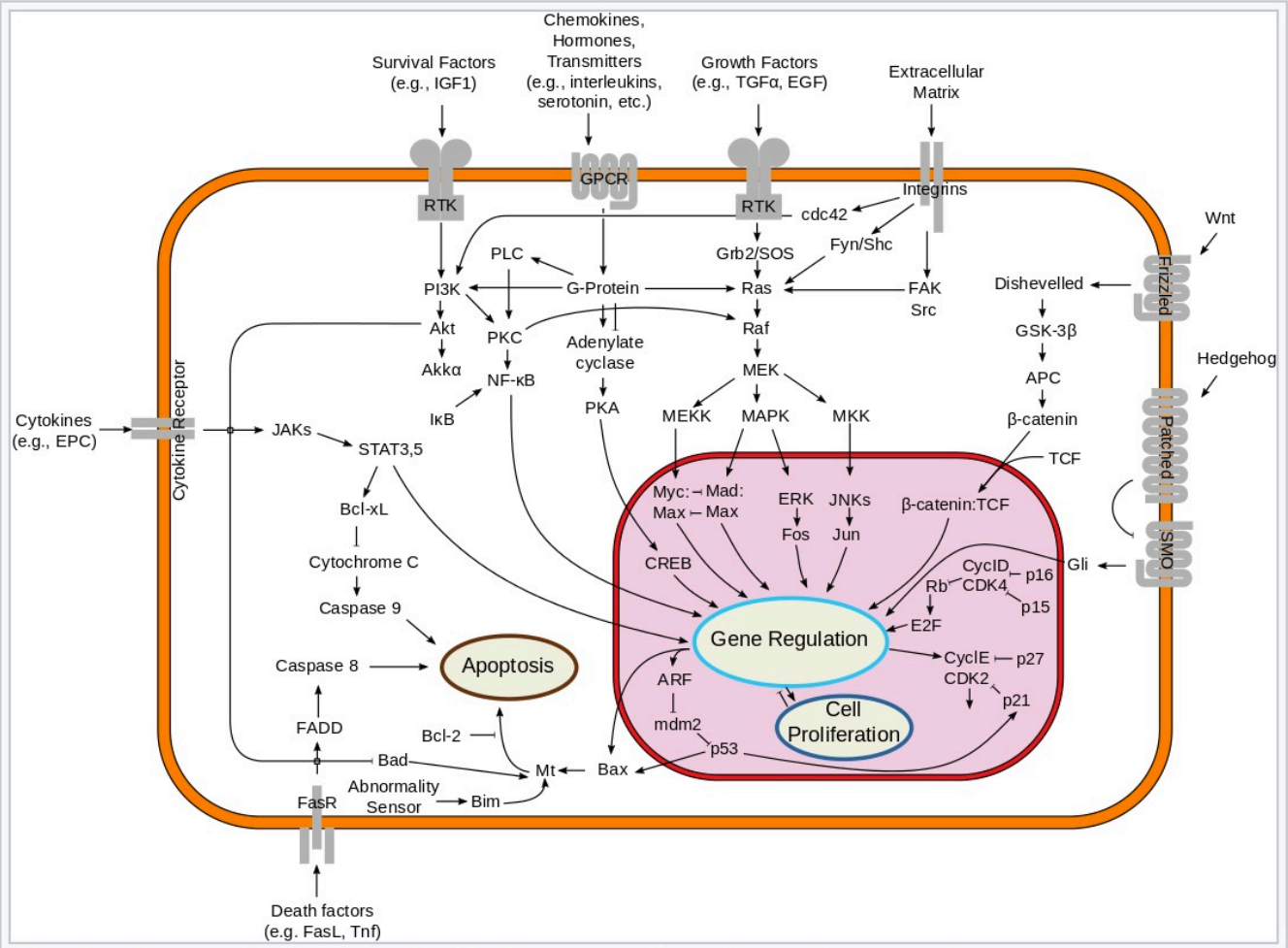
STAT3

Signal transducer and activator of transcription 3, also known as STAT3, is a transcription factor which in humans is encoded by the STAT3 gene.

The protein encoded by this gene is a member of the STAT protein family. In response to cytokines and growth factors, STAT family members are phosphorylated by receptor-associated kinases and then form homo- or heterodimers that translocate to the cell nucleus, where they act as transcription activators. This protein is activated through phosphorylation of tyrosine 705, in response to various cytokines and growth factors including interferons, epidermal growth factor (EGF), Interleukin (IL-)5, IL-6, hepatocyte growth factor (HGF), leukemia inhibitory factor (LIF), bone morphogenetic protein 2 (BMP-2), IL-10, and also the hormone leptin. STAT3 mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis. The small GTPase Rac1 has been shown to bind and regulate the activity of this protein. PIAS3 protein is a specific inhibitor of this protein. Three alternatively spliced transcript variants encoding distinct isoforms have been described.



Simplified representation of major signal transduction pathways in mammals.

The binding of Interleukin 6—family cytokines (including IL-6, oncostatin M and leukemia inhibitory factor) to the gp130 receptor triggers STAT3 phosphorylation by JAK2. Epidermal growth factor receptor and certain other receptor tyrosine kinases, such as c-MET, phosphorylate STAT3 in response to their ligands.

STAT3 is also a target of the c-src non-receptor tyrosine kinase.

STAT3-deficient mouse embryos cannot develop beyond embryonic day 7, when gastrulation begins.

It appears that at these early stages of development, STAT3 activation is required for self-renewal of embryonic stem cells (ESCs). Indeed, LIF, which is supplied to murine ESC cultures to maintain their undifferentiated state, can be omitted if STAT3 is activated through some other means.

STAT3 is essential for the differentiation of the TH17 helper T cells, which have been implicated in a variety of autoimmune diseases.

Loss-of-function mutations in the STAT3 gene result in Hyperimmunoglobulin E syndrome, associated with recurrent infections as well as disordered bone and tooth development.

Gain-of-function mutations in the STAT3 gene have been reported to cause multi-organ early onset auto-immune diseases; such as thyroid disease, diabetes, intestinal inflammation, and low blood counts.

Constitutive STAT3 activation is associated with various human cancers and commonly suggests poor prognosis.

It has anti-apoptotic as well as proliferative effects.

STAT3 can promote oncogenesis by being constitutively active through various pathways as mentioned elsewhere. Very recently a tumor suppressor role of STAT3 has also been reported.

STAT3 and Glioblastoma

Signal transducer and activator of transcription number 3 (STAT3) is an important pathogenic factor in glioblastoma (GBM) and can be specifically inhibited with Stattic. Metformin inhibits GBM cell proliferation and migration. Evidence from other tumor models suggests that metformin inhibits STAT3, but there is no specific data on brain tumor initiating cells (BTICs).We explored proliferation and migration of 7 BTICs and their differentiated counterparts (TCs) after treatment with Stattic, metformin or the combination thereof. Invasion was measured in situ on organotypic brain slice cultures. Protein expression of phosphorylated and total STAT3, as well as AMPK and mTOR signaling were explored using Western blot. To determine functional relevance of STAT3 inhibition by Stattic and metformin, we performed a stable knock-in of STAT3 in selected BTICs.Inhibition of STAT3 with Stattic reduced proliferation in all BTICs, but only in 4 out of 7 TCs. Migration and invasion were equally inhibited in BTICs and TCs. Treatment with metformin reduced STAT3-phosphorylation in all investigated BTICs and TCs. Combined treatment with Stattic and metformin led to significant additive effects on BTIC proliferation, but not migration or invasion. No additive effects on TCs could be detected. Stable STAT3 knock-in partly attenuated the effects of Stattic and metformin on BTICs.In conclusion, metformin was found to inhibit STAT3-phosphorylation in BTICs and TCs. Combined specific and unspecific inhibition of STAT3 might represent a promising new strategy in the treatment of glioblastoma [1)].

In glioblastoma, STAT3 was shown to have an oncogenic or a tumor suppressor role depending upon the mutational background of the tumor. A direct connection between the PTEN-Akt-FOXO axis (suppressive) and the leukemia inhibitory factor receptor beta (LIFRbeta)-STAT3 signaling pathway

(oncogenic) was shown. In addition, two recent studies performed in APC mutant mice showed that STAT3 has an inhibiting role in colon carcinogenesis depending on tumor stage.

Signal transducer and activator of transcription 3 (STAT3), a critical transcriptional activator in tumorigenesis, is persistently phosphorylated and associated with an unfavorable prognosis in glioblastoma multiforme (GBM). Although a set of specific targets has been identified, there have been no systematic analyses of STAT3 signaling based on GBM subtype.

A study compared STAT3-associated messenger RNA, protein, and microRNA expression profiles across different subtypes of GBM.

The analyses revealed a prominent role for STAT3 in the mesenchymal glioblastoma but not in other GBM subtypes, which can be reliably used to classify patients with mesenchymal GBM into 2 groups according to phosphorylated STAT3 expression level. Differentially expressed genes suggest an association between Notch and STAT3 signaling in the mesenchymal subtype. Their association was validated in the U87 cell, a malignant glioma cell line annotated as mesenchymal subtype. Specific associated proteins and microRNAs further profile the STAT3 signaling among GBM subtypes.

These findings suggest a prominent role for STAT3 signaling in mesenchymal GBM and highlight the importance of identifying signaling pathways that contribute to specific cancer subtypes [2)].

Yang et al tested antitumor effects of sorafenib (≤ 10 μM) on four human neuroblastoma cell lines, CHLA255, CHLA171, CHLA90 and SK-N-AS. Sorafenib inhibited cell proliferation and induced apoptosis of neuroblastoma tumor cells in a dose-dependent manner. Sorafenib inhibited phosphorylation of Signal Transducer and Activator of Transcription 3 (STAT3) proteins at Tyr705 in these cells, associated with inhibition of phosphorylated JAK2, an upstream kinase that mediates STAT3 phosphorylation. Expression of a constitutively-activated STAT3 mutant (pSTAT3-C) partially blocked the antitumor effects of sorafenib on neuroblastoma cells. Sorafenib also inhibited the phosphorylation of STAT3 induced by IL-6 and sphingosine-1-phosphate (S1P), a recently identified regulator for STAT3, in these tumor cells. Moreover, sorafenib downregulated phosphorylation of MAPK (p44/42) in neuroblastoma cells, consistent with inhibition of their upstream regulators MEK1/2 [3)].

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3)
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