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more commonly harbor PI3K pathway aberrations, may rely on other mechanisms to circumvent PI3K/mTOR inhibition. More studies are needed to elucidate the mechanisms by which modulation of signaling pathways drives tumor resistance to anti-cancer therapies.

Since the neoplastic phenotype of a cell is largely driven by its pattern of gene expression, another treatment strategy for TNBC focuses on targeting the transcription factors that are inappropriately activated in these tumors. STAT5 and STAT3 are two closely related members of the STAT family of transcription factors that regulate the expression of genes involved in cell growth, survival, and angiogenesis. In normal cells, STAT signaling is tightly regulated by inhibitory molecules including suppressor of cytokine signaling (SOCS) proteins, protein inhibitor of activated STAT (PIAS) proteins, and protein tyrosine phosphatases. Cancer cells frequently have persistent STAT activation, from hyperactivation of upstream tyrosine kinases or loss of function of negative regulators, which can then contribute to malignant transformation.

In cancer cells with inappropriate constitutive STAT3 activation, inhibition of this protein leads to a reversion of the malignant phenotype and cell death whereas normal cells lacking STAT3 activation are unharmed. Although STAT5 and STAT3 are structurally similar and recognize similar DNA response elements, these factors play contrasting roles in normal mammary function. STAT5 promotes terminal differentiation of mammary epithelial cells necessary for lactation while STAT3 promotes involution of the mammary gland following weaning. In contrast to STAT5 activation, STAT3 activation has been associated with worse prognosis in breast cancer patients in part due to its effect on evasion of apoptosis. This may contribute both to resistance to therapy and to subsequent recurrence. Whether a cell undergoes apoptosis is largely based on competition between pro- and anti-apoptotic proteins in the mitochondria. Anti-apoptotic proteins like Bcl-2 normally sequester pro-apoptotic proteins from binding to and activating Bak/Bax, which form pores in the mitochondrial outer membrane to trigger cell death. STAT3 is known to upregulate the Bcl-2 family of anti-apoptotic proteins, and Bcl-2 and Bcl-xl expression levels decline with JAK2 inhibition. The PI3K/AKT pathway also controls expression of mitochondrial apoptotic regulatory proteins, and inhibiting PI3K/mTOR leads to decreased levels of the inactive form of the pro-apoptotic protein Bad. Since STAT3 and PI3K signaling both modulate mitochondrial apoptosis, inhibiting both pathways may further tip the balance of pro- and anti-apoptotic proteins in favor of cell death. Indeed, Britschgi et al. found that combined inhibition of PI3K/mTOR and JAK2/STAT5 leads to activation of the pro-apoptotic protein Bim and degradation of the anti-apoptotic protein Mcl-1.

Breast tumors with co-activation of STAT5 and STAT3 generally have less aggressive features (low histologic grade, lymph node negative status, sensitivity to chemotherapy) than tumors with activated STAT3 alone, suggesting that the tumor-suppressive effect of STAT5 activation may be dominant over the tumor-promoting effect of STAT3 activation. Interestingly, STAT5-mediated gene repression is dominant over STAT3-mediated gene induction for shared target genes. Breast tumors with co-activation of STAT5 and STAT3 are also more likely to be estrogen- or progesterone-receptor positive, making them sensitive to hormonal therapy, and less likely to be triple-negative and thus more clinically aggressive. In a panel of primary breast tumors, 29% display dual activation of STAT3 and STAT5, 40% display STAT3 activation alone, and only 7% display activation of STAT5 alone. The relatively small number of breast cancers with STAT5 activation alone suggests that STAT5 activation may limit the aggressiveness of tumor cells, most likely via its physiologic function of promoting breast epithelial cell differentiation. In light of evidence that STAT5 activation is associated with differentiated breast tumors with more favorable prognoses while STAT3 is associated with more aggressive cancers, it is somewhat surprising that Britschgi et al. discover an apparently contradictory role for STAT5 activation in driving resistance to PI3K/mTOR inhibition. Given the dual functions of STAT5 in promoting proliferation as well as differentiation, the net effect of STAT5 activation on breast cancer pathogenesis may depend on other molecular events in the cell. The authors also report that TNBC lines have a higher baseline of phosphorylated STAT5 than luminal breast cancer cell lines. However, others have consistently observed constitutive activation of STAT3 instead of STAT5 in TNBC cell lines.

In summary, Britschgi et al. show that activation of JAK2/STAT5 signaling in response to PI3K/mTOR inhibition enhances the invasiveness and metastatic behavior of TNBC cells. The authors demonstrate that JAK2/STAT5 hyperactivation drives resistance to PI3K/mTOR inhibitors by first restoring activation of AKT downstream of PI3K inhibition and then upregulating IL-8 secretion, a
pro-metastatic chemokine that induces positive feedback on JAK2/STAT5 (Fig. 1). In the first wave of resistance, accumulation of insulin receptor (IR), insulin-like growth factor 1 receptor (IGF-1R), and insulin receptor substrate 1 (IRS1) lead to JAK2/STAT5 phosphorylation which in turn activates the PI3K/AKT pathway via interaction with the scaffold protein Gab2.18 This step is independent of CXCR1. In the second wave of resistance, STAT5 upregulates expression of IL-8, which binds to its receptor CXCR1 to trigger increased invasiveness and metastatic behavior.19 Britschgi et al. found that CXCR1 is differentially expressed among tumor cells, with only 3% of primary tumor cells expressing CXCR1 whereas almost all (96%) circulating tumor cells express CXCR1. The authors clearly demonstrate that inhibiting JAK2 preferentially leads to apoptosis of the CXCR1+ subpopulation which is thought to be responsible for tumor seeding and metastasis. Consequently, in addition to circumventing drug resistance, dual inhibition of PI3K/mTOR and JAK2/STAT5 may have the added benefit of reducing metastasis by specifically impacting the survival of tumor-initiating cells.

To our knowledge, this publication is the first description of a JAK2/STAT5 hyperactivation mechanism by which tumors escape from PI3K/mTOR inhibition. The clinical benefit from the combined treatment regimen proposed by Britschgi et al. is potentially of great importance for TNBCs, which are clinically aggressive and highly metastatic tumors. Therefore, this research highlights the importance of understanding the interactions among signaling pathways in cancer cells in order to improve the efficacy of cancer therapies.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References


18. Vafaizadeh V, Klemmt PA, Groner B. Stat5 assumes distinct functions in mammary gland development and mammary tumor formation. Front Biosci 2012; 17:1232-50; PMID:22201800; http://dx.doi.org/10.2741/3983