibits *IL-12* expression[50], at least in part, by downregulating REL[5]. Several RELA-regulated genes, such as *IL-6*, *IL-8* and inducible nitric oxide synthase 2 (*NOS2*), can be either upregulated or downregulated by STAT3 (TABLE 2). The finding that STAT3 can both inhibit IKK during acute inflammation and cooperate with RELA as a co-transcription factor for these genes in chronic inflammation-associated cancer provides a potential mechanistic explanation for this apparent paradox (FIG. 4). Further studies are required to clarify why under cancer-promoting chronic inflammatory conditions persistently activated RELA and STAT3 regulate one set of genes, which are mostly oncogenic, while leaving many of the T_H1 immunostimulatory genes inactive (FIG. 4).

Targeting STAT3 for cancer therapy

Oncogenic transcription factors are prime targets for cancer therapy, partly because multiple cytoplasmic signalling pathways converge on a limited number of nuclear transcription factors[26]. STAT3 and NF-κB (specifically RELA) are among the most frequently activated oncogenic transcription factors and, as discussed here, both regulate cancer-associated inflammation[23,25–28]. However, owing to the crucial role of NF-κB in inducing anti-tumour immune responses, its inhibition could actually promote tumour growth, and long-term blockade might cause substantial immune suppression[25]. Genetic studies demonstrate that ablation of the *Stat3* gene in either tumour cells or tumour-associated macrophages and other immune cells, even under chronic inflammatory conditions, inhibits carcinogenesis as well as the growth of established tumours[3,20,50,112]. Moreover, mice reconstituted with *Stat3*-deficient immune cells can mount potent anti-tumour immune responses[50]. Although prolonged *Stat3* gene ablation in mice ultimately causes T_H1-associated autoimmunity, a therapeutic window has been demonstrated[50]. Additionally, genetic studies in patients with hyper-IgE syndrome identified dominant-negative *STAT3* gene mutations — effectively abolishing STAT3 signalling — as the cause of the disease in some of the patients[113–115]. These studies in mice and humans suggest that although completely blocking STAT3 can

lead to severe disease either directly or indirectly, partial STAT3 inhibition for a limited duration — as in drug-based cancer therapy — can potentially convert tumour-promoting inflammation to anti-tumour immune responses without generating severe side effects.

Direct targeting of STAT3 as a new approach for more effective cancer therapy is highly desirable[26,27]. Although the inhibition of tyrosine kinases could potentially activate alternative pathways leading to increased metastasis and tumour growth[116,117], *Stat3* gene ablation in diverse tumour models results in the inhibition of tumour growth[20,50,112]. However, unlike tyrosine kinases and other molecular targets, transcription factors do not possess intrinsic enzymatic activity. This makes the development of small-molecule STAT3 inhibitors considerably more challenging, requiring alternative approaches such as the disruption of protein–protein or protein–DNA interactions. Nevertheless, two major approaches have been taken along these lines: structure-based design and random screening of compound libraries. In terms of structure-based design, the primary molecular target has so far been the phosphotyrosine–SH2 domain interactions that stabilize active STAT3 dimers. Phosphopeptides and their derivative peptidomimetics with reduced peptide properties have been designed that block STAT3 dimerization and DNA-binding activity[118–120]. In addition, screening of virtual compound libraries *in silico* against molecular models of STAT3 on the basis of its crystal structure has led to both peptide and non-peptide small molecules that disrupt STAT3 dimerization and transcriptional activity[121]. As a complementary approach, random screening of chemical libraries *in vitro* has yielded additional non-peptide small molecules with activity against STAT3 (REFS 122–124). These small molecules inhibit STAT3-mediated gene regulation, block tumour cell proliferation and selectively induce the apoptosis of tumour cells with activated STAT3 (REFS 121–124). In some cases, STAT3 inhibitors possess anti-tumour activity in mouse tumour models, including reducing cancer-promoting immune responses, while promoting anti-tumour immunity[50]. Although none of the STAT3 inhibitors developed to date is considered a clinical candidate, and further work is required to attain this goal, these studies have established proof-of-concept that direct targeting of STAT3 is feasible.

Oligonucleotides, including antisense RNA, small interfering RNA and decoy DNA-binding sites, have also been developed to inhibit STAT3 (REFS 112,125–127). A recent study also demonstrated the feasibility of targeting STAT3, using a conjugate of small interfering RNA linked to a Toll-like receptor ligand, in myeloid, dendritic and B cells through both local and systemic delivery. Knocking down STAT3 in the immune cells by this approach led to anti-tumour effects[128]. Although the clinical applicability of oligonucleotide-based approaches remains to be tested, several studies in animals suggested their potential use to target STAT3 for cancer therapy[128,129]. Another class of STAT3 inhibitors includes natural products and their derivatives with anti-tumour activities, such as cucurbitacin, resveratrol, galiellalactone, curcumin and indirubin[130–132]. The molecular mechanisms of action of these natural product inhibitors, which probably inhibit other oncogenic signalling pathways in addition to STAT3, remain to be fully determined. It is notable that some of these natural products inhibit JAK activity either directly or indirectly. Owing to the importance of IL-6–JAK signalling in inducing STAT3 activation, JAK family kinases (particularly JAK1 and JAK2) are crucial targets for inflammation-induced cancer and cancer-associated inflammation[133,134]. Some of the JAK family kinase inhibitors that block STAT3 signalling

can convert cancer-promoting inflammation to anti-tumour immunity, therefore providing proof-of-concept for this approach[135,136]. Recently, new classes of tyrosine kinase inhibitors that target JAK2 have been identified for clinical development[137].

Several US Food and Drug Administration-approved tyrosine kinase inhibitors already in the clinic, including sorafenib and sunitinib, can inhibit STAT3 signalling indirectly, resulting in tumour cell cycle arrest and apoptosis[138,139]. Sunitinib has further been shown to inhibit STAT3 activity in tumour-associated immune cells, modulating the tumour immunological microenvironment in favour of cancer therapy[139,140]. It inhibits immunosuppressive MDSCs and T regulatory cells in both mouse models and human clinical trials[139–141]. Although the inhibition of STAT3 signalling contributes to the anti-tumour activities of sorafenib and sunitinib, their precise molecular mechanisms of action in terms of STAT3 inhibition remain to be determined.

On the basis of the foregoing discussion, tyrosine kinase inhibitors that modulate the tumour immuno-logical environment by inhibiting STAT3 activity, combined with immunotherapeutic approaches, may lead to increased anti-tumour immune responses. In sum, targeting STAT3 — a central regulatory node on which many oncogenic and inflammatory pathways converge — holds as yet untapped promise for future cancer therapy. In addition to the inhibition of tumour cell proliferation and survival, such STAT3 inhibitors would be predicted to convert inflammation in the tumour microenvironment from tumour promoting to tumour suppressing.

Conclusions

From the earliest pathology studies dating back to the 1800s, cancer has been known to be associated with inflammation. Indeed, many human cancers arise and progress in the setting of chronic inflammatory states. Conversely, there are numerous examples in which induced inflammation and immunity can inhibit tumour growth or even eliminate established tumours. It has become clear that distinct types of inflammation can either promote or inhibit cancer induction and growth. STATs represent central regulators of cancer-associated inflammation and influence interactions between tumour cells and their immune microenvironment that determine whether the inflammation promotes or inhibits cancer. This regulation is accomplished largely through the induction or suppression of specific cytokines and growth factors, as well as through signalling by their cognate receptors. Together with NF-κB, STAT3 is a major mediator of pro-carcinogenic inflammation, and it also opposes NF-κB and STAT1-dependent immune responses that promote anti-tumour immunity. Because of its pivotal role in determining the nature of cancer-associated inflammation, STAT3 represents a promising therapeutic target for converting cancer-promoting inflammation to anti-tumour immunity.

Acknowledgements

We would like to thank members of our laboratories who have made major discoveries in the topics discussed here. We also thank the many laboratories that have contributed important publications relevant to the topics in this Review but which could not be cited owing to space limitations. Special thanks go to L. Wang and J. Deng for helping to prepare the figures and references, R. Buettner for compiling data on STAT3 inhibitors, and M. Kortylewski for critical reading of the manuscript.

Glossary

T_H1	A T_H1 response is mediated by CD4+ T cells and promoted by type 1 interferons and IL-12, this response mediates its effect through cytokines, particularly IFNγ, promoting cellular immune responses against intracellular infections and tumours.
Innate immune cells	Innate immune cells include natural killer cells, macrophages, neutrophils and dendritic cells, which provide immediate non-specific defence against pathogens. These cells identify and destroy virus-, bacteria- and fungus-infected cells and malignant cells.
Myeloid-derived suppressor cells	MDSCs. Heterogenous and plastic cells. When isolated from normal bone marrow, they do not exhibit imunosuppresive effects. However, when exposed to the tumour microenvironment, they inhibit both $CD4^+$ and $CD8^+$ T cells.
T_H17 T cells	Defined by the secretion of IL-17A but not IFNγ or IL-4. T_H17 cells have been implicated in protective immunity to intestinal and pulmonary bacterial infections, as well as pathological immunity in several autoimmune diseases.
Type 1 IFNs	Include multiple family members of the IFNα group and the related IFNβ. All type 1 IFNs bind to a single receptor, termed the type 1 or IFNα receptor. They mediate direct anti-viral activity against infected cells, and can also inhibit tumour growth and promote anti-tumour immune responses.
Natural killer cell	A type of lymphocyte that protects against infectious microbes and kills tumour cells through the recognition of specific cell membrane molecules that are upregulated under conditions of cell stress, such as infection or carcinogenic transformation.
Adaptive immunity	Mediated by antigen-specific T lymphocytes and antibodies produced by B cells. It takes longer to develop than innate immunity but has greater antigen specificity and includes the development of immunological memory.
Dendritic cells	Specialized and the most efficient antigen-presenting cells, which can activate T cells and thereby induce antigen-specific immune responses.
$CD8^+$ T cell	The T cell subset from which cytolytic T cells develop. These in turn directly recognize target cells based on the surface expression of antigenic peptide complexed with MHC I molecules and kill their targets by injecting granzymes that induce apoptosis.
Lamina propria	A constituent of the moist linings of mucous membranes, which line different tubes of the body, including the gastrointestinal tract.
Hyper-IgE syndrome	A rare immune and connective tissue disorder characterized by dermatitis, cyst-forming pneumonia and increased serum levels of

	immunoglobulin E antibody. In some patients it is caused by autosomal dominant *STAT3* mutations.
Decoy DNA-binding sites	DNA oligonucleotides with sequence-specific binding sites that sequester their cognate binding proteins, thereby preventing them from binding to the regulatory sequences of nuclear genes.

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At a glance

- Signal transducer and activator of transcription (STAT) proteins have dual roles: they transduce signals through the cytoplasm and function as transcription factors in the nucleus. Although some STAT proteins such as STAT1 increase anti-tumour immunity, STAT3 and others induce cancer-promoting inflammation.
- STAT3 signalling is a major intrinsic pathway for cancer inflammation owing to its frequent activation in malignant cells and key role in regulating many genes crucial for cancer inflammation in the tumour microenvironment.
- Persistent activation of STAT3, and to a lesser extent STAT5, in diverse human cancers increases proliferation, survival, angiogenesis and metastasis, while also inhibiting anti-tumour immunity.
- Many STAT3-regulated genes encode cytokines and growth factors, the receptors of which in turn activate the same STAT3 pathways, thereby propagating a stable feedforward loop between tumour cells and non-transformed stromal cells, including myeloid cells and T cells, promoting inflammatory responses that further support tumour growth and survival.
- Interleukin-6 (IL-6)–Janus kinase (JAK)–STAT3 signalling is important for cancers resulting from the activation of the intrinsic inflammatory pathway owing to genetic or epigenetic changes in tumour cells. Extrinsic environmental inflammatory factors such as sunlight, pathogens and chemical carcinogens can also activate STAT3 through different mechanisms.
- STAT3 interacts with nuclear factor-κB (NF-κB) at multiple levels and is activated by several NF-κB-regulated gene products, including IL-6. These two transcription factors regulate a multitude of genes important for STAT3 activation and cancer-promoting inflammation.
- STAT1-driven anti-tumour immune responses and STAT3-mediated immune modulatory pathways can be mutually antagonistic, suggesting that therapeutic interventions targeting specific STATs can tip this balance to convert tumour-promoting inflammation to anti-tumour immune responses. Therefore, STAT3 has emerged as a crucial target for cancer therapy and STAT3 inhibitors are actively being developed.
- Several tyrosine kinase inhibitors already in the clinic reduce STAT3 signalling by various mechanisms, thereby inducing tumour cell apoptosis and modulating inflammation in the tumour microenvironment in favour of therapeutic responses.

Box 1

NF-κB signalling and regulation of inflammatory genes

The nuclear factor-κB (NF-κB) family consists of five Rel proteins RELA, REL, RELB, p50 and p52. Among these proteins, only RELA, REL and RELB contain carboxy-terminal transactivation domains that are required for transcriptional activation. All of these proteins contain an amino-terminal Rel-homology domain crucial for dimerization, DNA binding and interaction with inhibitor of NF-κB (IκB) family inhibitors. NF-κB (both the homodimer and the heterodimer forms) is sequestered in the cytoplasm by IκB family proteins. After being phosphorylated by the IκB kinase IKK, IκB undergoes ubiqutin-dependent degradation and releases NF-κB, which then translocates to the nucleus. NF-κB dimers can also form complexes with IκB in the nucleus, and these are exported to the cytoplasm. The RELA–p50 heterodimer is the prototype NF-κB transcription factor. It is crucial for the expression of genes encoding pro-inflammatory mediators, such as interleukin-6 (IL-6), IL-1β, cyclooxygenase 2 and IL-23, which can also be cancer promoting. By contrast, the REL–p50 heterodimer mainly activates expression of T helper 1-immunostimulatory genes, including *IL-12*, *CD40* and *CD80*.

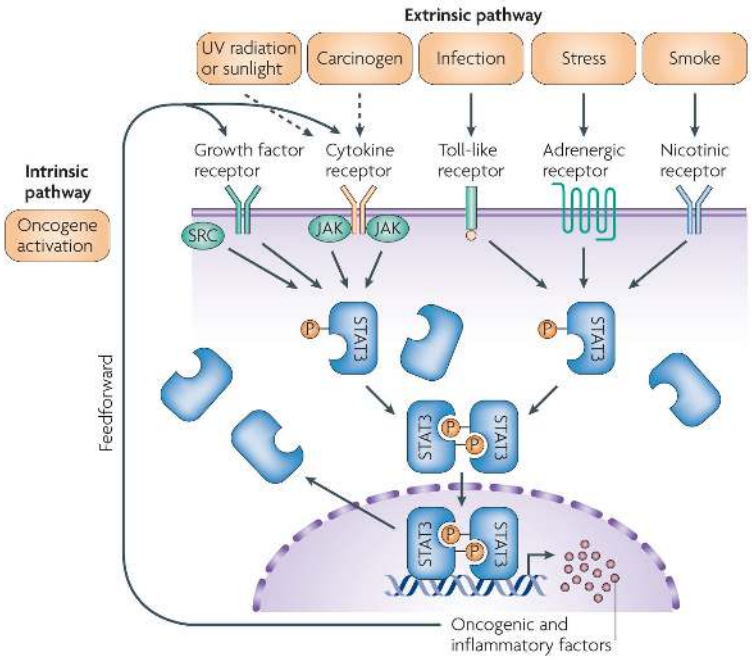

Figure 1. STAT3 connects inflammation and cancer

Inflammation and cancer are linked by both oncogenic (intrinsic) and environmental (extrinsic) pathways. The intrinsic pathway is activated by genetic or epigenetic alterations in transformed cells. Such alterations include those that cause the overexpression or the persistent activation of growth factor receptors with intrinsic tyrosine kinase activity and cytokine receptors with associated Janus kinase (JAK) family tyrosine kinases. Oncogenic mutations in receptor-associated JAK family members also underlie some types of cancer. These receptors (several examples are shown), as well as non-receptor tyrosine kinases such as SRC, can be activated by extrinsic pathways — environmental factors that are associated with cancer inflammation — which include ultraviolet (UV) radiation, chemical carcinogens, infection, stress and cigarette smoke. Activated tyrosine kinases induced by both intrinsic and extrinsic pathways phosphorylate signal transducer and activator of transcription 3 (STAT3), which in turn forms dimers that translocate to the nucleus, where they directly regulate gene expression. In addition to upregulating numerous genes involved in proliferation, survival, invasion and metastasis, STAT3 induces the expression of many cytokines, chemokines and other mediators, such as interleukin-6 and cyclooxygenase 2, that are associated with cancer-promoting inflammation. Importantly, receptors for many of these cytokines, chemokines and mediators in turn further activate STAT3, thus forming autocrine and paracrine feedforward loops that result in a stable change to the genetic programme and the promotion of cancer inflammation. P, phosphorylation.

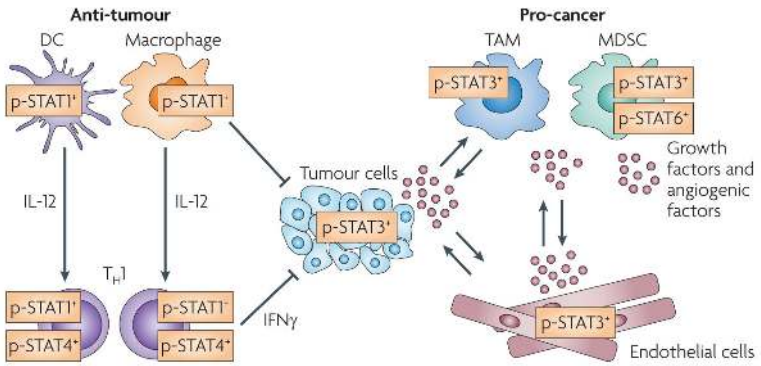

Figure 2. Different STAT proteins modulate pro-cancer and anti-tumour responses by myeloid cells

Myeloid cells, such as dendritic cells (DCs) and macrophages, can stimulate anti-tumour T helper 1 (T_H1) adaptive immunity and even cause direct tumour cell death, which is associated with the production of T_H1 cytokines, including interleukin-12 (IL-12) and interferon-γ (IFNγ). Activation of signal transducer and activator of transcription 1 (STAT1) (p-STAT1 denotes the activated phosphorylated form of STAT1) and STAT4 is important for anti-tumour T_H1 responses. However, tumour-associated macrophages (TAMs) harbouring activated STAT3 (p-STAT3) no longer exhibit anti-tumour effects in the tumour microenvironment. Instead, along with myeloid-derived suppressor cells (MDSCs), TAMs promote cancer progression when STAT3 is activated. Moreover, STAT3 activity in the tumour microenvironment contributes to the expression of pro-cancer inflammatory mediators and angiogenic and growth factors, leading to increased tumour growth. Both activated STAT3 and STAT6 also promote MDSC expansion. Similar STAT3-dependent factors are produced by tumour cells and endothelial cells, forming a crosstalk network among tumour myeloid cells, tumour cells and tumour endothelial cells important for tumour angiogenesis and metastasis.

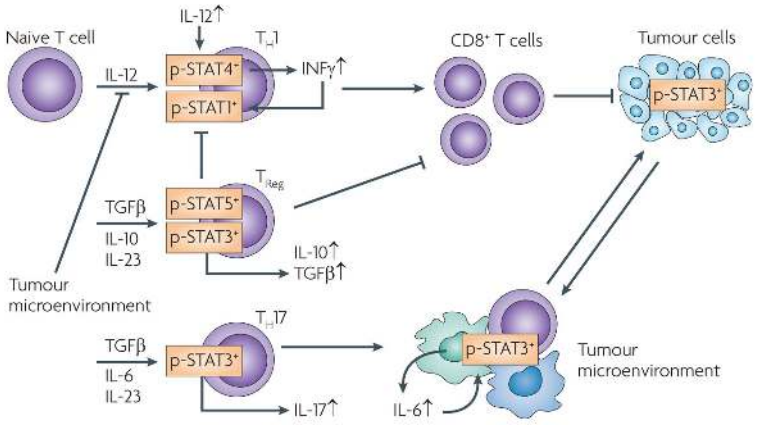

Figure 3. STAT proteins regulate cancer adaptive immunity

Signal transducer and activator of transcription 1 (STAT1) signalling in T cells promotes T helper 1 (T_H1) differentiation and interleukin-12 receptor (IL-12R) expression. IL-12R signalling through STAT4 (p-STAT4 denotes the activated phosphorylated form of STAT4) further promotes T_H1 expansion, which leads to interferon-γ (IFNγ) expression. In the T_H1 milieu, adaptive immune responses control tumour growth. $CD8^+$ T cells have a crucial role in cytotoxicity against tumour cells. Regulatory T (T_{Reg}) cells are important negative regulators of T_H1 anti-tumour immunity. STAT5 is crucial for T_{Reg} cell differentiation and expansion. Both STAT5 and STAT3 contribute to the expression of forkhead box P3, a marker for T_{Reg} cells. At the same time, STAT3 activation in tumour T_{Reg} cells promotes the expression of IL-10 and transforming growth factor-β (TGFβ), which are the mediators of T_{Reg} cell suppressive functions, leading to the downregulation of T_H1 anti-tumour immune responses. In the presence of increased IL-6, TGFβ and IL-23, all of which can be regulated by STAT3 in the tumour microenvironment, T_H17 T cells expand and produce IL-17. This IL-17 activates STAT3 in diverse immune cells and other stromal cells in the tumour microenvironment through IL-6, which can further promote tumour growth.

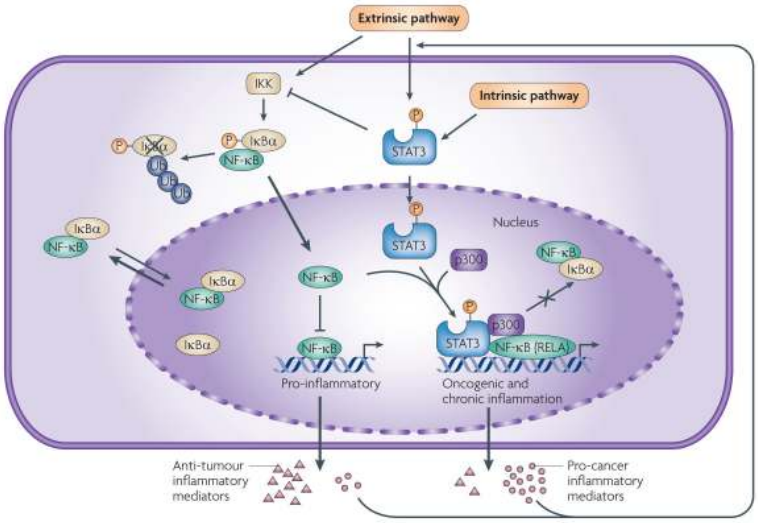

Figure 4. Multilevel interactions between STAT3 and NF-κB

In normal physiology, nuclear factor-κB (NF-κB) is sequestered in the cytoplasm by inhibitor of NF-κBα (IκBα). When IκB kinases (IKKs) are activated by various pathogens and/or proinflammatory cytokines, IκBα is phosphorylated and degraded, allowing NF-κB nuclear translocation (BOX 1). As a transcription factor, NF-κB (especially REL) upregulates many genes involved in stimulating T helper 1 (T_H1) immune responses that are necessary to control pathogens and to mediate anti-tumour immune responses. Several RELA downstream target genes encode factors that in turn activate signal transducer and activator of transcription 3 (STAT3) (TABLE 2). STAT3, which is also activated by intrinsic and extrinsic pathways, has the ability to inhibit IKK and thereby reduce NF-κB-associated T_H1 immunity. In addition, STAT3 contributes to the persistent activation of NF-κB during chronic inflammation and in transformed cells by prolonging nuclear retention of RELA. NF-κB–IκBα complexes can shuttle in and out of the nucleus in the absence of stimuli, although the rate of nuclear export is greater than that of nuclear import. STAT3 facilitates nuclear localization of RELA through p300 (also known as EP300)-mediated acetylation, which interferes with the NF-κB–IκBα interaction and prevents their nuclear export. When STAT3 activity is increased in tumours, NF-κB prefers the STAT3–p300 interaction. Although their cognate DNA-binding sites need not be immediately adjacent, NF-κB and STAT3 regulate the expression of numerous oncogenic and inflammatory mediators (TABLE 2). Many of these gene products in turn further activate STAT3. Therefore, STAT3 and NF-κB interact at multiple levels, thereby promoting cancer inflammation, restraining anti-tumour T_H1 immune responses and increasing tumour cell proliferation and survival as well as tumour angiogenesis and metastasis. P, phosphorylation; Ub, ubiquitylation.

Table 1

STAT family activation by specific cytokines and growth factors, and their target genes

STAT protein	Key activators	Main target genes	Example genes	Refs
STAT1	IFNγ, IFNα and IFNβ	T_H1-type immunostimulatory, and pro-apoptosis	*TBX21*, *CD80*, *CD40*, *IL-12*, *CDKN1A* and several caspases	59
STAT2	IFNα and IFNβ	T_H1-type immunostimulatory, and pro-apoptosis	*CD80* and *CD40*	59,69
STAT3	IL-6, IL-10, IL-23, IL-21, IL-11, LIF and OSM	T_H17-type, anti-apoptosis, pro-proliferation, angiogenic, and metastatic	*IL-17*, *IL-23*, *BCL-X_L*, *BCL-2*, *MCL1*, *CCND1* and *VEGF*	28,38, 57,66, 142–145
STAT4	IL-12	T_H1-type, especially IFNγ	*IFN*γ	59,100
STAT5A and STAT5B	IL-2, GM-CSF, IL-15, IL-7, IL-3, IL-5, growth homones and prolactin	Anti-apoptosis, pro-proliferation, and differentiation	*BCL-X_L*, *CCND2* and *FOXP3*	27, 146,147
STAT6	IL-4 and IL-13	T_H2-type, and anti-apoptosis	*GATA3* and *BCL-2*	59,148

CCND1, cyclin D1; CDKN1A, cyclin-dependent kinase inhibitor 1A; FOXP3, forkhead box P3; GM-CSF, granulocyte-macrophage colony stimulating factor; IFN, interferon; IL, interleukin; LIF, leukaemia inhibitory factor; OSM, oncostatin M; STAT, signal transducer and activator of transcription; TBX21, T-box 21; T_H, T helper; VEGF, vascular endothelial growth factor

Table 2

STAT3 and NF-κB target genes

Gene	Regulated by RELA?	Regulated by REL?	Upregulated by STAT3?*	Downregulated by STAT3?*	STAT3 activators?	Refs
BCL-X$_L$	✓		✓			28,36
MYC	✓		✓			28,36
BIRC5 (which encodes survivin)	✓		✓			28,36
MMP9	✓		✓			28,36
MMP2	✓		✓			28,36
CCND1 (which encodes cyclin D1)	✓		✓			28,36
HIF1α	✓		✓			28,36
ICAM1	✓		✓			36,149
TWIST1	✓		✓			36,150
VIM (which encodes vimentin)	✓		✓			36,151
MCL1			✓			28,152
HSP70 and *HSP90*	✓		✓			153
IL-10			✓		✓	85,101,143
VEGF	✓		✓		✓	4,28,36,154
FGF2 (also known as *BFGF*)	✓		✓		✓	4,84
COX2	✓		✓		✓	36,87
CXCL12 (also known as *SDF1*)			✓		✓	155
IL-11			✓		✓	13
IL-23	✓		✓		✓	5,56
IL-21	✓		✓		✓	142
IL-17	✓		✓		✓	6,39
IL-6	✓		✓	✓	✓	39,85,86,101,111
IL-12A (also known as *P35*)		✓		✓		5,108
CD80	✓	✓		✓		28,111
CD86	✓	✓		✓		28,111
CXCL10 (also known as *IP-10*)	✓			✓		28,156
IFNγ		✓		✓		101,111
IFNβ	✓	✓		✓		86,111
CCL5 (also known as *RANTES*)	✓			✓		86,156
NOS2	✓		✓	✓		36,78,101
IL-8	✓		✓	✓		32,75,111
IL-1β	✓		✓	✓		4,101,111
CCL2 (also known as *MCP1*)	✓		✓	✓		36,98,156,157

CCL, chemokine (C-C motif) ligand; COX2, cyclooxygenase 2; CXCL, chemokine (C-X-C motif) ligand; FGF, fibroblast growth factor; HIF1α, hypoxia inducible factor 1α; HSP, heat shock protein; ICAM1, intercellular adhesion molecule 1; IFN, interferon; IL, interleukin; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; STAT3, signal transducer and activator of transcription 3; VEGF, vascular endothelial growth factor.

* STAT3 inhibits anti-tumour immunostimulatory genes and upregulates genes crucial for oncogenesis and cancer inflammation. This involves a feedforward loop that further activates STAT3 in the tumour microenvironment.