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Review Article

The two faces of Janus kinases and their respective STATs in mammary gland development and cancer

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Abstract

Since its discovery as "just another kinase" more than twenty years ago, the family of JAK tyrosine kinases and their respective Signal Transducers and Activators of Transcription (STATs) has been a center of attention in the areas of signal transduction, development, and cancer. The subsequent designation of JAKs as Janus kinases after the mythical two-faced Roman God of the doorways accurately portrays the analogous and sometimes contrasting molecular and biological characteristics of these tyrosine kinases. The two "faces" of JAKs are their structurally similar kinase and pseudo-kinase domains. As essential parts of various transmembrane receptor complexes, these tyrosine kinases function at cellular gateways and relay signals from growth factors to their respective intracellular targets. The multifaceted nature of JAKs becomes evident from their ability to activate specific STATs during distinct phases of normal mammary gland development. Studies in breast cancer cells and genetically engineered mouse models also show that JAK/STAT signaling possesses a "two-faced" role during breast cancer initiation and progression. This review will highlight recent findings about important biological functions of JAKs and STATs during normal mammogenesis, with particular emphasis on the Jak2/Stat5 pathway as well as Jak1/2/Stat3 signaling complexes. In addition, we will discuss how the importance of these signaling networks changes during carcinogenesis. With JAK inhibitors currently under development to treat myeloproliferative disorders, determining the essential functions of JAKs at particular stages of disease initiation and progression is of critical importance to predict the efficacy of these agents for targeted therapies against breast cancer.

Keywords: Breast cancer, Janus kinase, mammary gland, protein–tyrosine kinase, signal transducers and activators of transcription, signal transduction, transcription factors

SEQUENTIAL JAK-MEDIATED ACTIVATION OF STATs DURING NORMAL MAMMOGENESIS

Among the different human cell types, Janus kinase (JAK)/ Signal Transducer and Activator of Transcription (STAT) signaling cascades transduce signals of more than 50 cytokines and peptide hormones.[1] A subset of these growth factors such as prolactin (PRL), growth hormone (GH), leukemia inhibitory factor (LIF), and oncostatin M (OSM) are crucial for mammary epithelial cell proliferation, differentiation, and apoptosis. The binding of these ligands to their respective receptors induces a conformational change that autoactivates the receptor-associated Janus tyrosine kinases through transphosphorylation of tyrosine residues. Active JAKs then phosphorylate critical tyrosines on the cytoplasmic portion of the receptor, thereby creating docking sites for the Src

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homology 2 (SH2)-domains of Signal Transducers and Activators of Transcription (STATs) that are subsequently phosphorylated by JAKs at conserved tyrosine residues. Activated STATs form stable homo- or heterodimers through reciprocal SH2–phosphotyrosine interactions and translocate to the nucleus where they function as latent transcription factors by binding to conserved recognition sites.[2-4]

The mammalian family of Janus kinases is composed of four members: Jak1, Jak2, Jak3, and the tyrosine kinase 2 (Tyk2). Among these, Jak1 and Jak2 are expressed in many tissues, including normal and neoplastic mammary epithelial cells. In contrast, the expression of Jak3 and Tyk2 is mostly limited to hematopoietic cells, and these kinases have not been subject to intensive studies in breast cancer. In normal mammary epithelial cells, Jak2 is known to mediate signals through single-chain receptors, in particular, the PRL-R and GH-R.[5] Jak1, on the other hand, is suggested to function together with Jak2 in signal transduction of gp130 receptor ligands such as LIF and OSM.[3] However, it has yet to be determined using gene deletion models that Jak1 and Jak2 are each necessary or sufficient to relay signals through these particular multi-chain receptors in the mammary gland. As described later, various hormones and cytokines such as PRL and LIF can initiate a completely different response (e.g., cell survival versus apoptosis) in epithelial subtypes, and therefore, Jak1 and Jak2 have multifaceted functions at particular stages of mammary gland development.

Depending on the cell type and ligand–receptor complex, each JAK activates one or more of the seven members of the STAT family: Stat1–4, Stat5a, Stat5b, and Stat6. With the exception of Stat2, all other STATs are expressed, albeit at various levels, throughout mammary gland development.[6] The expression of Stat4 could not be detected in cultured mammary epithelial cells, and it was therefore concluded that this signal transducer might be predominantly activated in the mammary stroma.[7] Although the transcriptional activation of the genes encoding Stat1, Stat3, Stat5a, Stat5b, and Stat6 may vary to some degree throughout the gestation cycle, the Jak1/Jak2-mediated phosphorylation of these signal transducers in response to specific growth factors is the key event for their activation and functionality. During postnatal mammary gland development, the sequential activation of individual STATs is precisely regulated. Elevated levels of Stat1 phosphorylation are found in the nulliparous and parous gland following postlactational remodeling.[7] Very recently, Klover *et al*.[8] reported the generation of a Stat1 conditional knockout model, and surprisingly, the deletion of this particular signal transducer using MMTV-Cre and WAP-Cre transgenics did not affect the functionality of the mammary gland in nulliparous or lactating females. In addition to Stat1, a basal activation of Stat5a and Stat5b occurs in response to PRL signaling in luminal epithelial cells within the ductal compartment of nonpregnant women and female mice.[9,10] The significant increase in the level of PRL during pregnancy leads to a very substantial elevation in the expression and activation of Stat5 and consequentially an upregulation of milk protein genes.[11,7] Stat5a, which has been originally identified as the 'mammary gland factor' (MGF),[12] is more abundant compared to Stat5b in the functionally differentiated mammary epithelium.[11,13] Similar to Stat5, Stat6 becomes increasingly phosphorylated during pregnancy when a significant subset of mammary epithelial cells switches from the production of interleukin (IL)12A, tumor necrosis factor (TNF)α, and interferon gamma (IFNγ) to the secretion of IL4, IL13, and IL5 in response to pregnancy hormones, including PRL.[14] This might also explain why the phosphorylation of Stat1, which is a main downstream effector of IFNγ signaling, is lower during this stage of mammogenesis. Finally, the activation of Stat3 within less than 24 hours following weaning the offspring heralds the beginning of the postlactational remodeling period. While LIF may serve as the initial upstream ligand to activate this particular STAT protein,[15] recent work by Tiffen *et al*.[16] suggests that the subsequent Stat3-mediated expression of OSM is required as part of an autocrine loop for a sustained activation of this signal transducer. The Stat3-mediated apoptosis of functionally differentiated epithelial cells and increase in the levels of phosphorylated Stat1 concludes the precisely controlled activation of STATs at distinct phases during normal mammary gland development. As discussed in the following sections, any disturbance in the state of equilibrium of these JAK/STAT pathways, in particular, Jak2/Stat5 and Jak1/Stat3 signaling, leads to developmental defects and contributes to mammary carcinogenesis.

JAK2/STAT5 SIGNALING CONTROLS THE GENESIS AND NUMERIC EXPANSION OF LUMINAL ALVEOLAR PROGENITORS THAT ARE THE CELLULAR BASIS FOR MAMMARY TUMORIGENESIS

Both Stat5 proteins share an overall 96% amino acid similarity, but gene deletion studies in single knockout mice lacking either protein show that only the functional ablation of Stat5a leads to impaired alveologenesis during pregnancy and lactation.[17,18] This is likely a consequence of the dissimilar expression of the *Stat5a* and *Stat5b* loci in the mammary epithelium. Following multiple gestation cycles, however, Stat5a-deficient mammary epithelial cells are able to upregulate Stat5b, which partially restores normal alveolar

development and milk protein gene expression.[19] In contrast to Stat5a single knockout mice, the deletion of both *Stat5* genes causes a complete absence of alveolar cells, and transplant experiments as well as the examination of a Stat5 conditional knockout model show that this phenotypic abnormality is the result of cell autonomous functions of Stat5a and Stat5b.[20-22,10] Besides activation of the JAK/STAT pathway, binding of PRL to its receptor stimulates additional signal transducers such as Src, mitogen activated protein (MAP) kinases, phosphatidylinositol 3-kinase (PI3K), and protein kinase C (PKC) (for citations please refer to Wagner and Rui[5]). The striking phenotypic similarities between Stat5 knockout mice and females that are deficient in PRL or the PRL receptor[23,24] suggested that important biologically relevant functions of PRL signaling during normal mammary gland development are mediated primarily through the JAK/STAT pathway.

Although there is a wealth of knowledge about the activation and functionality of STATs, much less is known about the biological significance of Jak1 and Jak2 downstream of various growth factor receptors in the mammary gland. Conventional gene deletion models of each of these two JAKs die perinatally due to neurological or hematopoietic defects.[25-28] Studies using an orthotopic transplantation model of Jak2-deficient embryonic mammary gland anlagen into wild-type recipient mice as well as the development and analysis of a Jak2 conditional knockout model show that this kinase is required for the development of secretory alveolar cells.[10,29] On a mechanistic level, the examination of mice conditionally deficient in Jak2 clearly demonstrated that this kinase is the essential link between PRL signaling and Stat5 activation in the normal mammary gland. Jak2-deficient mammary epithelial cells lack phosphorylated Stat5 even after administration of extraphysiological levels of PRL,[10] and the functionality of this kinase is not compensated by Jak1 or receptor tyrosine kinases such as ErbB2, as previously suggested. As discussed later, this has significant implications for the prevention of cancer in mice with enhanced PRL autocrine signaling in their mammary glands. Interestingly, while the ablation of Jak2 had no effect on ductal elongation and branching morphogenesis, nulliparous mammary glands in Jak2-deficient females were completely devoid of alveolar buds that usually reside at the terminal end of ducts, suggesting that this kinase is essential for the specification of alveolar progenitors prior to pregnancy.[5,10] In line with this notion, a recent report by Yamaji *et al*.[30] demonstrated that deficiency in Stat5 caused a reduction in the number of CD61+ luminal progenitors that are committed to the alveolar lineage and that normally multiply in response to PRL signaling during pregnancy. This work also showed that exogenous expression of Stat5a was sufficient to restore the numeric expansion and differentiation of luminal progenitors. Given that the mammary gland develops normally in Stat5b single knockout mice,[18] the outcome of this Stat5a rescue experiment might not be entirely surprising. On the other hand, if the proposed functional redundancy between both Stat5 isoforms is correct, an identical expression of exogenous Stat5b might also be able to restore, at least in part, the specification and proliferation of luminal alveolar progenitors in mice that conditionally lack the entire endogenous *Stat5a/b* locus.

The fact that Jak2/Stat5 signaling is critical for the genesis of alveolar progenitors may have significant implications for breast cancer prevention. This particular epithelial subtype resides at the terminal ends of the ductal tree. This region is known as the terminal duct lobular unit (TDLU),[31] and it has been suggested that TDLUs are the sites in the human breast where a subset of breast cancers originate.[32] This may explain why, besides age and genetic susceptibility, the reproductive status of a woman is the strongest and most reliable risk factor for breast cancer.[33] In support of these observations in humans, ErbB2-induced mammary cancers in a mouse model arise predominantly from luminal alveolar progenitors, and the selective elimination of these cells from the developing mammary gland prevents mammary tumorigenesis in mice expressing wild-type ErbB2.[34] There is epidemiological and molecular evidence that hormone-responsive breast epithelial cells exhibit an elevated susceptibility to neoplastic transformation, and recent findings suggest that these cells might also contribute to basal-type or hormone receptor-negative breast cancers. For example, loss of BRCA1 has been reported to be associated with an expansion of luminal progenitors in the normal human breast.[35] Similarly, studies in a BRCA1-deficient mouse model showed that the mammary-specific deletion of this tumor suppressor led to an accumulation of CD61+ luminal progenitors during pregnancy, which is precisely the cell type that is dependent on the Jak2-mediated activation of Stat5.[36] Besides the encouraging results about the prevention of mammary cancer in the Stat5- and Jak2-deficient models as discussed later in this article, future studies might show whether the inhibition of Jak2/Stat5 signaling could be an effective strategy for the prevention of BRAC1-associated, hormone receptor negative breast cancers.

GAIN-OF-FUNCTION OF JAK2/STAT5 SIGNALING MEDIATES EVASION FROM APOPTOSIS AND SELF-SUFFICIENCY IN GROWTH SIGNALS

Conditional gene deletion models provide unique opportunities to study essential biological functions of a gene at various stages of mammary gland development beyond the

arrested development of a conventional knockout. While the MMTV-Cre–mediated deletion of Jak2 or Stat5 throughout the mammary epithelium revealed that this JAK/STAT pathway is essential for the genesis of alveolar progenitors, a selective WAP-Cre–induced ablation of Jak2 or Stat5 in the lactating mammary gland showed that these downstream mediators of PRL signaling are equally important for the survival of functionally differentiated alveolar cells.[10,22] Following a normal lactation period, the mammary gland undergoes a series of molecular events that culminate in the programmed cell death of the vast majority of secretory epithelial cells. This involution process, which requires the downregulation of survival factors and the activation of pro-apoptotic signals, is characterized by a rapid switch between JAK/STAT signaling cascades. While the levels of circulating PRL and therefore active Stat5 decline, local growth factors such as LIF and OSM accumulate in the mammary gland in response to milk stasis and initiate the phosphorylation of Stat3.[15,16] In support of this paradigm, deficiency in Stat3 prolongs the functional competence of secretory epithelial cells and causes a delay in programmed cell death.[37,38] On the mechanistic level, Abell *et al*.[39] proposed that Stat3 regulates the expression of the smaller PI3 kinase regulatory subunits p50α and p55α. These subunits then downregulate the activity of the PI3K holoenzyme (p85α/p110), and subsequently Akt, which is a known survival pathway for functionally differentiated mammary epithelial cells. It has been repeatedly demonstrated that a gain-of-function of Stat5 can extend the survival of differentiated mammary epithelial cells in the absence of elevated lactogenic hormones.[40,41] In addition, a recent study by Creamer *et al*.[42] shows that expression of active Stat5 results in a significant delay in postlactational remodeling despite the initiation of Stat3-mediated pro-apoptotic signaling events and the transcriptional upregulation of p50α and p55α. The extended survival of terminally differentiated cells during involution in this model might be a direct consequence of the Stat5-mediated sustained expression of Akt1. Active Stat5 has been shown to bind to two or more consensus sequences within the *Akt1* locus in a growth factor-dependent manner, and it enhances the transcription of a unique *Akt1* mRNA from a distinct promoter *in vitro* and *in vivo*. This novel transcript encodes for the full-length Akt1 serine–threonine kinase. In support of the proposed regulation of Akt1 downstream of Stat5, all mammary-specific models that express active Stat5 share striking phenotypic similarities with transgenic mice that express exogenous *Akt1* under regulation of the MMTV-LTR.[43-45] It was also previously reported that expression of Akt1 promotes the survival of the functionally differentiated mammary epithelium despite activation of Stat3.[43,45] Therefore, a gain-of-function of Stat5 or elevated expression of Akt1 is sufficient to override, at least in part, the functionality of Stat3. At this point, it is still unclear how this biological phenomenon is being accomplished if, as suggested, the shorter PI3K regulatory subunits p50α and p55α are sufficient to inhibit the p85α/p110 PI3K holoenzyme from its subsequent activation of Akt. In these efforts, it is necessary to verify the biological significance of the shorter PI3K subunits during mammogenesis using p50α/p55α double knockout mice.[46] Also, the effects of active Stat5 on the expression and assembly of the catalytically active PI3 kinase still need to be examined in more detail. As an integral part of a multifaceted signaling complex, active Stat5 is able to associate with adapter proteins and PI3K subunits.[47] Sakamoto *et al*.[48] have shown that Stat5 might directly modify the activity of the PI3 kinase in the mammary gland through binding to the SH2 domain-containing regulatory subunit p85α. While the biological significance of this particular interaction needs to verified, it is evident that a gain-of-function of p110α or loss of phosphatase and tensin homolog (PTEN) recapitulates several of the phenotypic abnormalities associated with the overexpression of active Stat5.[49,50]

Collectively, the phenotypic and molecular analyses of several genetically engineered models revealed that similar to a gain-of-function of the PI3 kinase and Akt1, a prolonged or constitutive activation of Jak2/Stat5 signaling facilitates evasion from apoptosis and self-sufficiency in growth signals, which are two important hallmarks of cancer.[51] In line with this notion, it has been demonstrated that Stat5a has oncogenic properties,[41,52] but the exact mechanisms by which this STAT protein promotes neoplastic transformation are still not entirely known. Nonetheless, the proposed molecular interactions between JAK/STAT and PI3K/Akt signaling [Figure 1] provides a model by which active Stat5 may function as a potent modifier for PI3K signal transduction, i.e. one of the most commonly altered pathways in hereditary and sporadic forms of breast cancer.

MECHANISMS OF ABERRANT ACTIVATION OF JAK/STAT SIGNALING CASCADES IN HUMAN BREAST CANCER

Chromosomal translocations that result in oncogenic Jak2 fusion gene products such as Tel–Jak2, Bcr–Jak2, and Pcm1–Jak2 are mainly associated with the initiation and progression of myeloproliferative disorders and a subset of leukemias (for references see[53,54]). Similar genetic events have not been detected in a significant portion of adenocarcinomas, including human breast cancers. These types of malignancies acquire active JAKs through alternative mechanisms such as a) epigenetic silencing of suppressors of JAK/STAT

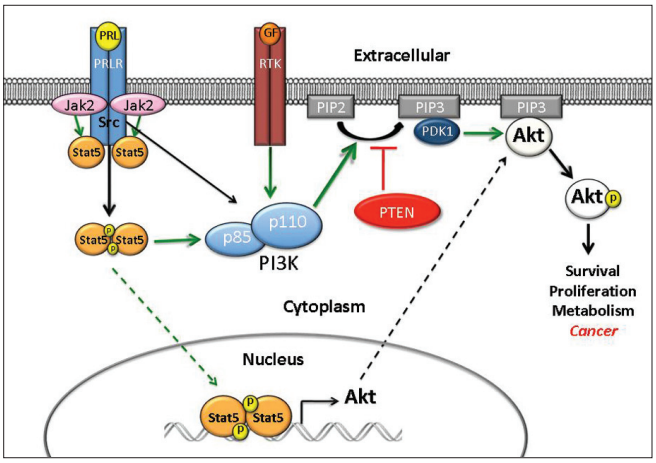

Figure 1: Interaction between Jak2/Stat5 signaling and the PI3K/Akt1 pathway in mammary epithelial cells. Active Stat5 modifies signaling through the PI3 kinase and Akt1 by at least two distinct mechanisms in luminal epithelial cells, i.e. by binding to the regulatory subunit of the PI3 kinase and by enhancing the transcriptional activation of the *Akt1* gene from a mammary-specific promoter

signaling, b) aberrant increase in autocrine signaling, and to a lesser extent, c) missense mutations within JAKs. The recent discovery of constitutively activating mutations of *Jak2* (e.g. Jak^{V617F}) in myeloproliferative disorders spurred a number of investigations into identifying similar somatic abnormalities within JAKs in solid cancers. Collectively, these studies showed that the prominent V617F mutation in Jak2 does not contribute to the activation of Stat5 and Stat3 in adenocarcinomas.[55,56] Two recent reports describe a rare occurrence of missense mutations within the pseudokinase domain of Jak1 in breast, lung, and hepatocellular carcinomas,[57,58] but their biological relevance and contribution to carcinogenesis remain elusive.

In contrast to the lack or low incidence of somatic mutations within JAKs, the epigenetic silencing of suppressors of JAK/STAT signaling are more frequently observed in breast cancers. The main negative regulators of JAKs and STATs are protein tyrosine phosphatases (PTPs), suppressors of cytokine signaling (SOCS), and protein inhibitors of activated STATs (PIAS).[59] These proteins possess diverse functions as inhibitors, including the dephosphorylation or proteosomal degradation of JAKs, and their association with STATs to alter their localization, DNA binding, and transcriptional activation. Among the three families of JAK/STAT inhibitors, PTPs and SOCS have been shown to be epigenetically silenced through DNA methylation in a variety of human cancers. Specifically, silencing of the *SOCS1* gene has been reported in 9% of primary breast cancer cases.[60] In addition, loss of caveolin-1, a potent suppressor of Jak2/Stat5 signaling, contributes to neoplastic transformation and mammary tumorigenesis in humans and in genetically engineered mouse models.[61,62]

Beside the suppression of negative regulators of JAK/STAT signaling, breast cancer cells initiate the synthesis of hormones and cytokines as part of autocrine signaling networks to overcome external growth factor dependence. Specifically, PRL,[63,64] erythropoietin (EPO),[65,66] and IL-6[67,68] are frequently co-overexpressed with their respective receptors in breast cancer cells, and all of these cytokines are potent activators of JAK/STAT signaling cascades. EPO has attracted considerable attention recently when the US Food and Drug Administration warned against the use of this growth factor to increase hemoglobin levels during breast cancer treatment. Administration of EPO to late-stage breast cancer patients promoted disease progression,[69] and it has also been reported recently that this cytokine may offset the treatment of ERα-positive and Her2-positive breast cancers with tamoxifen and trastuzumab.[65,66] This clearly demonstrates that the aberrantly expressed EPO receptor plays an important functional role in cancer cell growth and survival, and this may not be entirely surprising since the intracellular signaling domains of the receptors for EPO and PRL are functionally identical.[70]

It has been recognized for some time that high circulating levels of PRL are associated with an increased breast cancer risk in humans (for references see[71]). In support of this notion, elevated levels of PRL in circulation are known to cause mammary cancers in transgenic mice.[72] In addition to the pituitary PRL, breast cancer cells locally synthesize this growth factor and upregulate the expression of the PRL receptor.[63,64] The importance of this hormone as part of an autocrine loop for mammary carcinogenesis was experimentally verified in transgenic mice that express PRL locally in the mammary epithelium. These animals develop luminal-type neoplasia with both estrogen receptor positive and negative lesions.[73] Although PRL signals mainly through Jak2 and Stat5 in normal luminal breast epithelial cells, this hormone is capable of aberrantly activating Stat3 in human breast cancer cell lines.[74] A more recent study shows that PRL activates Jak1 in a Jak2-dependent manner,[75] and this finding may provide an underlying mechanism by which PRL activates Stat3 and MAP kinases that, as discussed later, seem to play a more important role than Stat5 in breast cancer progression. Collectively, these observations suggest that signaling networks undergo a substantial rewiring process during or following neoplastic transformation. The changes within the PRL signaling network between normal and neoplastic epithelial cells exemplify another "two-faced" nature of JAKs in their ability to activate additional STATs and thereby contribute to different biological processes.

RECIPROCAL ACTIVATION OF STAT5 AND STAT3 DURING MALIGNANT PROGRESSION IN BREAST CANCER

Depending on the expression of growth factors and their receptors, along with downstream changes in growth regulatory networks, the activation of individual STATs may vary among diverse breast cancer subtypes or different stages of disease progression. There is increasing evidence that Stat1 has tumor suppressive functions,[8] and this signal transducer also plays a role in growth arrest and in pro-apoptotic signaling during chemotherapy.[76] In addition, activation of Stat1 and the concomitant upregulation of *SOCS1* and *interferon regulatory factor-1* (*IRF-1*) expression in human mammary carcinoma was reported to be a predictor of a good prognosis.[77] Similarly, expression of active Stat5, which was observed in approximately 76% of human breast tumors, positively correlated with tumor differentiation.[78] A study by Nevalainen *et al*.[79] suggested that Stat5 is as an independent prognostic factor for overall patient survival. The examination of Stat5 activation in more than 1100 primary breast cancers in that study revealed that the nuclear expression of Stat5 was gradually lost during cancer progression and was absent in the vast majority of metastases. One mechanism that may facilitate the inactivation of Stat5 in metastatic cells is the upregulation of the protein tyrosine phosphatase 1B (PTP1B) that targets active Jak2.[80] In line with the notion that the functionality of Stat5 is diminished in disease progression, Sultan *et al*.[81] reported that active Stat5 promoted the differentiation of breast cancer cells and increased the cell surface levels of E-cadherin. Collectively, the examination of Stat5 expression and activation during human breast cancer progression, as well as studies in PRL- and Stat5-induced tumor models in rodents, revealed another side of the multifaceted nature of Jak2/Stat5 signaling in mammary carcinogenesis. While activation of Stat5 and a simultaneous increase in cell survival may initially promote neoplastic transformation, a continuous activation of this signal transducer mediates the maintenance of a more differentiated and less metastatic tumor phenotype.[5] A similar "two-faced" function may apply to other signal transducers during cancer progression. Specifically, Hutchinson *et al*.[82] examined the effects of a gain-of-function of Akt1 during mammary tumorigenesis. While the expression of active Akt1 decreased the latency of ErbB2-induced mammary tumorigenesis, the sustained upregulation of this kinase prevented cancer invasion and metastasis. As mentioned earlier, Akt1 has recently been shown to be a transcriptional target of Stat5,[42] and it is, therefore, tempting to speculate that Stat5 exerts its suggested role as a metastasis suppressor through increased expression of Akt1. Transgenic mice that allow expression of hyperactive and wild-type Stat5 in a ligand-inducible manner[42,30] are suitable experimental models to assess *in vivo* whether a) Stat5 can control the levels of *Akt1* in preneoplastic and cancerous lesions and b) the ablation or continuous expression of Stat5 in mammary tumors affects the metastatic dissemination of cancer cells.

As discussed earlier, Stat5 and Stat3 are successively activated during lactation and involution in the normal mammary gland, and both STATs seem to function in a similar sequential order during breast tumorigenesis. As the expression and activation of Stat5 declines, the level of phosphorylated Stat3 increases significantly in malignant breast cancer cells. A number of independent studies have reported that the majority of primary breast cancers (about 50–60%) exhibit a constitutive activation of Stat3 and that this particular signal transducer plays an important role in breast cancer cell growth and metastatic progression.[83,84] A recent report by Barbieri and colleagues shows that the constitutive activation of Stat3 results in accelerated mammary tumorigenesis and an increase in the metastatic potential of ErbB2 expressing cancer cells.[85] In contrast, a knockout of Stat3 prior to tumorigenesis shows that this signal transducer is not required for neoplastic transformation.[86,87] However, the ablation of Stat3 was sufficient to suppress the anchorage-independent growth of breast cancer cells and their ability to metastasize. Therefore, targeting Stat3 may not be a relevant strategy for cancer prevention, but the functional inhibition of this signal transducer as part of a targeted therapy for advanced breast cancers may prevent the metastatic dissemination of malignant cells.

TARGETING THE MULTIFACETED FUNCTIONS OF JAKS AND THEIR RESPECTIVE STATS FOR THE PREVENTION AND TREATMENT OF BREAST CANCERS

Since transcription factors, which include STATs, rely more extensively on protein–protein and protein–DNA interactions for their functionality, they are less accessible biological targets and often referred to as "un-druggable." Nevertheless, a number of agents have been identified in screens that inhibit STATs, and these compounds might be useful for the treatment of specific human malignancies. For example, a very recent report showed that the drug pimozide is a Stat5 inhibitor that might be effective for the treatment of chronic myelogenous leukemia (CML) and potentially other myeloproliferative diseases.[88] Considering the multifaceted role of Stat5 during breast cancer initiation and the suggested function of this transcription factor as a metastasis suppressor, targeting Stat5 might be a suitable strategy for cancer prevention but not to treat late-stage

breast cancers. In contrast, Stat3 is an unlikely target for breast cancer prevention. Since the inhibition of this particular STAT is suggested to reduce cancer cell invasion and metastasis, Stat3 inhibitors such as OPB-31121 (Otsuka Pharmaceutical Development and Commercialization, Inc., Princeton, NJ) might be suitable for the treatment of invasive breast cancer, but their efficacy needs to be tested in a clinical setting. Unlike transcription factors, protein kinases may become the most important group of drug targets besides G-protein–coupled receptors.[89] It is therefore not surprising that more than a dozen studies are currently underway to test investigational JAK inhibitors to treat hematopoietic malignancies and carcinomas.[90-92] The selectivity of these new agents to specifically target their corresponding JAKs still needs to be determined. Due to differences in the mechanisms of JAK activation, not all drugs that might effectively inhibit mutant Jak2 in hematopoietic disorders are necessarily useful for the treatment of carcinomas that, as discussed earlier, utilize alternative modes of JAK/STAT activation. Also, Jak1 and Jak2 are co-activated in solid cancers, and it needs to be determined whether they have therapeutically relevant redundant functions. If so, dual kinase inhibitors such as INCB018424 from Incyte, Wilmington, DE might be useful for the treatment of cancers where both kinases are functionally equivalent for cancer cell growth and survival.

It is evident that the specificity and effectiveness of pharmacological agents for the targeted inhibition of JAKs and STATs need to be more carefully examined. In parallel, genetically engineered preclinical models are being employed to study the significance of individual signal transducers during mammary carcinogenesis, and these models may herald the usefulness of particular therapeutic strategies to prevent and treat breast cancer. In support of the notion that Stat5 plays a key role during the onset and early progression of mammary cancer, it has been demonstrated that the functional ablation of Stat5a is sufficient to delay the formation of T-antigen– and TGFα-induced mammary cancers.[93,94] Cyclin D1 is one of the downstream targets of Stat5 that might link PRL signaling to the cell cycle machinery,[48,95] and it has been suggested that lack of this cell cycle regulator protects against the onset of ErbB2- and Myc-induced mammary tumorigenesis.[96] While the outcome of these experiments might suggest that targeting Stat5 and its downstream effectors is a suitable strategy for breast cancer prevention, it was premature to suggest that targeting these proteins is equally important for the treatment of established cancers. To more accurately assess whether specific signal transducers are appropriate therapeutic targets, it is necessary to delete a gene or ablate the function of its encoded protein in fully neoplastic cancer cells *in vivo*.[97] The design and examination of such experimental models can lead to a completely different outcome and conclusion. Two recent studies by Sakamoto and colleagues[98,99] show that the deletion of the *Jak2* gene (and consequently, the inhibition of Stat5) in the mammary epithelium prior to tumor onset completely protected female mice from developing mammary tumors in response to an overexpression of ErbB2 and PRL. The conditional knockout of this Janus kinase from fully neoplastic cells, however, had no effect on tumor cell growth and survival *in vitro* or *in vivo*. Collectively, these studies suggest that targeting Jak2 might be an appropriate way to prevent mammary cancer, but inhibiting the function of this particular tyrosine kinase is unlikely a suitable strategy to treat established breast cancer. The findings by Sakamoto and others about the multifaceted role of Jak2/Stat5 signaling in mammary tumorigenesis are in line with observations in human breast cancer specimens that the activation of Stat5 is gradually lost during cancer progression. On the other hand, given the suggested importance of Stat3 in late-stage cancers and the proposed joint function of Jak1 and Jak2 for the activation of this particular STAT protein, future studies may show whether a combined inhibition of both Jak1 and Jak2 can halt the growth and prevent the metastatic dissemination of cancer cells *in vivo*. To develop such a complex model, it would be first necessary to establish a Jak1 conditional knockout mouse since a conventional gene targeting approach for this kinase results in prenatal lethality.[25]

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