Biochimica et Biophysica Acta 1815 (2011) 104–114

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

The role of Stat5 transcription factors as tumor suppressors or oncogenes

G. Ferbeyre [a,*], R. Moriggl [b,*]

[a] Département de Biochimie, Université de Montréal, Montréal, Québec H3C 3J7, Canada
[b] Ludwig Boltzmann Institute for Cancer Research, Vienna, Austria

ARTICLE INFO

Article history:
Received 9 September 2010
Received in revised form 8 October 2010
Accepted 8 October 2010
Available online 20 October 2010

Keywords:
Stat5
Jak–Stat signaling
Senescence
Mouse models

ABSTRACT

Stat5 is constitutively activated in many human cancers affecting the expression of cell proliferation and cell survival controlling genes. These oncogenic functions of Stat5 have been elegantly reproduced in mouse models. Aberrant Stat5 activity induces also mitochondrial dysfunction and reactive oxygen species leading to DNA damage. Although DNA damage can stimulate tumorigenesis, it can also prevent it. Stat5 can inhibit tumor progression like in the liver and it is a tumor suppressor in fibroblasts. Stat5 proteins are able to regulate cell differentiation and senescence activating the tumor suppressors SOCS1, p53 and PML. Understanding the context dependent regulation of tumorigenesis through Stat5 function will be central to understand proliferation, survival, differentiation or senescence of cancer cells.

© 2010 Elsevier B.V. All rights reserved.

Contents

* Corresponding authors. G. Ferbeyre is to be contacted at Université de Montréal, Département de Biochimie, E-515, C.P. 6128, Succ. Centre-Ville, Montréal, Qc H3C 3J7. Tel.: +1 514 343 7571; fax: +1 514 343 2210. R. Moriggl, Ludwig Boltzmann Institute for Cancer Research, 1090 Vienna, Austria. Tel.: +43 1427764111; fax: +43 142779641.
E-mail addresses: g.ferbeyre@umontreal.ca (G. Ferbeyre), Richard.Moriggl@lbicr.lbg.ac.at (R. Moriggl).

0304-419X/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbcan.2010.10.004

1. Introduction

Stat5a was discovered as a transcription factor regulating milk protein expression. It was initially called Mammary Gland Factor (MGF) [1] but renamed Stat5 according to homology within the Stat family [2,3]. A follow up manuscript identified that two distinct genes encode two isoforms, named Stat5a and Stat5b [4]. Many cancer relevant cytokines and growth factors were shown to activate Stat5 [5,6] and several steroid hormone receptors synergize with Stat5 activity (Fig. 1). The interest of Stat5 in oncology comes from the initial observations of its activation in many human cancers where it can reside in the nucleus or in the cytoplasm (Fig. 2). Mutations in Stat5 genes have not been found in human tumors, with the exception of myeloid leukemia, where the Stat5b C-terminal part fuses with RARα [7,8]. However, mutations in signaling pathways acting upstream of Stat5 proteins are abundant in many cancer types, especially in those of the hematopoietic system [9]. Surprisingly, recent studies have pointed out to possible tumor suppressor activities of Stat5 in hepatic cells or fibroblasts [10]. Data are emerging that Stat5 proteins control genes with either oncogenic or tumor suppressor activities. The molecular and cellular contexts influencing the gene expression profile and the activities of Stat5 are now under scrutiny. Ideally, interventions to modulate this pathway should aim at inhibiting its oncogenic activities without interfering with tumor suppression. Here we review the contexts where oncogenic and tumor suppressor activities of Stat5 proteins have been described. We discuss and anticipate future progress in the field.

2. Activation of Stat5 proteins and insights from different cancers

It is conceivable that multiple factors such as epigenetic changes, regulation by miRNA [11], altered proteolytic pathways, gene amplification and aberrant growth factor signaling contribute to activation of Stat5 proteins in human cancers [9,12–14] . Phosphorylation of Stat5 by tyrosine kinases is so far the best-documented mechanism of Stat5 activation, especially in hematopoietic cancers (see Fig. 1) but defects in the negative regulatory mechanisms of Stat5 activation mediated by tyrosine phosphatases, SOCS and PIAS family proteins also play important roles. Many hormones such as glucocorticoids, estrogens, progesterones or androgens influence the outcome of Stat5 activation. Physical interactions between hormone regulated transcription factors and Stat5 may account for the effects of these hormones on Stat5-mediated gene transcription (Fig. 1).

2.1. The role of Stat5 protein activation in hematopoietic neoplasms

High Stat5 activity is particularly linked to myeloid cell transformation including granulocyte, macrophage, erythroid and megakaryocyte lineages. Persistent activation of Stat5 was found in chronic myelogenous leukemia (CML), erythroleukemia, acute lymphocytic leukemia (ALL), myeloproliferative diseases (MPDs) like polycythemia vera, thrombocytopenia, idiopathic myelofibrosis, mastocytosis, or severe congenital neutropenia [15,16]. Most frequently, Stat5 activity is induced by hyperactive tyrosine kinases such as Jak2. In fact, Jak2 (V617F) is the most frequently mutated tyrosine kinase in the

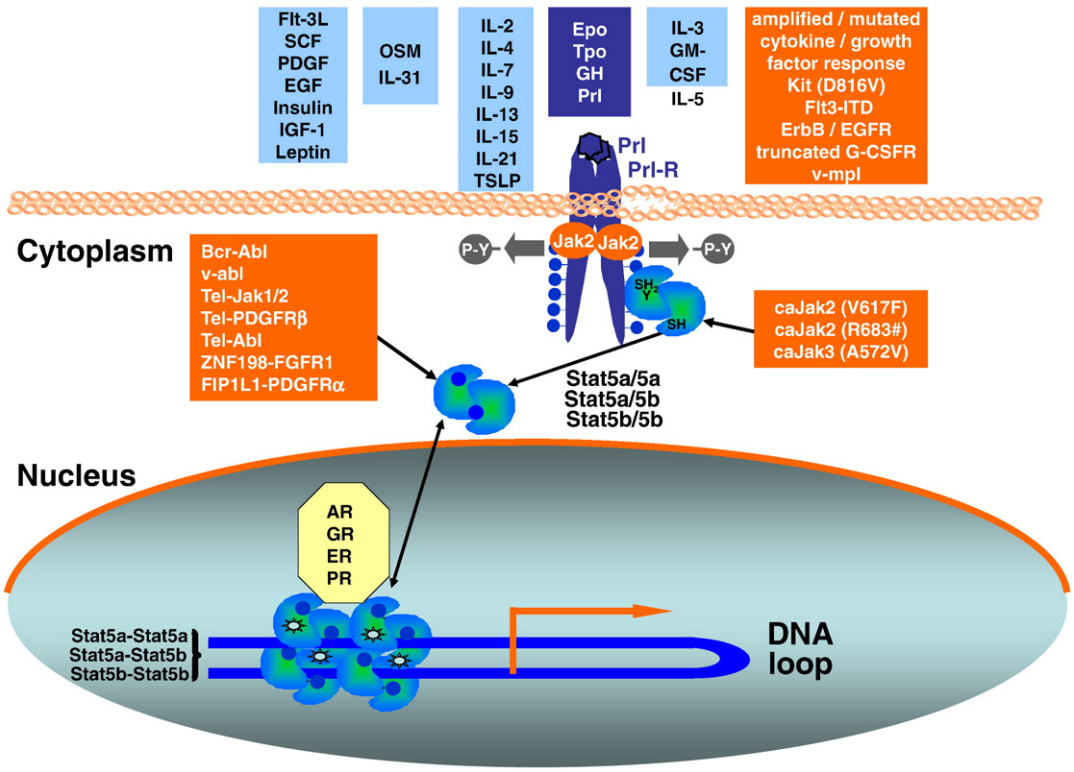

Fig. 1. Stat5 activation by cytokines or growth factors and interaction with nuclear hormone receptors. Exemplified is prolactin receptor signaling. Cytokines, growth factors or mutated components from these signaling pathways are grouped based on their function and protein similarities. Major mutations in tyrosine kinases or fusion of tyrosine kinases are given as detailed and listed in the text. The critical interactions leading to modulation of Stat5 activity may occur in the cytoplasm where the Jak kinases coupled to cytokine receptors phosphorylate Stat5 promoting nuclear translocation. Steroid hormones also influence Stat5 activity via protein–protein interactions between the nuclear receptors (AR, androgen receptor; GR, glucocorticoid receptor; ER, estrogen receptor; PR, progesterone receptor) and Stat5 that modulate promoter recognition and transcriptional activation. Stat5a and Stat5b proteins can form homo- or heterodimers and they can also interact through their N-terminal domain with Stat dimers inducing DNA loop structures on chromatin, so called oligomers. Abbreviations: EGF: (epidermal growth factor receptor); EPO: (erythropoietin); GH: (growth hormone); GM-CSF: (granulocyte-macrophage colony stimulating factor); G-CSF: (granulocyte-colony stimulating factor); IGF-1: (insulin like growth factor-1); IL: (interleukin); OSM: (oncostatin M); PDGF: (platelet derived growth factor); Prl: (prolactin); P-Y: (phospho-tyrosine); SCF: (stem cell factor); TPO: (thrombopoietin); TSLP: (thymic stromal lymphopoietin).

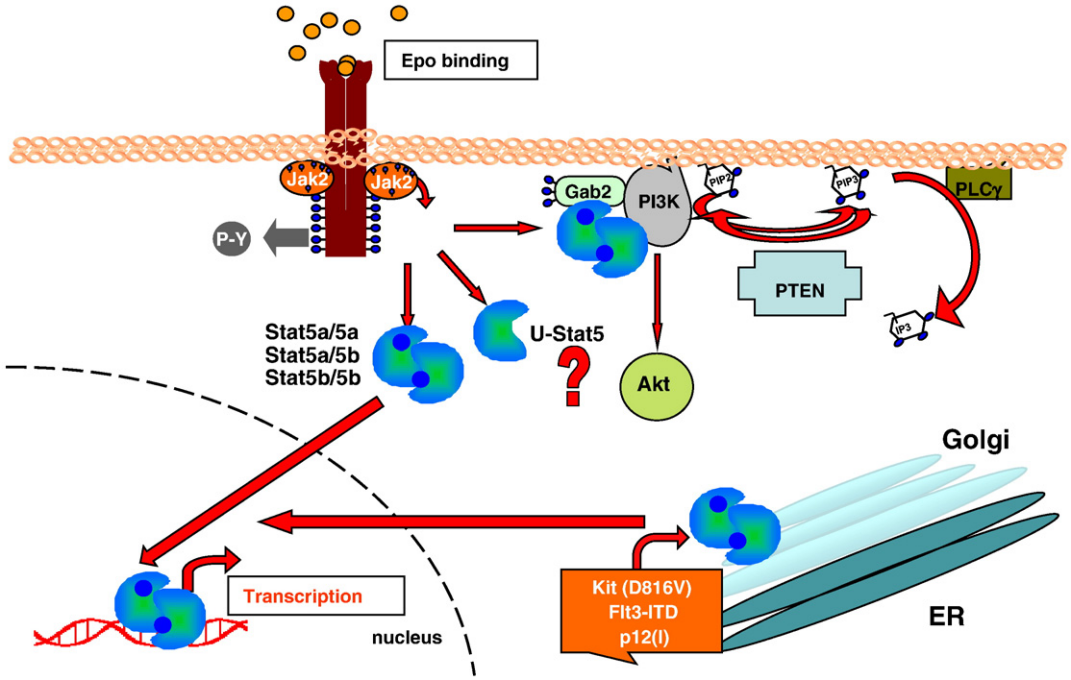

Fig. 2. Canonical and non-canonical Stat5 signaling. Jak2 links Stat5 activation to cytokine receptors such as exemplified with the erythropoietin receptor, while several mutated growth factor receptors such as Flt3-ITD or Kit (D816V) can activate Stat5 from the ER-Golgi membrane networks. Alternatively, also unphosphorylated Stat5 (U-Stat5) might have signaling capacity as implicated in signal transduction from the insulin and insulin like growth factor receptor systems. Activated Stat5 can translocate to the nucleus to regulate gene expression or it can mediate PI3K/Akt signaling in the cytoplasm.

human kinome [17–19]. Recently, nuclear Jak2 was linked with tyrosine phosphorylation of histone H3 tails [20], but it is unknown how nuclear Jak2 may interact with Stat5. Interestingly, different mutations of Jak2 at amino acid position R683 were linked with ALL, which occurs with five times higher frequency in Down's syndrome children [21]. Erythropoietin and thrombopoietin receptor mutations that activate Stat5 have also been found in MPD [13,22–24]. These mutated receptors activate Stat5 via Jak2 [22,23]. Mutations/amplification in growth factor receptor genes such as Kit (D816V) or Flt-3 (ITD) are associated to acute myeloid leukemia (AML) [25–27] and mast cell neoplasms [28,29]. Intriguingly, these receptors activate Stat5 from the endoplasmic reticulum [27,30] (Fig. 2).

Further important drivers for ALL or CML are tyrosine kinase translocation products, which are particularly frequent in leukemias. These include the fusion proteins TEL/JAK2 and BCR/ABL, which activate Stat5 proteins [31–34]. Stat5 activity is important for the transformed phenotype of *bcr/abl*$^{+}$ cells [35–37]. *Bcr/abl* but not *Tel/Jak2* was capable of inducing leukemia in Stat5$^{\Delta N}$ mice [38,39] but it was later shown that this allele was hypomorphic (see below). Using a complete Stat5a/b knockout it was verified that Stat5-deficient fetal liver cells were resistant to transformation by the *v-abl* or *bcr/abl* oncogenes [40]. A subsequent study proved also that leukemia maintenance by the Abelson oncogenes depends on Stat5 protein function [41]. Together these studies justified efforts to target Stat5 in myeloid neoplasms [41–44]. The N-terminal oligomerisation or the C-terminal transactivation domains of Stat5 proteins might serve as attractive protein domains for targeting since they may control differential gene expression by these proteins [45,46].

A general role for Stat5 protein activation in hematopoietic neoplasms came also from mouse transplant models. Retroviral transduction of Stat5 or gain-of-function mutants of Stat5 into hematopoietic cells followed by transplantation into wild type recipient mice caused MPD [46], lymphoblastic lymphoma [47,48] or pre-B lymphomas [49]. Stat5 activation conferred also a strong clonal advantage to myeloid progenitors bearing mutations in the G-CSF receptor [50]. In addition, gain-of-function mutants of Stat5 initiate leukemia formation mainly through promotion of self renewal and survival in myeloid cell types [28,45,46]. The role of Stat5 in lymphomas is less studied, however, the ability of Stat5 to regulate self renewal and Bcl6 in B cells suggest a mechanism by which Stat5 could promote lymphomagenesis [51]. Of interest, IL-21, a Stat5 activator is highly expressed in Hodgkin lymphomas (HL) and expression of constitutively active Stat5 in primary human B cells leads to immortalized cells that look like HL cells [52].

2.2. Activation or inactivation of Stat5 proteins by viruses: HTLV-I and HIV

The human T cell lymphotropic virus-I (HTLV-I) causes adult T cell leukemia and tropical spastic paraparesis. Stat5 is constitutively activated in HTLV-I-transformed cells [53]. The p12(I) protein, encoded by the pX open reading frame I of HTLV-1 contributes to Stat5 activation. This protein localizes to the endoplasmic reticulum and the Golgi and binds to the cytoplasmic domain of the interleukin-2 receptor (IL-2R)β chain in complex with Jak1 and Jak3 kinases (Fig. 2). As a result of this interaction, p12(I) increases Stat5 DNA binding and transcriptional activity [54].

In contrast, HIV viruses use several mechanisms to escape recognition of distinct T cell subsets controlled by Stat5 proteins. Here, down regulation or alteration of Stat5 activation pathways was associated with changed IL-7 signaling [55,56]. A recent study carried out with human and simian immunodeficiency viruses in macaques showed that infection down regulates both Stat5a and Stat5b mRNA and protein expression [57]. These viruses induce as a consequence severe hematopoietic defects. The escape of Stat5-dependent T cell functions by HIV also results in higher tumor incidence, since immunodeficient HIV patients have a higher risk to develop cancer, often associated with additional infectious diseases which themselves drive tumorigenesis.

2.3. Breast cancer

Stat5 proteins are important for the development and functions of the mammary gland [58,59]. Autocrine loops of growth hormone (GH) and prolactin (Prl) were described in breast cancers [60–62], explaining pYStat5 activity in those tumors. There is also experimental data showing that increased GH expression correlates with malignant behavior [63–65]. Stat5 can also be activated by the epidermal growth factor receptor (EGFR/ErbB) pathway [66]. Overall, Stat5 was suggested to have a dual role in breast cancer. On the one hand Stat5 promotes malignant transformation in mammary epithelial cells [67] and it is important for cancer initiation. For example, a dominant-negative Stat5a was able to induce apoptosis in an estrogen positive breast cancer cell line [68] and ablation of one Stat5a allele in mice engineered to express T antigen in mammary epithelial cells was sufficient to reduce tumor incidence [69]. On the other hand, Stat5 activity is related to a better prognosis for patient survival since it indicates mammary epithelial cell differentiation [58,59,70] and delayed metastatic progression. Interestingly, a recent study with breast epithelial cells links Stat5 activation with increased cell survival upon Prl action through direct transcriptional activation of the Akt1 kinase [71].

2.4. Prostate cancer

A large fraction (~95%) of hormone refractory prostate cancer displays persistent Stat5 activity [72], often in association with GH and Prl expression [73,74]. A mouse model of Stat5 activation by Prl recapitulates prostate tumorigenesis from precancerous lesions to invasive carcinoma [75]. High pYStat5 correlates with high histological Gleason grade of human prostate cancer and bad prognosis [74]. Experimental cell line models suggest that high pYStat5 levels maintain the malignant phenotype. Importantly, Stat5 synergizes with the androgen receptor (AR; Fig. 1) increasing nuclear localization and transcriptional activity of Stat5 [72]. Adenoviral gene delivery of a dominant-negative Stat5a mutant induced cell death and inhibited growth or invasive properties of human prostate cancer cells [76,77].

2.5. Lung, head and neck cancers

The Jak–Stat pathway is frequently activated in lung and head and neck cancer [78]. In the lung little is known about a role for Stat5 in tumorigenesis. However, studies by Grandis and colleagues demonstrated that Stat5 contributes to growth and the formation of squamous cell carcinoma of the head and neck (SCCHN) and resistance to EGFR inhibition [79–81]. The mechanism of increased Stat5 activity in these solid tumors is not defined, but activation of Stat5 via Src and the EGFR in SCCHN cell lines was proposed [79,80].

2.6. Liver cancer

Stat5b activation was found in hepatocellular carcinoma (HCC) clinical samples in association with advanced tumor stages. Stat5b enhances HCC aggressiveness through induction of epithelial–mesenchymal transition [82]. In apparent contrast, loss of Stat5 in mice caused steatosis, liver fibrosis and promoted chemically induced liver cancer [83]. This was partly explained by a compensatory pYStat1/pYStat3 and TGF-β axis, where a new role for the Stat5 N-terminus was described in binding directly TGF-β [83,84] (Fig. 3). Alternatively and provoking, it might also hint to a lack of tumor suppressor functions by Stat5 (see Section 5).

2.7. Melanoma

The study of hereditary malignant melanoma in the fish *Xiphophorus* established a link between tyrosine kinase receptors and Stat5 in melanomas [85]. pYStat5 was found in 62% of melanoma patients analyzed [86] and this activation could contribute to resistance to the anti-proliferative activity of interferons [87] and cell survival [88].

2.8. Other malignancies

Furthermore, activated Stat5 was found in intraductal papillary mucinous neoplasms but not in normal pancreatic benign adenomas [89]. Cucurbitacin B, an experimental drug for pancreatic cancer caused dose- and time-dependent G(2)-M-phase arrest and apoptosis

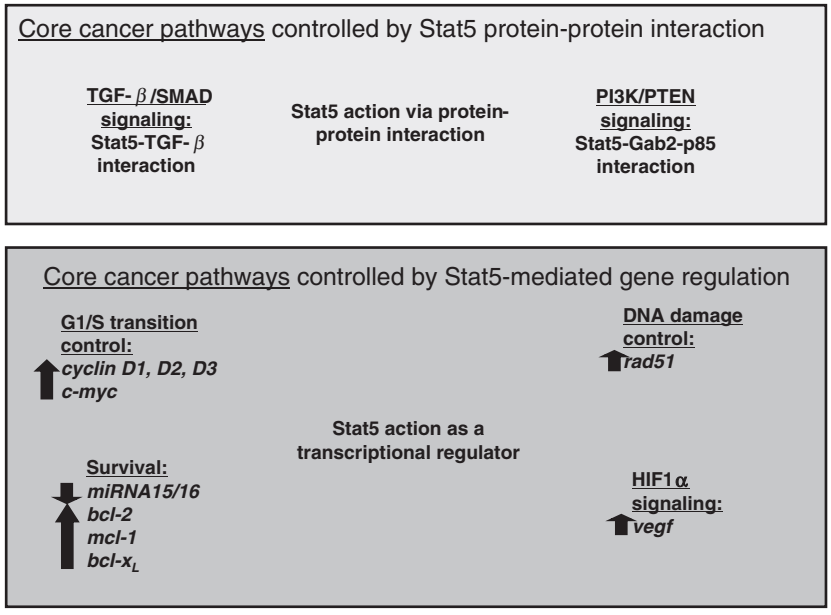

Fig. 3. Core cancer pathways (definition according to Vogelstein and Kinzler [127]) like TGF-β, PI3K/PTEN, HIF1α signaling, survival, G1/S transition or DNA damage control are controlled by Stat5 action. The TGF-β and PI3K/PTEN signaling pathway are directly influenced by Stat5 protein–protein interaction (above). TGF-β can be bound to the Stat5 N-terminus or activated pYStat5 can bind to Gab2, a scaffold molecule activating PI3K/AKT signaling. The HIF1α signaling, survival, G1/S transition or DNA damage control pathways are directly regulated by Stat5 via gene induction (black arrow up) or repression (black arrow down). Key Stat5 target genes for core cancer pathways are indicated by italic names.

of pancreatic cancer cells in association with inhibition of activated Jak2, Stat3, and Stat5 [90]. Stat5 activity was further linked to glioblastoma and colon carcinoma progression or invasion [91,92]. Stat5b was found up regulated in cervical cancers in association with HPV infection while Stat5a was down-regulated [93]. Finally, in ovarian cancer, a link was proposed between Stat5 activation and angiogenesis regulation [94] (Fig. 3).

3. Stat5-regulated transcription: A matter of protein–protein interaction

Stat5 proteins are considered transcriptional activators when tyrosine phosphorylated and bound to DNA. However, they have less strong transactivation domains compared to other Stat family members [95]. On the other hand, Stat5 proteins boost transcription in concerted action with other transcriptional regulators, e.g. the glucocorticoid and androgen receptors (GR; AR; Fig. 1) [13,72,96–100]. Some Stat5 target genes have clusters of Stat5 binding sites (TTCNNNGAA) that may also increase Stat5-transcriptional activity [101–104]. A key factor in target recognition is the interplay between Stat5 dimers and oligomers bound to DNA since the latter can recognize non-consensus elements [105,106].

Stat5 proteins do repress genes [107,108] and microarray studies of cells with gene deletion of Stat5 transcription factors revealed not only significantly down-regulated genes, but also many up regulated genes [104,109,110]. One example is ovarian Stat5b, which represses 20α-hydroxysteroid dehydrogenase [111] or lymphoid Stat5 that represses Igκ recombination [112]. Stat5 proteins were shown to act repressive for primitive and transactivating for definitive erythropoiesis [113]. Interestingly, Stat5 was also shown to repress miRNA15/16, which causes up regulated bcl-2 and bcl-x_L mRNA expression [103]. The underlying mechanism is less studied and it might depend on the concerted action with corepressor molecules or other transcription factors.

Stat5a and Stat5b proteins exert not only overlapping but also distinct functions. This originates from individual cell-specific differences in mRNA levels [80,114–116], slightly different DNA binding specificity [117], altered half life of pYStat5 isoforms, nucleo-cytoplasmic shuttling [118,119] or differential activation by serine phosphorylation [120,121]. The cell type specific differences in Stat5a or Stat5b protein expression have also consequences for cancer initiation or progression. Mammary-directed expression of wild type Stat5a resulted in mammary tumors [122] and both isoforms have differential activities in association with the ERα or ERβ isoforms [117]. In contrast, other tumors like HCC or glioblastoma rely on Stat5b activation [82,91]. These studies indicate that factors controlled by distinct Stat5 isoforms may also modulate organ specific oncogenic functions. One such factor is Bcl6, a well known transcriptional regulator protein in lymphoid, mammary epithelial or liver cells. Stat5b was shown to directly cause Bcl6 up regulation controlling the self renewal of memory B cells [51]. In contrast, Stat5a repressed Bcl6 expression in breast cancer cell lines [123]. Bcl6 recognizes identical DNA sequences as Stat5 and can repress Stat5 actions as shown for mammary gland cell differentiation [123–125]. In turn, Stat5a can repress Bcl6 expression at the level of transcriptional elongation [125,126].

4. Mechanisms of oncogenic activity of Stat5 proteins and target gene regulation

Vogelstein and Kinzler proposed in a landmark paper of 2004 that the majority of cancer mutations affect 12 core pathways [127], Jak–Stat signaling being one of them (Fig. 3). Stat5-target genes [104,128] can drive several other core oncogenic pathways in tumors where Stat5 is activated either through protein–protein interaction or through transcriptional regulation (Fig. 3). It is not understood, what combination of tumor suppressor or oncogene mutations must cooperate to promote and to rely on Stat5 protein function for growth and survival.

4.1. Anti-apoptotic functions of Stat5 proteins

Several Stat5 regulated genes have been implicated in conferring an anti-apoptotic or pro-survival phenotype. These include bcl-2, bcl-x_L, pim-1, A1, serine protease inhibitors Spi2.1 and Spi2.2 and Mcl-1 [103,104,110,128–132]. Interestingly, the pro-apoptotic miRNAs, miR15/16, which repress bcl-2 and bcl-x_L are repressed by Stat5 by a mechanism that required the N-terminal protein–protein interaction with an unknown corepressor [103]. The bcl-2 or bcl-x_L gene loci contain multiple functional Stat5 binding sites, some in the promoter others in the exon–intron region [102,103]. Moreover, Stat5 was shown in mammary epithelial cells to confer survival upon Prl action via direct regulation of the Akt gene locus promoting enhanced Akt1 isoform expression [71].

Pim-1 to -3 belong to a family of serine/threonine kinases involved in the control of cell growth, differentiation and apoptosis [133]. It was proposed that the major expression of Pim-1 is mediated through activation of the Jak–Stat pathway [134]. Pim-2 was induced in cells with Flt3 mutations, but there is no direct proof that pim-2 is a direct Stat5 target gene. Pim kinases might act in a redundant function. Triple deletion of Pim-1 to -3 caused several remarkable similar phenotypes to deletion of Stat5 genes in lymphocytes, myeloid or liver epithelial cells [135].

A role of survival gene induction for oncogenic Stat5 action is beyond doubt. However, Stat5 proteins have also important roles in the cytoplasm to activate the PI3K/Akt kinase cascade through Gab2 adaptor protein interaction (Figs. 2 and 3) [46,136–138]. In colon cancer, cytoplasmic Stat5 controls cell cycle progression, invasion and migration, while in normal colon epithelial cells Stat5 is confined to the nucleus [92].

4.2. Cell proliferation and control through IGF-1 signaling

Activated Stat5 proteins induce genes that accelerate cell cycle progression such as cyclin D2 and c-Myc [40,41,131,139–141] (Figs. 1 and 3). Stat5 plays also an essential role in mediating the growth and cell proliferation effects of GH [97,142]. Hepatic deletion of Stat5 genes caused a defect in GH-induced target genes essential for postnatal body growth, sexual maturation or RNA biosynthesis, similar to hepatic deletion of the GR gene [97,142]. While Stat5a controls the PRL-induced proliferation, differentiation, and function of mammary secretory epithelium, Stat5b is the main actor for hepatocytes and biliary epithelial cells to modulate cellular metabolism and bile regulation to prevent liver fibrosis upon chronic hepatic damage [83,84,143]. An important growth regulatory gene of hepatic Stat5b action is IGF-1 [101,144–147]. Bioactive IGF-1 (in complex with the proteins ALS and IGFBP-3, both well known GH–GHR–Jak2–Stat5b targets) is the key regulator for postnatal body growth and a general growth factor for most cell types [97,148]. GH also inhibits the expression of IGFBP-1 through Stat5b action, which impairs FoxO1 expression [149]. Bioactive IGF-1 is a predisposing factor for many cancer types such as prostate cancer [150], and it may play a role in the blast crisis of CML patients [151]. IGF-1 was also implicated in MPD or AML, since these cells are hypersensitive to IGF-1 stimulation [151–153]. However, it is questionable whether pYStat5 induces IGF-1 in myeloid cells. On the other hand, IGF-1 plays a protective role for chronic liver damage [97,143].

4.3. DNA damage response

DNA damage and the DNA damage response (DDR) represent an early barrier for tumor formation [154–159] and it is one core cancer

pathway (Fig. 3). Hence, modulation of this response is essential for carcinogenesis. Although the DNA damage response prevents cancer formation upon oncogene expression early in the carcinogenesis process, once other mutations inactivate tumor suppression responses, the DNA damage induced by oncogenes can accelerate tumor progression [157,158]. The mechanism by which Stat5 induces DNA damage is not well understood, but as reported for oncogenic *ras* [160], Stat5 can induce changes in mitochondrial functions leading to the production of reactive oxygen species (ROS) and DNA damage [158,161]. The eventual progression of cells with DNA damage along malignant transformation depends not only on the status of the tumor suppressors activated by DNA damage but also on their ability to repair their DNA. Hence, the oncogenic functions of Stat5 may depend on connections to DNA repair genes.

So far, the only well characterized DNA repair gene downstream of Stat5 is RAD51. RAD51 is one of six human homologous proteins of the *E. coli* RecA protein that play a central role in homologous recombination and repair of DNA double-strand breaks (DSBs). DSBs are increased upon high ROS production or upon altered peroxidation, both processes are involved in DNA damage response of many different cancer types and associated with histone H2aX phosphorylation and sensing with ATM/ATR checkpoint control. The expression of RAD51 and several RAD51-paralogs is regulated in a Stat5-dependent manner in BCR/ABL or ZNF198-FGFR1 transformed cells [162,163].

Intriguingly, the Stat5 target genes bcl-2 and bcl-x_L suppress Rad51-dependent homologous recombination [164], mismatch repair [165], and double-strand break repair [166]. The outcome of DNA repair inhibition for tumorigenesis must be context dependent. Suppression of DNA repair pathways can increase the frequency of mutations to promote tumorigenesis. However, during early carcinogenesis, inhibition of repair may reinforce the senescence pathway (see discussion later) that protects normal cells from transformation. Moreover, it is clear that DSBs are induced by chemotherapy treatment, but whether Stat5 activation can change the fate of chemotherapy of cancer cells is not clear.

4.4. Invasion, metastasis and epithelial to mesenchymal transition (EMT)

Active Stat5 promotes invasion and metastasis in prostate cancer. High expression of Stat5 in prostate cancer cells is correlated with low E-cadherin expression and heterotypic adhesion of tumor to endothelial cells [167]. Intriguingly, the opposite was described in breast cancer where induction of Stat5a by Prl inhibited the ability of tumor cells to invade normal tissues and stimulated the expression of the tumor suppressor E-cadherin [168], which enabled epithelial polarity. Moreover, the motility and anchorage independent growth of breast cancer cells was shown to be dependent on protein–protein interactions with the ER in isoform specific way [117].

Stat proteins regulate also the metalloproteinase family. The more motile and invasive phenotype of epithelial cancer cells correlates with epithelial to mesenchymal transition (EMT). Several reports imply Stat5 protein function in EMT [81,82,169], but a role as direct EMT inducer or blocker is still controversial [170].

5. Can Stat5 proteins also function as tumor suppressor proteins?

The Jak–Stat pathway exerts important tumor suppressing functions that are mainly attributed to interferon signaling. In particular, Stat1 is considered a potent tumor suppressor [171], with the exception of leukemia where Stat1 can partly promote leukemogenesis [172]. Hints for a tumor suppressor role for Stat5 proteins were first obtained in breast cancer patients, where activated Stat5 proteins are predictors of good prognosis [173]. Stat5a induced E-cadherin and the association of beta-catenin to the cell surface with homotypic cell clustering through E-Cadherin mediated junctions [168]. Stat5b has hepatoprotective functions in chronic liver damage [83,143]. This is in line with a potential tumor suppressor function. However, it apparently contradicts a report indicating that Stat5b activation contributes to EMT upon hepatitis infection [82]. A recent study has shown that loss of Stat5 in mouse embryonic fibroblasts and hepatocytes leads to enhanced cell cycle progression linked to a lower expression of the CDK inhibitors $p15^{INK4b}$ and $p21^{CIP}$ [10]. This is again consistent with a tumor suppressor role of Stat5 in the liver or in fibroblasts [10].

5.1. Mouse models of Stat5 inactivation

Mouse models of Stat5 inactivation have been described. Single knockout animals are viable but display distinct phenotypes due to expression pattern differences between both isoforms [58,174]. Mice deficient for Stat5a show a defective differentiation of the mammary gland [58]. In contrast, the absence of Stat5b led to dwarfism in males, sexual gene conversion, altered growth hormone (GH) regulated liver enzyme regulation [174] and defects in NK cell activity [175]. The original double knockout, targeting both Stat5a and Stat5b (now referred to as $Stat5^{\Delta N}$) led to incomplete deletion of the coding exons (for overview see [176]). Surprisingly, $Stat5^{\Delta N}$ mice were viable, but they displayed severe defects in the immune system, a block in postnatal body growth in male and females, or a defective female reproductive tract [177]. Today, $Stat5^{\Delta N}$ mice are considered hypomorphic because they express significant levels of N-terminally truncated Stat5a and Stat5b molecules able to enter the nucleus.

A complete double knockout of both Stat5 genes ($Stat5^{Null}$) resulted in no Stat5a/b proteins and diminished hematopoiesis. The animals die on a pure C57Bl/6 or Balb/c genetic background, most likely due to defects in erythropoiesis and iron metabolism [178,179]. Surprisingly, some $Stat5^{Null}$ mice can survive up to eight weeks on a mixed Sv129xC57Bl/6 background. These mice display strong Stat3 tyrosine phosphorylation and it has been proposed that Stat3 may compensate in some tissues for Stat5 loss [40,180]. Irrespective, $Stat5^{Null}$ survivor mice suffer from lymphopenia, develop autoimmune infiltrates or display neutrophil infiltration. They lack $CD8^+$ T, $CD25^+Foxp3^+$ T suppressor, differentiated B or NK cells, to name a few prominent lineage defects (reviewed in [176]).

Whereas mice lacking Stat1 are tumor prone, reports of increased tumor frequency in mouse models of loss of Stat5a or Stat5b function are missing [171]. Stat1 tumor suppressor functions are linked to the induction of growth inhibitory genes such as IRF-1, p21 and caspase 3. In regard to Stat5, mammary-directed expression of a carboxyl-terminally truncated dominant-negative Stat5a form resulted in mammary tumors [122]. It is questionable if single knockouts of Stat5a or Stat5b were analyzed in detail for spontaneous late stage tumor spectra, a theme usually done in ageing models. Certainly, Stat5 is behaving in most tumor types rather oncogenic than anti-tumorigenic, but one must not forget that tumor cells have a reorganization of their gene expression pattern and signaling pathways. This occurs due to mutations and epigenetic silencing of genes that control the cell cycle and cell proliferation. Stat5 can be pro-tumorigenic in the context of the aberrant genetic alterations associated to tumorigenesis while it could suppress tumor formation in normal cells (Fig. 4). How a normal cell overcomes these barriers upon cytokine action might remain a central theme of Stat5 function in cancer cells for the future.

Undoubtedly, long term tumor studies with conditional tumor mouse models are needed to finally elucidate a potential tumor suppressing role for Stat5. Not the least since $Stat5^{Null}$ mice are not viable for longer times and suffer from autoimmune disease and hematopoietic failure. It is also plausible that Stat5 may gain tumor suppressor activities upon its constitutive activation. Therefore, those activities cannot be observed in mouse models with disabled Stat5 protein function as described for senescence induction (see

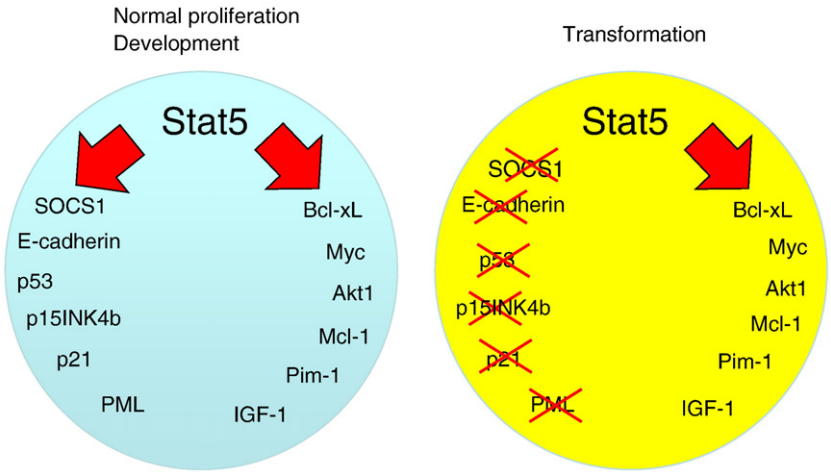

Fig. 4. Two models help to explain context dependent tumor suppression and oncogenic activities of Stat5 proteins. Stat5 activity supports normal proliferation and development under healthy conditions, where it acts mainly tumor suppressive upon acute oncogenic threats (left). However, upon the chronic genetic and epigenetic alterations that characterize tumorigenesis (right), Stat5 activities gain context dependent pro-tumorigenic functions. Key proteins involved in the regulation of proliferation, differentiation, cell cycle arrest or survival are highlighted since they are either directly regulated or influenced by Stat5 activity.

Section 5.3). Moreover, in some tissues loss of Stat5 protein function caused higher Stat1 protein expression. Similarly, loss of Stat5 caused in certain cell types elevated pYStat3 activation levels [98]. However, due to the important role of Stat5 proteins in innate and acquired immunity it is clear that loss of Stat5 protein function in immune cells will have consequences for tumor formation as discussed above with HIV infection.

5.2. Cell differentiation

Constitutively active Stat5a induces on the one hand cell differentiation in mouse transplant models [45,136], but on the other hand it promotes MPD and leukemia progression. These opposing effects suggest cooperating hits which might occur in hematopoietic cancer stem cells which then block largely the differentiation capacity of cytokine induced Stat5 clonally (Fig. 4). Similarly, persistently active Stat5a induces differentiation in mouse leukemia M1 cells through autocrine production of IL-6 [181]. Treatment with Hexamethylenebisacetamide (HMBA) induces cell differentiation and causes tyrosine phosphorylation of Jak2 and Stat5a in murine erythroleukemia cell lines. Other chemical inducers like DMSO and butyrate also induce a sustained activation of Jak2–Stat5 proteins. These results suggest that persistent activation of the Stat5 signaling facilitates differentiation [182]. High Stat5 induction was also shown to promote erythroid differentiation in a GATA-1-dependent context [183], whereas low Stat5a induction was consistent with self renewal of hematopoietic progenitor cells in human $CD34^+$ cells [184].

Stat5 plays also an important role for B and T cell differentiation [40,112], most likely in response to IL-7R signaling, which promotes cell survival and expansion. IL-7-induced Stat5 represses Igκ recombination in pro-B cells. It was shown that it cooperates subsequently with the pre-B cell receptor to facilitate expansion [112]. Moreover, the good prognostic value of Stat5 activity in established breast cancer mirrors Stat5 functions in mammary epithelial cell differentiation.

5.3. Cell senescence

Persistent Stat5a activation can trigger a permanent cell cycle arrest with all the characteristics of cell senescence such as activation of p53, suppression of E2F target gene expression by the retinoblastoma family, activation of the PML-tumor suppressor pathway and a constitutive activation of the DNA damage response [159,185]. This program can be viewed as the response of a normal cell to an activated oncogene but is supported by the direct action of Stat5 on target genes such as SOCS1 [104] and PML [161]. SOCS1 is shown to mediate p53 activation and senescence in response to Stat5 [186]. In addition, SOCS1 was sufficient to induce senescence via p53 [186]. PML is also a regulator of cell senescence downstream of Jak–Stat signaling and like SOCS1, PML is also capable of activating the p53 pathway [187]. These results suggest that Stat5 is part of a signaling pathway that induces PML, SOCS1 and/or p53 in response to cytokines or other oncogenes that may cause senescence.

Many benign tumors show evidence of accumulation of senescent cells leading to the concept that cell senescence keeps benign neoplasms in check [188–195]. In a subset of patients with benign breast tumors it has been found that they express a mutant hyperactive PrlR [196]. It is very plausible that those tumors represent the *in vivo* counterpart of the persistent Stat5a-senescent mechanism we described in primary fibroblasts and primary mammary epithelial cells [159,185]. Differentiation of hematopoietic cells in context of Stat5 activation might mimic partly the senescence phenotype in adherent cells.

6. Concluding remarks

Stat5 protein activation can promote transformation, cell differentiation or senescence. This duality of action is not a particularity of Stat5 signaling since they have been observed for many other oncogenes [197]. We need to understand how mutations in cancer cells overtake tumor suppressive functions of Stat5 enhancing their oncogenic functions. Treatments should focus on restoring this balance rather than achieving a complete inhibition of a particular signaling pathway, which is required in normal cells.

Current biological research has profited from reductionism to understand molecular mechanisms, but cancer is a very heterogeneous and complex disease. We need to study the full spectrum of Stat5 target genes, interacting proteins and post-translational modifications in *in vivo* models of Stat5 activation and suppression. So far, most studies we cited relied on a single cytokine response and consequences for Stat5 gene induction in certain immortalized cell lines at one given time point in tissue culture models. It is time to unravel the molecular basics of more complex actions since cytokines, growth factors and steroid action signal in parallel when measured in cancers. We call for a definition of Stat5-dependent tumor suppression or cancer cell stimulation as subsets of interactions, target genes or post-translational modifications. The definition of those subsets may offer better therapeutic targets than a global alteration of Stat5

functions, which will be probably very toxic. Such challenges will keep Stat5 researchers occupied.

Acknowledgements

We thank Veronika Sexl and Antonis Koromilas for critical reading. This work was supported by grants SFB-F28 from the Austrian Basic Research Funds (FWF) to RM and CIHR 82887 to GF.

References

[1] M. Schmitt-Ney, B. Happ, R.K. Ball, B. Groner, Developmental and environmental regulation of a mammary gland-specific nuclear factor essential for transcription of the gene encoding beta-casein, Proc. Natl Acad. Sci. USA 89 (1992) 3130–3134.
[2] H. Wakao, F. Gouilleux, B. Groner, Mammary gland factor (MGF) is a novel member of the cytokine regulated transcription factor gene family and confers the prolactin response, EMBO J. 13 (1994) 2182–2191.
[3] F. Gouilleux, H. Wakao, M. Mundt, B. Groner, Prolactin induces phosphorylation of Tyr694 of Stat5 (MGF), a prerequisite for DNA binding and induction of transcription, EMBO J. 13 (1994) 4361–4369.
[4] X. Liu, G.W. Robinson, F. Gouilleux, B. Groner, L. Hennighausen, Cloning and expression of Stat5 and an additional homologue (Stat5b) involved in prolactin signal transduction in mouse mammary tissue, Proc. Natl Acad. Sci. USA 92 (1995) 8831–8835.
[5] A.L. Mui, H. Wakao, A.M. O'Farrell, N. Harada, A. Miyajima, Interleukin-3, granulocyte-macrophage colony stimulating factor and interleukin-5 transduce signals through two STAT5 homologs, EMBO J. 14 (1995) 1166–1175.
[6] H. Wakao, N. Harada, T. Kitamura, A.L. Mui, A. Miyajima, Interleukin 2 and erythropoietin activate STAT5/MGF via distinct pathways, EMBO J. 14 (1995) 2527–2535.
[7] C. Arnould, C. Philippe, V. Bourdon, M.J. Grégoire, R. Berger, P. Jonveaux, The signal transducer and activator of transcription STAT5b gene is a new partner of retinoic acid receptor alpha in acute promyelocytic-like leukaemia, Hum. Mol. Genet. 8 (1999) 1741–1749.
[8] S. Dong, D.J. Tweardy, Interactions of STAT5b-RARalpha, a novel acute promyelocytic leukemia fusion protein, with retinoic acid receptor and STAT3 signaling pathways, Blood 99 (2002) 2637–2646.
[9] S.N. Constantinescu, M. Girardot, C. Pecquet, Mining for JAK–STAT mutations in cancer, Trends Biochem. Sci. 33 (2008) 122–131.
[10] J.H. Yu, B.M. Zhu, M. Wickre, G. Riedlinger, W. Chen, A. Hosui, G.W. Robinson, L. Hennighausen, The transcription factors STAT5A and STAT5B negatively regulate cell proliferation through the activation of Cdkn2b and Cdkn1a expression, Hepatology (2010) (Accepted manuscript online: 5 AUG 2010), 52 (2010)1808–1818.
[11] M. Girardot, C. Pecquet, S. Boukour, L. Knoops, A. Ferrant, W. Vainchenker, S. Giraudier, S.N. Constantinescu, miR-28 is a thrombopoietin receptor targeting microRNA detected in a fraction of myeloproliferative neoplasm patient platelets, Blood 116 (2010) 437–445.
[12] Y. Wang, D. Cai, C. Brendel, C. Barett, P. Erben, P.W. Manley, A. Hochhaus, A. Neubauer, A. Burchert, Adaptive secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) mediates imatinib and nilotinib resistance in BCR/ABL+progenitors via JAK-2/STAT-5 pathway activation, Blood 109 (2007) 2147–2155.
[13] C. Pecquet, J. Staerk, R. Chaligne, V. Goss, K.A. Lee, X. Zhang, J. Rush, J. Van Hees, H. A. Poirel, J.M. Scheiff, W. Vainchenker, S. Giraudier, R.D. Polakiewicz, S.N. Constantinescu, Induction of myeloproliferative disorder and myelofibrosis by thrombopoietin receptor W515 mutants is mediated by cytosolic tyrosine 112 of the receptor, Blood 115 (2010) 1037–1048.
[14] O. Kabbarah, L. Chin, Revealing the genomic heterogeneity of melanoma, Cancer Cell 8 (2005) 439–441.
[15] N. Kotecha, N.J. Flores, J.M. Irish, E.F. Simonds, D.S. Sakai, S. Archambeault, E. Diaz-Flores, M. Coram, K.M. Shannon, G.P. Nolan, M.L. Loh, Single-cell profiling identifies aberrant STAT5 activation in myeloid malignancies with specific clinical and biologic correlates, Cancer Cell 14 (2008) 335–343.
[16] A. Ecker, O. Simma, A. Hoelbl, L. Kenner, H. Beug, R. Moriggl, V. Sexl, The dark and the bright side of Stat3: proto-oncogene and tumor-suppressor, Front. Biosci. 14 (2009) 2944–2958.
[17] R. Kralovics, F. Passamonti, A.S. Buser, S.S. Teo, R. Tiedt, J.R. Passweg, A. Tichelli, M. Cazzola, R.C. Skoda, A gain-of-function mutation of JAK2 in myeloproliferative disorders, N Engl J. Med. 352 (2005) 1779–1790.
[18] R. Zhao, S. Xing, Z. Li, X. Fu, Q. Li, S.B. Krantz, Z.J. Zhao, Identification of an acquired JAK2 mutation in polycythemia vera, J. Biol. Chem. 280 (2005) 22788–22792.
[19] S. Aboudola, G. Murugesan, H. Szpurka, G. Ramsingh, X. Zhao, N. Prescott, R.R. Tubbs, J.P. Maciejewski, E.D. Hsi, Bone marrow phospho-STAT5 expression in non-CML chronic myeloproliferative disorders correlates with JAK2 V617F mutation and provides evidence of in vivo JAK2 activation, Am. J. Surg. Pathol. 31 (2007) 233–239.
[20] M.A. Dawson, A.J. Bannister, B. Gottgens, S.D. Foster, T. Bartke, A.R. Green, T. Kouzarides, JAK2 phosphorylates histone H3Y41 and excludes HP1alpha from chromatin, Nature 461 (2009) 819–822.
[21] D. Bercovich, I. Ganmore, L.M. Scott, G. Wainreb, Y. Birger, A. Elimelech, C. Shochat, G. Cazzaniga, A. Biondi, G. Basso, G. Cario, M. Schrappe, M. Stanulla, S. Strehl, O.A. Haas, G. Mann, V. Binder, A. Borkhardt, H. Kempski, J. Trka, B. Bielorei, S. Avigad, B. Stark, O. Smith, N. Dastugue, J.P. Bourquin, N.B. Tal, A.R. Green, S. Izraeli, Mutations of JAK2 in acute lymphoblastic leukaemias associated with Down's syndrome, Lancet 372 (2008) 1484–1492.
[22] S.S. Watowich, X. Xie, U. Klingmuller, J. Kere, M. Lindlof, S. Berglund, A. de la Chapelle, Erythropoietin receptor mutations associated with familial erythrocytosis cause hypersensitivity to erythropoietin in the heterozygous state, Blood 94 (1999) 2530–2532.
[23] A. de la Chapelle, A.L. Traskelin, E. Juvonen, Truncated erythropoietin receptor causes dominantly inherited benign human erythrocytosis, Proc. Natl Acad. Sci. USA 90 (1993) 4495–4499.
[24] R. Kralovics, K. Indrak, T. Stopka, B.W. Berman, J.F. Prchal, J.T. Prchal, Two new EPO receptor mutations: truncated EPO receptors are most frequently associated with primary familial and congenital polycythemias, Blood 90 (1997) 2057–2061.
[25] R. Zheng, M. Levis, O. Piloto, P. Brown, B.R. Baldwin, N.C. Gorin, M. Beran, Z. Zhu, D. Ludwig, D. Hicklin, L. Witte, Y. Li, D. Small, FLT3 ligand causes autocrine signaling in acute myeloid leukemia cells, Blood 103 (2004) 267–274.
[26] D.G. Gilliland, J.D. Griffin, The roles of FLT3 in hematopoiesis and leukemia, Blood 100 (2002) 1532–1542.
[27] F. Hayakawa, M. Towatari, H. Kiyoi, M. Tanimoto, T. Kitamura, H. Saito, T. Naoe, Tandem-duplicated Flt3 constitutively activates STAT5 and MAP kinase and introduces autonomous cell growth in IL-3-dependent cell lines, Oncogene 19 (2000) 624–631.
[28] N. Harir, C. Boudot, K. Friedbichler, K. Sonneck, R. Kondo, S. Martin-Lanneree, L. Kenner, M. Kerenyi, S. Yahiaoui, V. Gouilleux-Gruart, J. Gondry, L. Benit, I. Dusanter-Fourt, K. Lassoued, P. Valent, R. Moriggl, F. Gouilleux, Oncogenic Kit controls neoplastic mast cell growth through a Stat5/PI3-kinase signaling cascade, Blood 112 (2008) 2463–2473.
[29] C. Baumgartner, S. Cerny-Reiterer, K. Sonneck, M. Mayerhofer, K.V. Gleixner, R. Fritz, M. Kerenyi, C. Boudot, F. Gouilleux, J.W. Kornfeld, C. Sillaber, R. Moriggl, P. Valent, Expression of activated STAT5 in neoplastic mast cells in systemic mastocytosis: subcellular distribution and role of the transforming oncoprotein KIT D816V, Am. J. Pathol. 175 (2009) 2416–2429.
[30] K.U. Birkenkamp, M. Geugien, H.H. Lemmink, W. Kruijer, E. Vellenga, Regulation of constitutive STAT5 phosphorylation in acute myeloid leukemia blasts, Leukemia 15 (2001) 1923–1931.
[31] K. Spiekermann, M. Pau, R. Schwab, K. Schmieja, S. Franzrahe, W. Hiddemann, Constitutive activation of STAT3 and STAT5 is induced by leukemic fusion proteins with protein tyrosine kinase activity and is sufficient for transformation of hematopoietic precursor cells, Exp. Hematol. 30 (2002) 262–271.
[32] N. Carlesso, D.A. Frank, J.D. Griffin, Tyrosyl phosphorylation and DNA binding activity of signal transducers and activators of transcription (STAT) proteins in hematopoietic cell lines transformed by Bcr/Abl, J. Exp. Med. 183 (1996) 811–820.
[33] A. Klejman, S.J. Schreiner, M. Nieborowska-Skorska, A. Slupianek, M. Wilson, T.E. Smithgall, T. Skorski, The Src family kinase Hck couples BCR/ABL to STAT5 activation in myeloid leukemia cells, EMBO J. 21 (2002) 5766–5774.
[34] J.M. Ho, B.K. Beattie, J.A. Squire, D.A. Frank, D.L. Barber, Fusion of the ets transcription factor TEL to Jak2 results in constitutive Jak–Stat signaling, Blood 93 (1999) 4354–4364.
[35] C. Sillaber, F. Gesbert, D.A. Frank, M. Sattler, J.D. Griffin, STAT5 activation contributes to growth and viability in Bcr/Abl-transformed cells, Blood 95 (2000) 2118–2125.
[36] R.P. de Groot, J.A. Raaijmakers, J.W. Lammers, R. Jove, L. Koenderman, STAT5 activation by BCR-Abl contributes to transformation of K562 leukemia cells, Blood 94 (1999) 1108–1112.
[37] M. Nieborowska-Skorska, M.A. Wasik, A. Slupianek, P. Salomoni, T. Kitamura, B. Calabretta, T. Skorski, Signal transducer and activator of transcription (STAT)5 activation by BCR/ABL is dependent on intact Src homology (SH)3 and SH2 domains of BCR/ABL and is required for leukemogenesis, J. Exp. Med. 189 (1999) 1229–1242.
[38] V. Sexl, R. Piekorz, R. Moriggl, J. Rohrer, M.P. Brown, K.D. Bunting, K. Rothammer, M.F. Roussel, J.N. Ihle, Stat5a/b contribute to interleukin 7-induced B-cell precursor expansion, but abl- and bcr/abl-induced transformation are independent of stat5, Blood 96 (2000) 2277–2283.
[39] J. Schwaller, E. Parganas, D. Wang, D. Cain, J.C. Aster, I.R. Williams, C.K. Lee, R. Gerthner, T. Kitamura, J. Frantsve, E. Anastasiadou, M.L. Loh, D.E. Levy, J.N. Ihle, D. G. Gilliland, Stat5 is essential for the myelo- and lymphoproliferative disease induced by TEL/JAK2, Mol. Cell 6 (2000) 693–704.
[40] A. Hoelbl, B. Kovacic, M.A. Kerenyi, O. Simma, W. Warsch, Y. Cui, H. Beug, L. Hennighausen, R. Moriggl, V. Sexl, Clarifying the role of Stat5 in lymphoid development and Abelson-induced transformation, Blood 107 (2006) 4898–4906.
[41] A. Hoelbl, C. Schuster, B. Kovacic, B. Zhu, M. Wickre, M.A. Hoelzl, S. Fajmann, F. Grebien, W. Warsch, G. Stengl, L. Hennighausen, V. Poli, H. Beug, R. Moriggl, V. Sexl, Stat5 is indispensable for the maintenance of bcr/abl-positive leukaemia, EMBO Mol. Med. 2 (2010) 98–110.
[42] H. Schepers, D. van Gosliga, A.T. Wierenga, B.J. Eggen, J.J. Schuringa, E. Vellenga, STAT5 is required for long-term maintenance of normal and leukemic human stem/progenitor cells, Blood 110 (2007) 2880–2888.
[43] I.B. Weinstein, Cancer. Addiction to oncogenes—the Achilles heel of cancer, Science 297 (2002) 63–64.
[44] D. Ye, N. Wolff, L. Li, S. Zhang, R.L. Ilaria Jr., STAT5 signaling is required for the efficient induction and maintenance of CML in mice, Blood 107 (2006) 4917–4925.
[45] R. Moriggl, V. Sexl, L. Kenner, C. Duntsch, K. Stangl, S. Gingras, A. Hoffmeyer, A. Bauer, R. Piekorz, D. Wang, K.D. Bunting, E.F. Wagner, K. Sonneck, P. Valent, J.N. Ihle, H. Beug, Stat5 tetramer formation is associated with leukemogenesis, Cancer Cell 7 (2005) 87–99.

[46] G. Li, K.L. Miskimen, Z. Wang, X.Y. Xie, W. Tse, F. Gouilleux, R. Moriggl, K.D. Bunting, Effective targeting of STAT5-mediated survival in myeloproliferative neoplasms using ABT-737 combined with rapamycin, Leukemia 24 (2010) 1397–1405.
[47] K. Bessette, M.L. Lang, R.A. Fava, M. Grundy, J. Heinen, L. Horne, R. Spolski, A. Al-Shami, H.C. Morse III, W.J. Leonard, J.A. Kelly, A Stat5b transgene is capable of inducing CD8+ lymphoblastic lymphoma in the absence of normal TCR/MHC signaling, Blood 111 (2008) 344–350.
[48] J.A. Kelly, R. Spolski, P.E. Kovanen, T. Suzuki, J. Bollenbacher, C.A. Pise-Masison, M.F. Radonovich, S. Lee, N.A. Jenkins, N.G. Copeland, H.C. Morse III, W.J. Leonard, Stat5 synergizes with T cell receptor/antigen stimulation in the development of lymphoblastic lymphoma, J. Exp. Med. 198 (2003) 79–89.
[49] T. Tsuruyama, T. Nakamura, G. Jin, M. Ozeki, Y. Yamada, H. Hiai, Constitutive activation of Stat5a by retrovirus integration in early pre-B lymphomas of SL/Kh strain mice, Proc. Natl Acad. Sci. USA 99 (2002) 8253–8258.
[50] F. Liu, G. Kunter, M.M. Krem, W.C. Eades, J.A. Cain, M.H. Tomasson, L. Hennighausen, D.C. Link, Csf3r mutations in mice confer a strong clonal HSC advantage via activation of Stat5, J. Clin. Invest. 118 (2008) 946–955.
[51] F.A. Scheeren, M. Naspetti, S. Diehl, R. Schotte, M. Nagasawa, E. Wijnands, R. Gimeno, F.A. Vyth-Dreese, B. Blom, H. Spits, STAT5 regulates the self-renewal capacity and differentiation of human memory B cells and controls Bcl-6 expression, Nat. Immunol. 6 (2005) 303–313.
[52] F.A. Scheeren, S.A. Diehl, L.A. Smit, T. Beaumont, M. Naspetti, R.J. Bende, B. Blom, K. Karube, K. Ohshima, C.J. van Noesel, H. Spits, IL-21 is expressed in Hodgkin lymphoma and activates STAT5: evidence that activated STAT5 is required for Hodgkin lymphomagenesis, Blood 111 (2008) 4706–4715.
[53] T.S. Migone, J.X. Lin, A. Cereseto, J.C. Mulloy, J.J. O'Shea, G. Franchini, W.J. Leonard, Constitutively activated Jak–STAT pathway in T cells transformed with HTLV-I, Science 269 (1995) 79–81.
[54] C. Nicot, J.C. Mulloy, M.G. Ferrari, J.M. Johnson, K. Fu, R. Fukumoto, R. Trovato, J. Fullen, W.J. Leonard, G. Franchini, HTLV-1 p12(I) protein enhances STAT5 activation and decreases the interleukin-2 requirement for proliferation of primary human peripheral blood mononuclear cells, Blood 98 (2001) 823–829.
[55] A.M. Crawley, S. Faucher, J.B. Angel, Soluble IL-7Ralpha (sCD127) inhibits IL-7 activity and is increased in HIV infection, J. Immunol. 184 (2010) 4679–4687.
[56] O. Juffroy, F. Bugault, O. Lambotte, I. Landires, J.P. Viard, L. Niel, A. Fontanet, J.F. Delfraissy, J. Theze, L.A. Chakrabarti, Dual mechanism of impairment of interleukin-7 (IL-7) responses in human immunodeficiency virus infection: decreased IL-7 binding and abnormal activation of the JAK/STAT5 pathway, J. Virol. 84 (2010) 96–108.
[57] S. Prost, M. Le Dantec, S. Auge, R. Le Grand, S. Derdouch, G. Auregan, N. Deglon, F. Relouzat, A.M. Aubertin, B. Maillere, I. Dusanter-Fourt, M. Kirszenbaum, Human and simian immunodeficiency viruses deregulate early hematopoiesis through a Nef/PPARgamma/STAT5 signaling pathway in macaques, J. Clin. Invest. 118 (2008) 1765–1775.
[58] X. Liu, G.W. Robinson, K.U. Wagner, L. Garrett, A. Wynshaw-Boris, L. Hennighausen, Stat5a is mandatory for adult mammary gland development and lactogenesis, Genes Dev. 11 (1997) 179–186.
[59] K. Miyoshi, J.M. Shillingford, G.H. Smith, S.L. Grimm, K.U. Wagner, T. Oka, J.M. Rosen, G.W. Robinson, L. Hennighausen, Signal transducer and activator of transcription (Stat) 5 controls the proliferation and differentiation of mammary alveolar epithelium, J. Cell Biol. 155 (2001) 531–542.
[60] M. Raccurt, P.E. Lobie, E. Moudilou, T. Garcia-Caballero, L. Frappart, G. Morel, H.C. Mertani, High stromal and epithelial human gh gene expression is associated with proliferative disorders of the mammary gland, J. Endocrinol. 175 (2002) 307–318.
[61] B.K. Vonderhaar, Prolactin involvement in breast cancer, Endocr Relat Cancer 6 (1999) 389–404.
[62] H.C. Mertani, T. Zhu, E.L. Goh, K.O. Lee, G. Morel, P.E. Lobie, Autocrine human growth hormone (hGH) regulation of human mammary carcinoma cell gene expression. Identification of CHOP as a mediator of hGH-stimulated human mammary carcinoma cell survival, J. Biol. Chem. 276 (2001) 21464–21475.
[63] K.K. Kaulsay, H.C. Mertani, J. Tornell, G. Morel, K.O. Lee, P.E. Lobie, Autocrine stimulation of human mammary carcinoma cell proliferation by human growth hormone, Exp. Cell Res. 250 (1999) 35–50.
[64] S. Mukhina, H.C. Mertani, K. Guo, K.O. Lee, P.D. Gluckman, P.E. Lobie, Phenotypic conversion of human mammary carcinoma cells by autocrine human growth hormone, Proc. Natl Acad. Sci. USA 101 (2004) 15166–15171.
[65] T. Zhu, B. Starling-Emerald, X. Zhang, K.O. Lee, P.D. Gluckman, H.C. Mertani, P.E. Lobie, Oncogenic transformation of human mammary epithelial cells by autocrine human growth hormone, Cancer Res. 65 (2005) 317–324.
[66] M.T. Kloth, A.D. Catling, C.M. Silva, Novel activation of STAT5b in response to epidermal growth factor, J. Biol. Chem. 277 (2002) 8693–8701.
[67] V. Vafaizadeh, P. Klemmt, C. Brendel, K. Weber, C. Doebele, K. Britt, M. Grez, B. Fehse, S. Desrivieres, B. Groner, Mammary epithelial reconstitution with gene-modified stem cells assigns roles to Stat5 in luminal alveolar cell fate decisions, differentiation, involution, and mammary tumor formation, Stem Cells 28 (2010) 928–938.
[68] H. Yamashita, H. Iwase, The role of stat5 in estrogen receptor-positive breast cancer, Breast Cancer 9 (2002) 312–318.
[69] S. Ren, H.R. Cai, M. Li, P.A. Furth, Loss of Stat5a delays mammary cancer progression in a mouse model, Oncogene 21 (2002) 4335–4339.
[70] K.U. Wagner, H. Rui, Jak2/Stat5 signaling in mammogenesis, breast cancer initiation and progression, J. Mammary Gland Biol. Neoplasia 13 (2008) 93–103.
[71] B.A. Creamer, K. Sakamoto, J.W. Schmidt, A.A. Triplett, R. Moriggl, K.U. Wagner, Stat5 promotes survival of mammary epithelial cells through transcriptional activation of a distinct promoter in Akt1, Mol. Cell. Biol. 30 (2010) 2957–2970.
[72] S.H. Tan, A. Dagvadorj, F. Shen, L. Gu, Z. Liao, J. Abdulghani, Y. Zhang, E.P. Gelmann, T. Zellweger, Z. Culig, T. Visakorpi, L. Bubendorf, R.A. Kirken, J. Karras, M.T. Nevalainen, Transcription factor Stat5 synergizes with androgen receptor in prostate cancer cells, Cancer Res. 68 (2008) 236–248.
[73] L.K. Chopin, T.L. Veveris-Lowe, A.F. Philipps, A.C. Herington, Co-expression of GH and GHR isoforms in prostate cancer cell lines, Growth Horm. IGF Res. 12 (2002) 126–136.
[74] H. Li, T.J. Ahonen, K. Alanen, J. Xie, M.J. LeBaron, T.G. Pretlow, E.L. Ealley, Y. Zhang, M. Nurmi, B. Singh, P.M. Martikainen, M.T. Nevalainen, Activation of signal transducer and activator of transcription 5 in human prostate cancer is associated with high histological grade, Cancer Res. 64 (2004) 4774–4782.
[75] V. Rouet, R.L. Bogorad, C. Kayser, K. Kessal, C. Genestie, A. Bardier, D.R. Grattan, B. Kelder, J.J. Kopchick, P.A. Kelly, V. Goffin, Local prolactin is a target to prevent expansion of basal/stem cells in prostate tumors, Proc. Natl Acad. Sci. USA 107 (2010) 15199–15204.
[76] T.J. Ahonen, J. Xie, M.J. LeBaron, J. Zhu, M. Nurmi, K. Alanen, H. Rui, M.T. Nevalainen, Inhibition of transcription factor Stat5 induces cell death of human prostate cancer cells, J. Biol. Chem. 278 (2003) 27287–27292.
[77] A.V. Kazansky, D.M. Spencer, N.M. Greenberg, Activation of signal transducer and activator of transcription 5 is required for progression of autochthonous prostate cancer: evidence from the transgenic adenocarcinoma of the mouse prostate system, Cancer Res. 63 (2003) 8757–8762.
[78] S.Y. Lai, F.M. Johnson, Defining the role of the JAK–STAT pathway in head and neck and thoracic malignancies: implications for future therapeutic approaches, Drug Resist. Updat. 13 (2010) 67–78.
[79] S. Xi, Q. Zhang, W.E. Gooding, T.E. Smithgall, J.R. Grandis, Constitutive activation of Stat5b contributes to carcinogenesis in vivo, Cancer Res. 63 (2003) 6763–6771.
[80] P.L. Leong, S. Xi, S.D. Drenning, K.F. Dyer, A.L. Wentzel, E.C. Lerner, T.E. Smithgall, J.R. Grandis, Differential function of STAT5 isoforms in head and neck cancer growth control, Oncogene 21 (2002) 2846–2853.
[81] P. Koppikar, V.W. Lui, D. Man, S. Xi, R.L. Chai, E. Nelson, A.B. Tobey, J.R. Grandis, Constitutive activation of signal transducer and activator of transcription 5 contributes to tumor growth, epithelial–mesenchymal transition, and resistance to epidermal growth factor receptor targeting, Clin. Cancer Res. 14 (2008) 7682–7690.
[82] T.K. Lee, K. Man, R.T. Poon, C.M. Lo, A.P. Yuen, I.O. Ng, K.T. Ng, W. Leonard, S.T. Fan, Signal transducers and activators of transcription 5b activation enhances hepatocellular carcinoma aggressiveness through induction of epithelial–mesenchymal transition, Cancer Res. 66 (2006) 9948–9956.
[83] A. Hosui, A. Kimura, D. Yamaji, B.M. Zhu, R. Na, L. Hennighausen, Loss of STAT5 causes liver fibrosis and cancer development through increased TGF-{beta} and STAT3 activation, J. Exp. Med. 206 (2009) 819–831.
[84] Y. Cui, A. Hosui, R. Sun, K. Shen, O. Gavrilova, W. Chen, M.C. Cam, B. Gao, G.W. Robinson, L. Hennighausen, Loss of signal transducer and activator of transcription 5 leads to hepatosteatosis and impaired liver regeneration, Hepatology 46 (2007) 504–513.
[85] C. Wellbrock, E. Geissinger, A. Gomez, P. Fischer, K. Friedrich, M. Schartl, Signalling by the oncogenic receptor tyrosine kinase Xmrk leads to activation of STAT5 in *Xiphophorus melanoma*, Oncogene 16 (1998) 3047–3056.
[86] A. Mirmohammadsadegh, M. Hassan, W. Bardenheuer, A. Marini, A. Gustrau, S. Nambiar, A. Tannapfel, H. Bojar, T. Ruzicka, U.R. Hengge, STAT5 phosphorylation in malignant melanoma is important for survival and is mediated through SRC and JAK1 kinases, J. Invest. Dermatol. 126 (2006) 2272–2280.
[87] C. Wellbrock, C. Weisser, J.C. Hassel, P. Fischer, J. Becker, C.S. Vetter, I. Behrmann, M. Kortylewski, P.C. Heinrich, M. Schartl, STAT5 contributes to interferon resistance of melanoma cells, Curr. Biol. 15 (2005) 1629–1639.
[88] J.C. Hassel, D. Winnemoller, M. Schartl, C. Wellbrock, STAT5 contributes to antiapoptosis in melanoma, Melanoma Res. 18 (2008) 378–385.
[89] T.R. Kataoka, T. Ioka, Y. Tsukamoto, M. Matsumura, S. Ishiguro, Y. Nishizawa, Nuclear expression of STAT5 in intraductal papillary mucinous neoplasms of the pancreas, Int. J. Surg. Pathol. 15 (2007) 277–281.
[90] N.H. Thoennissen, G.B. Iwanski, N.B. Doan, R. Okamoto, P. Lin, S. Abbassi, J.H. Song, D. Yin, M. Toh, W.D. Xie, J.W. Said, H.P. Koeffler, Cucurbitacin B induces apoptosis by inhibition of the JAK–STAT pathway and potentiates antiproliferative effects of gemcitabine on pancreatic cancer cells, Cancer Res. 69 (2009) 5876–5884.
[91] Q.C. Liang, H. Xiong, Z.W. Zhao, D. Jia, W.X. Li, H.Z. Qin, J.P. Deng, L. Gao, H. Zhang, G.D. Gao, Inhibition of transcription factor STAT5b suppresses proliferation, induces G1 cell cycle arrest and reduces tumor cell invasion in human glioblastoma multiforme cells, Cancer Lett. 273 (2009) 164–171.
[92] H. Xiong, W.Y. Su, Q.C. Liang, Z.G. Zhang, H.M. Chen, W. Du, Y.X. Chen, J.Y. Fang, Inhibition of STAT5 induces G1 cell cycle arrest and reduces tumor cell invasion in human colorectal cancer cells, Lab. Invest. 89 (2009) 717–725.
[93] R.C. Sobti, N. Singh, S. Hussain, V. Suri, M. Bharadwaj, B.C. Das, Deregulation of STAT-5 isoforms in the development of HPV-mediated cervical carcinogenesis, J. Recept. Signal Transduct. Res. 30 (2010) 178–188.
[94] H. Chen, D. Ye, X. Xie, B. Chen, W. Lu, VEGF, VEGFRs expressions and activated STATs in ovarian epithelial carcinoma, Gynecol. Oncol. 94 (2004) 630–635.
[95] R. Moriggl, S. Berchtold, K. Friedrich, G.J. Standke, W. Kammer, M. Heim, M. Wissler, E. Stocklin, F. Gouilleux, B. Groner, Comparison of the transactivation domains of Stat5 and Stat6 in lymphoid cells and mammary epithelial cells, Mol. Cell. Biol. 17 (1997) 3663–3678.
[96] R. Moriggl, V. Gouilleux-Gruart, R. Jahne, S. Berchtold, C. Gartmann, X. Liu, L. Hennighausen, A. Sotiropoulos, B. Groner, F. Gouilleux, Deletion of the carboxyl-terminal transactivation domain of MGF-Stat5 results in sustained DNA binding and a dominant negative phenotype, Mol. Cell. Biol. 16 (1996) 5691–5700.

[97] D. Engblom, J.W. Kornfeld, L. Schwake, F. Tronche, A. Reimann, H. Beug, L. Hennighausen, R. Moriggl, G. Schutz, Direct glucocorticoid receptor-Stat5 interaction in hepatocytes controls body size and maturation-related gene expression, Genes Dev. 21 (2007) 1157–1162.
[98] H. Dolznig, F. Grebien, E.M. Deiner, K. Stangl, A. Kolbus, B. Habermann, M.A. Kerenyi, M. Kieslinger, R. Moriggl, H. Beug, E.W. Mullner, Erythroid progenitor renewal versus differentiation: genetic evidence for cell autonomous, essential functions of EpoR, Stat5 and the GR, Oncogene 25 (2006) 2890–2900.
[99] E. Stoecklin, M. Wissler, R. Moriggl, B. Groner, Specific DNA binding of Stat5, but not of glucocorticoid receptor, is required for their functional cooperation in the regulation of gene transcription, Mol. Cell. Biol. 17 (1997) 6708–6716.
[100] E. Stocklin, M. Wissler, F. Gouilleux, B. Groner, Functional interactions between Stat5 and the glucocorticoid receptor, Nature 383 (1996) 726–728.
[101] D.J. Chia, B. Varco-Merth, P. Rotwein, Dispersed chromosomal Stat5b-binding elements mediate growth hormone-activated insulin-like growth factor-I gene transcription, J. Biol. Chem. 285 (2010) 17636–17647.
[102] S. Dumon, S.C. Santos, F. Debierre-Grockiego, V. Gouilleux-Gruart, L. Cocault, C. Boucheron, P. Mollat, S. Gisselbrecht, F. Gouilleux, IL-3 dependent regulation of Bcl-xL gene expression by STAT5 in a bone marrow derived cell line, Oncogene 18 (1999) 4191–4199.
[103] G. Li, K.L. Miskimen, Z. Wang, X.Y. Xie, J. Brenzovich, J.J. Ryan, W. Tse, R. Moriggl, K.D. Bunting, STAT5 requires the N-domain for suppression of miR15/16, induction of bcl-2, and survival signaling in myeloproliferative disease, Blood 115 (2010) 1416–1424.
[104] B. Basham, M. Sathe, J. Grein, T. McClanahan, A. D'Andrea, E. Lees, A. Rascle, In vivo identification of novel STAT5 target genes, Nucleic Acids Res. 36 (2008) 3802–3818.
[105] E. Soldaini, S. John, S. Moro, J. Bollenbacher, U. Schindler, W.J. Leonard, DNA binding site selection of dimeric and tetrameric Stat5 proteins reveals a large repertoire of divergent tetrameric Stat5a binding sites, Mol. Cell. Biol. 20 (2000) 389–401.
[106] S. John, U. Vinkemeier, E. Soldaini, J.E. Darnell Jr., W.J. Leonard, The significance of tetramerization in promoter recruitment by Stat5, Mol. Cell. Biol. 19 (1999) 1910–1918.
[107] G. Luo, L. Yu-Lee, Transcriptional inhibition by Stat5. Differential activities at growth-related versus differentiation-specific promoters, J. Biol. Chem. 272 (1997) 26841–26849.
[108] A.B. Maurer, C. Wichmann, A. Gross, H. Kunkel, T. Heinzel, M. Ruthardt, B. Groner, M. Grez, The Stat5-RARalpha fusion protein represses transcription and differentiation through interaction with a corepressor complex, Blood 99 (2002) 2647–2652.
[109] K.H. Clodfelter, M.G. Holloway, P. Hodor, S.H. Park, W.J. Ray, D.J. Waxman, Sex-dependent liver gene expression is extensive and largely dependent upon signal transducer and activator of transcription 5b (STAT5b): STAT5b-dependent activation of male genes and repression of female genes revealed by microarray analysis, Mol. Endocrinol. 20 (2006) 1333–1351.
[110] M. Gatzka, R. Piekorz, R. Moriggl, J. Rawlings, J.N. Ihle, A role for STAT5A/B in protection of peripheral T-lymphocytes from postactivation apoptosis: insights from gene expression profiling, Cytokine 34 (2006) 143–154.
[111] R.P. Piekorz, S. Gingras, A. Hoffmeyer, J.N. Ihle, Y. Weinstein, Regulation of progesterone levels during pregnancy and parturition by signal transducer and activator of transcription 5 and 20alpha-hydroxysteroid dehydrogenase, Mol. Endocrinol. 19 (2005) 431–440.
[112] S. Malin, S. McManus, C. Cobaleda, M. Novatchkova, A. Delogu, P. Bouillet, A. Strasser, M. Busslinger, Role of STAT5 in controlling cell survival and immunoglobulin gene recombination during pro-B cell development, Nat. Immunol. 11 (2010) 171–179.
[113] M. Schmerer, I. Torregroza, A. Pascal, M. Umbhauer, T. Evans, STAT5 acts as a repressor to regulate early embryonic erythropoiesis, Blood 108 (2006) 2989–2997.
[114] P.M. Grimley, F. Dong, H. Rui, Stat5a and Stat5b: fraternal twins of signal transduction and transcriptional activation, Cytokine Growth Factor Rev. 10 (1999) 131–157.
[115] L. Hennighausen, G.W. Robinson, Interpretation of cytokine signaling through the transcription factors STAT5A and STAT5B, Genes Dev. 22 (2008) 711–721.
[116] J.Z. Tang, Z.H. Zuo, X.J. Kong, M. Steiner, Z. Yin, J.K. Perry, T. Zhu, D.X. Liu, P.E. Lobie, Signal transducer and activator of transcription (STAT)-5A and STAT5B differentially regulate human mammary carcinoma cell behavior, Endocrinology 151 (2010) 43–55.
[117] J. Frasor, K. Park, M. Byers, C. Telleria, T. Kitamura, L.Y. Yu-Lee, J. Djiane, O.K. Park-Sarge, G. Gibori, Differential roles for signal transducers and activators of transcription 5a and 5b in PRL stimulation of ERalpha and ERbeta transcription, Mol. Endocrinol. 15 (2001) 2172–2181.
[118] R. Zeng, Y. Aoki, M. Yoshida, K. Arai, S. Watanabe, Stat5B shuttles between cytoplasm and nucleus in a cytokine-dependent and -independent manner, J. Immunol. 168 (2002) 4567–4575.
[119] J. Iyer, N.C. Reich, Constitutive nuclear import of latent and activated STAT5a by its coiled coil domain, FASEB J. 22 (2008) 391–400.
[120] H. Yamashita, J. Xu, R.A. Erwin, W.L. Farrar, R.A. Kirken, H. Rui, Differential control of the phosphorylation state of proline-juxtaposed serine residues Ser725 of Stat5a and Ser730 of Stat5b in prolactin-sensitive cells, J. Biol. Chem. 273 (1998) 30218–30224.
[121] K. Friedbichler, M.A. Kerenyi, B. Kovacic, G. Li, A. Hoelbl, S. Yahiaoui, V. Sexl, E.W. Mullner, S. Fajmann, S. Cerny-Reiterer, P. Valent, H. Beug, F. Gouilleux, K.D. Bunting, R. Moriggl, Stat5a serine 725 and 779 phosphorylation is a prerequisite for hematopoietic transformation, Blood 116 (2010) 1548–1558.
[122] E. Iavnilovitch, R.D. Cardiff, B. Groner, I. Barash, Deregulation of Stat5 expression and activation causes mammary tumors in transgenic mice, Int. J. Cancer 112 (2004) 607–619.
[123] T.H. Tran, F.E. Utama, J. Lin, N. Yang, A.B. Sjolund, A. Ryder, K.J. Johnson, L.M. Neilson, C. Liu, K.L. Brill, A.L. Rosenberg, A.K. Witkiewicz, H. Rui, Prolactin inhibits BCL6 expression in breast cancer through a Stat5a-dependent mechanism, Cancer Res. 70 (2010) 1711–1721.
[124] S. Logarajah, P. Hunter, M. Kraman, D. Steele, S. Lakhani, L. Bobrow, A. Venkitaraman, S. Wagner, BCL-6 is expressed in breast cancer and prevents mammary epithelial differentiation, Oncogene 22 (2003) 5572–5578.
[125] S.R. Walker, E.A. Nelson, D.A. Frank, STAT5 represses BCL6 expression by binding to a regulatory region frequently mutated in lymphomas, Oncogene 26 (2007) 224–233.
[126] R.D. Meyer, E.V. Laz, T. Su, D.J. Waxman, Male-specific hepatic Bcl6: growth hormone-induced block of transcription elongation in females and binding to target genes inversely coordinated with STAT5, Mol. Endocrinol. 23 (2009) 1914–1926.
[127] B. Vogelstein, K.W. Kinzler, Cancer genes and the pathways they control, Nat. Med. 10 (2004) 789–799.
[128] E.A. Nelson, S.R. Walker, W. Li, X.S. Liu, D.A. Frank, Identification of human STAT5-dependent gene regulatory elements based on interspecies homology, J. Biol. Chem. 281 (2006) 26216–26224.
[129] F. Gesbert, J.D. Griffin, Bcr/Abl activates transcription of the Bcl-X gene through STAT5, Blood 96 (2000) 2269–2276.
[130] M. Nieborowska-Skorska, G. Hoser, P. Kossev, M.A. Wasik, T. Skorski, Complementary functions of the antiapoptotic protein A1 and serine/threonine kinase pim-1 in the BCR/ABL-mediated leukemogenesis, Blood 99 (2002) 4531–4539.
[131] M. Huang, J.F. Dorsey, P.K. Epling-Burnette, R. Nimmanapalli, T.H. Landowski, L.B. Mora, G. Niu, D. Sinibaldi, F. Bai, A. Kraker, H. Yu, L. Moscinski, S. Wei, J. Djeu, W.S. Dalton, K. Bhalla, T.P. Loughran, J. Wu, R. Jove, Inhibition of Bcr-Abl kinase activity by PD180970 blocks constitutive activation of Stat5 and growth of CML cells, Oncogene 21 (2002) 8804–8816.
[132] K.J. Aichberger, M. Mayerhofer, M.T. Krauth, H. Skvara, S. Florian, K. Sonneck, C. Akgul, S. Derdak, W.F. Pickl, V. Wacheck, E. Selzer, B.P. Monia, R. Moriggl, P. Valent, C. Sillaber, Identification of mcl-1 as a BCR/ABL-dependent target in chronic myeloid leukemia (CML): evidence for cooperative antileukemic effects of imatinib and mcl-1 antisense oligonucleotides, Blood 105 (2005) 3303–3311.
[133] M. Lilly, A. Kraft, Enforced expression of the Mr 33,000 Pim-1 kinase enhances factor-independent survival and inhibits apoptosis in murine myeloid cells, Cancer Res. 57 (1997) 5348–5355.
[134] T. Nosaka, T. Kawashima, K. Misawa, K. Ikuta, A.L. Mui, T. Kitamura, STAT5 as a molecular regulator of proliferation, differentiation and apoptosis in hematopoietic cells, EMBO J. 18 (1999) 4754–4765.
[135] H. Mikkers, M. Nawijn, J. Allen, C. Brouwers, E. Verhoeven, J. Jonkers, A. Berns, Mice deficient for all PIM kinases display reduced body size and impaired responses to hematopoietic growth factors, Mol. Cell. Biol. 24 (2004) 6104–6115.
[136] N. Harir, C. Pecquet, M. Kerenyi, K. Sonneck, B. Kovacic, R. Nyga, M. Brevet, I. Dhennin, V. Gouilleux-Gruart, H. Beug, P. Valent, K. Lassoued, R. Moriggl, F. Gouilleux, Constitutive activation of Stat5 promotes its cytoplasmic localization and association with PI3-kinase in myeloid leukemias, Blood 109 (2007) 1678–1686.
[137] K.D. Bunting, X.Y. Xie, I. Warshawsky, E.D. Hsi, Cytoplasmic localization of phosphorylated STAT5 in human acute myeloid leukemia is inversely correlated with Flt3-ITD, Blood 110 (2007) 2775–2776.
[138] G. Li, Z. Wang, K.L. Miskimen, Y. Zhang, W. Tse, K.D. Bunting, Gab2 promotes hematopoietic stem cell maintenance and self-renewal synergistically with STAT5, PLoS ONE 5 (2010) e9152.
[139] A. Martino, J.H.t. Holmes, J.D. Lord, J.J. Moon, B.H. Nelson, Stat5 and Sp1 regulate transcription of the cyclin D2 gene in response to IL-2, J. Immunol. 166 (2001) 1723–1729.
[140] N. Jena, M. Deng, E. Sicinska, P. Sicinski, G.Q. Daley, Critical role for cyclin D2 in BCR/ABL-induced proliferation of hematopoietic cells, Cancer Res. 62 (2002) 535–541.
[141] B.N. Friedrichsen, H.E. Richter, J.A. Hansen, C.J. Rhodes, J.H. Nielsen, N. Billestrup, A. Moldrup, Signal transducer and activator of transcription 5 activation is sufficient to drive transcriptional induction of cyclin D2 gene and proliferation of rat pancreatic beta-cells, Mol. Endocrinol. 17 (2003) 945–958.
[142] F. Tronche, C. Opherk, R. Moriggl, C. Kellendonk, A. Reimann, L. Schwake, H.M. Reichardt, K. Stangl, D. Gau, A. Hoeflich, H. Beug, W. Schmid, G. Schutz, Glucocorticoid receptor function in hepatocytes is essential to promote postnatal body growth, Genes Dev. 18 (2004) 492–497.
[143] L. Blaas, J.W. Kornfeld, D. Schramek, M. Musteanu, G. Zollner, J. Gumhold, F. van Zijl, D. Schneller, H. Esterbauer, G. Egger, M. Mair, L. Kenner, W. Mikulits, R. Eferl, R. Moriggl, J. Penninger, M. Trauner, E. Casanova, Disruption of the growth hormone–signal transducer and activator of transcription 5–insulin like growth factor 1 axis severely aggravates liver fibrosis in a mouse model of cholestasis, Hepatology 51 (2010) 1319–1326.
[144] I. Meton, E.P. Boot, J.S. Sussenbach, P.H. Steenbergh, Growth hormone induces insulin-like growth factor-I gene transcription by a synergistic action of STAT5 and HNF-1alpha, FEBS Lett. 444 (1999) 155–159.
[145] H.W. Davey, T. Xie, M.J. McLachlan, R.J. Wilkins, D.J. Waxman, D.R. Grattan, STAT5b is required for GH-induced liver IGF-I gene expression, Endocrinology 142 (2001) 3836–3841.
[146] J. Woelfle, J. Billiard, P. Rotwein, Acute control of insulin-like growth factor-I gene transcription by growth hormone through Stat5b, J. Biol. Chem. 278 (2003) 22696–22702.

[147] J. Woelfle, D.J. Chia, P. Rotwein, Mechanisms of growth hormone (GH) action. Identification of conserved Stat5 binding sites that mediate GH-induced insulin-like growth factor-I gene activation, J. Biol. Chem. 278 (2003) 51261–51266.
[148] P. Klover, W. Chen, B.M. Zhu, L. Hennighausen, Skeletal muscle growth and fiber composition in mice are regulated through the transcription factors STAT5a/b: linking growth hormone to the androgen receptor, FASEB J. 23 (2009) 3140–3148.
[149] M. Ono, D.J. Chia, R. Merino-Martinez, A. Flores-Morales, T.G. Unterman, P. Rotwein, Signal transducer and activator of transcription (Stat) 5b-mediated inhibition of insulin-like growth factor binding protein-1 gene transcription: a mechanism for repression of gene expression by growth hormone, Mol. Endocrinol. 21 (2007) 1443–1457.
[150] M.A. Rowlands, D. Gunnell, R. Harris, L.J. Vatten, J.M. Holly, R.M. Martin, Circulating insulin-like growth factor peptides and prostate cancer risk: a systematic review and meta-analysis, Int. J. Cancer 124 (2009) 2416–2429.
[151] A. Lakshmikuttyamma, E. Pastural, N. Takahashi, K. Sawada, D.P. Sheridan, J.F. DeCoteau, C.R. Geyer, Bcr-Abl induces autocrine IGF-1 signaling, Oncogene 27 (2008) 3831–3844.
[152] A.E. Wahner Hendrickson, P. Haluska, P.A. Schneider, D.A. Loegering, K.L. Peterson, R. Attar, B.D. Smith, C. Erlichman, M. Gottardis, J.E. Karp, J.M. Carboni, S.H. Kaufmann, Expression of insulin receptor isoform A and insulin-like growth factor-1 receptor in human acute myelogenous leukemia: effect of the dual-receptor inhibitor BMS-536924 in vitro, Cancer Res. 69 (2009) 7635–7643.
[153] K.T. Doepfner, O. Spertini, A. Arcaro, Autocrine insulin-like growth factor-I signaling promotes growth and survival of human acute myeloid leukemia cells via the phosphoinositide 3-kinase/Akt pathway, Leukemia 21 (2007) 1921–1930.
[154] J. Bartkova, Z. Horejsi, K. Koed, A. Kramer, F. Tort, K. Zieger, P. Guldberg, M. Sehested, J.M. Nesland, C. Lukas, T. Orntoft, J. Lukas, J. Bartek, DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis, Nature 434 (2005) 864–870.
[155] J. Bartkova, N. Rezaei, M. Liontos, P. Karakaidos, D. Kletsas, N. Issaeva, L.V. Vassiliou, E. Kolettas, K. Niforou, V.C. Zoumpourlis, M. Takaoka, H. Nakagawa, F. Tort, K. Fugger, F. Johansson, M. Sehested, C.L. Andersen, L. Dyrskjot, T. Orntoft, J. Lukas, C. Kittas, T. Helleday, T.D. Halazonetis, J. Bartek, V.G. Gorgoulis, Oncogene-induced senescence is part of the tumorigenesis barrier imposed by DNA damage checkpoints, Nature 444 (2006) 633–637.
[156] R. Di Micco, M. Fumagalli, A. Cicalese, S. Piccinin, P. Gasparini, C. Luise, C. Schurra, M. Garre, P.G. Nuciforo, A. Bensimon, R. Maestro, P.G. Pelicci, F. d'Adda di Fagagna, Oncogene-induced senescence is a DNA damage response triggered by DNA hyper-replication, Nature 444 (2006) 638–642.
[157] V.G. Gorgoulis, L.V. Vassiliou, P. Karakaidos, P. Zacharatos, A. Kotsinas, T. Liloglou, M. Venere, R.A. Ditullio Jr., N.G. Kastrinakis, B. Levy, D. Kletsas, A. Yoneta, M. Herlyn, C. Kittas, T.D. Halazonetis, Activation of the DNA damage checkpoint and genomic instability in human precancerous lesions, Nature 434 (2005) 907–913.
[158] F.A. Mallette, G. Ferbeyre, The DNA damage signaling pathway connects oncogenic stress to cellular senescence, Cell Cycle (Georgetown Tex.) 6 (2007) 1831–1836.
[159] F.A. Mallette, M.F. Gaumont-Leclerc, G. Ferbeyre, The DNA damage signaling pathway is a critical mediator of oncogene-induced senescence, Genes Dev. 21 (2007) 43–48.
[160] O. Moiseeva, V. Bourdeau, A. Roux, X. Deschenes-Simard, G. Ferbeyre, Mitochondrial dysfunction contributes to oncogene-induced senescence, Mol. Cell. Biol. 29 (2009) 4495–4507.
[161] F.A. Mallette, O. Moiseeva, V. Calabrese, B. Mao, M.F. Gaumont-Leclerc, G. Ferbeyre, Transcriptome analysis and tumor suppressor requirements of STAT5-induced senescence, Ann. NY Acad. Sci. 1197 (2010) 142–151.
[162] A. Slupianek, G. Hoser, I. Majsterek, A. Bronisz, M. Malecki, J. Blasiak, R. Fishel, T. Skorski, Fusion tyrosine kinases induce drug resistance by stimulation of homology-dependent recombination repair, prolongation of G(2)/M phase, and protection from apoptosis, Mol. Cell. Biol. 22 (2002) 4189–4201.
[163] C. Heath, N.C. Cross, Critical role of STAT5 activation in transformation mediated by ZNF198-FGFR1, J. Biol. Chem. 279 (2004) 6666–6673.
[164] Y. Saintigny, A. Dumay, S. Lambert, B.S. Lopez, A novel role for the Bcl-2 protein family: specific suppression of the RAD51 recombination pathway, EMBO J. 20 (2001) 2596–2607.
[165] Y. Hou, F. Gao, Q. Wang, J. Zhao, T. Flagg, Y. Zhang, X. Deng, Bcl2 impedes DNA mismatch repair by directly regulating the hMSH2–hMSH6 heterodimeric complex, J. Biol. Chem. 282 (2007) 9279–9287.
[166] Q. Wang, F. Gao, W.S. May, Y. Zhang, T. Flagg, X. Deng, Bcl2 negatively regulates DNA double-strand-break repair through a nonhomologous end-joining pathway, Mol. Cell 29 (2008) 488–498.
[167] L. Gu, P. Vogiatzi, M. Puhr, A. Dagvadorj, J. Lutz, A. Ryder, S. Addya, P. Fortina, C. Cooper, B. Leiby, A. Dasgupta, T. Hyslop, L. Bubendorf, K. Alanen, T. Mirtti, M.T. Nevalainen, Stat5 promotes metastatic behavior of human prostate cancer cells in vitro and in vivo, Endocr. Relat. Cancer 17 (2010) 481–493.
[168] A.S. Sultan, J. Xie, M.J. LeBaron, E.L. Ealley, M.T. Nevalainen, H. Rui, Stat5 promotes homotypic adhesion and inhibits invasive characteristics of human breast cancer cells, Oncogene 24 (2005) 746–760.
[169] S.A. Benitah, P.F. Valeron, H. Rui, J.C. Lacal, STAT5a activation mediates the epithelial to mesenchymal transition induced by oncogenic RhoA, Mol. Biol. Cell 14 (2003) 40–53.
[170] A.S. Sultan, H. Brim, Z.A. Sherif, Co-overexpression of Janus kinase 2 and signal transducer and activator of transcription 5a promotes differentiation of mammary cancer cells through reversal of epithelial–mesenchymal transition, Cancer Sci. 99 (2008) 272–279.
[171] C. Schindler, D.E. Levy, T. Decker, JAK–STAT signaling: from interferons to cytokines, J. Biol. Chem. 282 (2007) 20059–20063.
[172] B. Kovacic, D. Stoiber, R. Moriggl, E. Weisz, R.G. Ott, R. Kreibich, D.E. Levy, H. Beug, M. Freissmuth, V. Sexl, STAT1 acts as a tumor promoter for leukemia development, Cancer Cell 10 (2006) 77–87.
[173] M.T. Nevalainen, J. Xie, J. Torhorst, L. Bubendorf, P. Haas, J. Kononen, G. Sauter, H. Rui, Signal transducer and activator of transcription-5 activation and breast cancer prognosis, J. Clin. Oncol. 22 (2004) 2053–2060.
[174] G.B. Udy, R.P. Towers, R.G. Snell, R.J. Wilkins, S.H. Park, P.A. Ram, D.J. Waxman, H. W. Davey, Requirement of STAT5b for sexual dimorphism of body growth rates and liver gene expression, Proc. Natl Acad. Sci. USA 94 (1997) 7239–7244.
[175] K. Imada, E.T. Bloom, H. Nakajima, J.A. Horvath-Arcidiacono, G.B. Udy, H.W. Davey, W.J. Leonard, Stat5b is essential for natural killer cell-mediated proliferation and cytolytic activity, J. Exp. Med. 188 (1998) 2067–2074.
[176] J.W. Kornfeld, F. Grebien, M.A. Kerenyi, K. Friedbichler, B. Kovacic, B. Zankl, A. Hoelbl, H. Nivarti, H. Beug, V. Sexl, M. Muller, L. Kenner, E.W. Mullner, F. Gouilleux, R. Moriggl, The different functions of Stat5 and chromatin alteration through Stat5 proteins, Front. Biosci. 13 (2008) 6237–6254.
[177] S. Teglund, C. McKay, E. Schuetz, J.M. van Deursen, D. Stravopodis, D. Wang, M. Brown, S. Bodner, G. Grosveld, J.N. Ihle, Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses, Cell 93 (1998) 841–850.
[178] M.A. Kerenyi, F. Grebien, H. Gehart, M. Schifrer, M. Artaker, B. Kovacic, H. Beug, R. Moriggl, E.W. Mullner, Stat5 regulates cellular iron uptake of erythroid cells via IRP-2 and TfR-1, Blood 112 (2008) 3878–3888.
[179] B.M. Zhu, S.K. McLaughlin, R. Na, J. Liu, Y. Cui, C. Martin, A. Kimura, G.W. Robinson, N.C. Andrews, L. Hennighausen, Hematopoietic-specific Stat5-null mice display microcytic hypochromic anemia associated with reduced transferrin receptor gene expression, Blood 112 (2008) 2071–2080.
[180] Z. Yao, Y. Kanno, M. Kerenyi, G. Stephens, L. Durant, W.T. Watford, A. Laurence, G. W. Robinson, E.M. Shevach, R. Moriggl, L. Hennighausen, C. Wu, J.J. O'Shea, Nonredundant roles for Stat5a/b in directly regulating Foxp3, Blood 109 (2007) 4368–4375.
[181] T. Kawashima, K. Murata, S. Akira, Y. Tonozuka, Y. Minoshima, S. Feng, H. Kumagai, H. Tsuruga, Y. Ikeda, S. Asano, T. Nosaka, T. Kitamura, STAT5 induces macrophage differentiation of M1 leukemia cells through activation of IL-6 production mediated by NF-kappaB p65, J. Immunol. 167 (2001) 3652–3660.
[182] T. Yamashita, H. Wakao, A. Miyajima, S. Asano, Differentiation inducers modulate cytokine signaling pathways in a murine erythroleukemia cell line, Cancer Res. 58 (1998) 556–561.
[183] A.T. Wierenga, E. Vellenga, J.J. Schuringa, Down-regulation of GATA1 uncouples STAT5-induced erythroid differentiation from stem/progenitor cell proliferation, Blood 115 (2010) 4367–4376.
[184] A.T. Wierenga, E. Vellenga, J.J. Schuringa, Maximal STAT5-induced proliferation and self-renewal at intermediate STAT5 activity levels, Mol. Cell. Biol. 28 (2008) 6668–6680.
[185] F.A. Mallette, M.F. Gaumont-Leclerc, G. Huot, G. Ferbeyre, Myc down-regulation as a mechanism to activate the Rb pathway in STAT5A-induced senescence, J. Biol. Chem. 282 (2007) 34938–34944.
[186] V. Calabrese, F.A. Mallette, X. Deschenes-Simard, S. Ramanathan, J. Gagnon, A. Moores, S. Ilangumaran, G. Ferbeyre, SOCS1 links cytokine signaling to p53 and senescence, Mol. Cell 36 (2009) 754–767.
[187] V. Bourdeau, D. Baudry, G. Ferbeyre, PML links aberrant cytokine signaling and oncogenic stress to cellular senescence, Front. Biosci. 14 (2009) 475–485.
[188] P. Castro, D. Giri, D. Lamb, M. Ittmann, Cellular senescence in the pathogenesis of benign prostatic hyperplasia, Prostate 55 (2003) 30–38.
[189] P. Castro, C. Xia, L. Gomez, D.J. Lamb, M. Ittmann, Interleukin-8 expression is increased in senescent prostatic epithelial cells and promotes the development of benign prostatic hyperplasia, Prostate 60 (2004) 153–159.
[190] J. Choi, I. Shendrik, M. Peacocke, D. Peehl, R. Buttyan, E.F. Ikeguchi, A.E. Katz, M.C. Benson, Expression of senescence-associated beta-galactosidase in enlarged prostates from men with benign prostatic hyperplasia [In Process Citation], Urology 56 (2000) 160–166.
[191] S. Courtois-Cox, S.M. Genther Williams, E.E. Reczek, B.W. Johnson, L.T. McGillicuddy, C.M. Johannessen, P.E. Hollstein, M. MacCollin, K. Cichowski, A negative feedback signaling network underlies oncogene-induced senescence, Cancer Cell 10 (2006) 459–472.
[192] V.C. Gray-Schopfer, S.C. Cheong, H. Chong, J. Chow, T. Moss, Z.A. Abdel-Malek, R. Marais, D. Wynford-Thomas, D.C. Bennett, Cellular senescence in naevi and immortalisation in melanoma: a role for p16? Br. J. Cancer 95 (2006) 496–505.
[193] C. Michaloglou, L.C. Vredeveld, M.S. Soengas, C. Denoyelle, T. Kuilman, C.M. van der Horst, D.M. Majoor, J.W. Shay, W.J. Mooi, D.S. Peeper, BRAFE600-associated senescence-like cell cycle arrest of human naevi, Nature 436 (2005) 720–724.
[194] M. Collado, M.A. Blasco, M. Serrano, Cellular senescence in cancer and aging, Cell 130 (2007) 223–233.
[195] M. Collado, J. Gil, A. Efeyan, C. Guerra, A.J. Schuhmacher, M. Barradas, A. Benguria, A. Zaballos, J.M. Flores, M. Barbacid, D. Beach, M. Serrano, Tumour biology: senescence in premalignant tumours, Nature 436 (2005) 642.
[196] R.L. Bogorad, C. Courtillot, C. Mestayer, S. Bernichtein, L. Harutyunyan, J.B. Jomain, A. Bachelot, F. Kuttenn, P.A. Kelly, V. Goffin, P. Touraine, Identification of a gain-of-function mutation of the prolactin receptor in women with benign breast tumors, Proc. Natl Acad. Sci. USA 105 (2008) 14533–14538.
[197] S.V. Sharma, J. Settleman, Exploiting the balance between life and death: targeted cancer therapy and "oncogenic shock", Biochem. Pharmacol. 80 (2010) 666–673.