**STK11 Loss: A Novel Mechanism for Melanoma Metastasis with Therapeutic Implications**

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STK11 is implicated as a tumor suppressor in epithelial cancer invasion and metastasis. In their new article in the *Journal of Investigative Dermatology*, Dzung et al. (2021) show that loss of STK11 in cutaneous melanoma cells leads to an invasive metastatic phenotype through the activation of the signal transducer and activator of transcription (STAT) 3/5 and FAK signaling pathways. These results suggest that inhibition of STAT3/5 and FAK in STK11-deficient melanoma cells could serve as a novel therapeutic strategy against metastatic melanoma.


**Background**

Cutaneous melanoma is the most aggressive form and the leading cause of mortality among skin cancers (Leonardi et al., 2018). Loss of STK11 (or LKB1) is associated with metastatic behavior in several epithelial cancers by altering cellular metabolism and motility (Hermann et al., 2011). However, the function of STK11 in nonepithelial cancers, for example, melanoma, has not been completely understood. STK11 plays an important role in the regulation of melanocyte transformation and increased mucocutaneous pigmentation in precancerous polyposis of the gastrointestinal tract in Peutz-Jeghers Syndrome (PJS) (Paffenberger et al., 2018). Approximately 50% of melanomas harbor BRAF sequence variations, which functionally inactivate some STK11-dependent pathways, suggesting a tumor suppressor role for STK11 in melanoma (Zheng et al., 2009). Previous studies have shown that STK11 is a negative regulator of signal transducer and activator of transcription (STAT) 3 in gastrointestinal polyposis (Paffenberger et al., 2018). In addition, STK11 represses FAK signaling, which is associated with increased metastasis and invasion in epithelial cancers (Marcus and Zhou, 2010). Targeting these signal pathways could be beneficial in the treatment of metastatic melanoma.

**STK11 loss as a key contributor to metastatic melanoma**

In their new article in the *Journal of Investigative Dermatology*, Dzung et al. (2021) investigated the cell-autonomous consequence of STK11 loss in BRAFV600E and NRASQ61R sequence variant melanoma cells. Reduced sensitivity to BRAF inhibitors was observed after deleting STK11 in melanoma cells both in vitro and in vivo. They showed that STK11 loss led to BRAF inhibitor resistance through the inhibition of the adenosine monophosphate–activated protein kinase (AMPK) pathway. However, they did not observe the same effect on MAPK/extracellular signal–regulated kinase (MEK) inhibitors in NRASQ61R sequence variant melanoma. The STK11 expression level was reduced during progression from primary to metastatic melanoma, reaching its lowest level in human brain metastasis samples. A key role for STK11 inactivation in melanoma formation and metastasis has been previously shown by Liu et al. (2012). In an activated KRAS melanoma mouse model, loss of STK11 leads to the expansion of CD24⁺ metastatic tumor subpopulation through the induction of Src family kinase (Liu et al., 2012). In addition, it has been shown that STK11 loss promotes invasion in metastatic melanoma by impairing directional migration toward the extracellular matrix (Chan et al., 2014). Dzung et al. (2021) findings are consistent with the previous reports, which showed a similar role for STK11 in epithelial cancers: Taliaferro-Smith et al. (2009) have shown that STK11 prevents adhesion and invasion of breast cancer cells by the modulation of AMPK. Inactivation of STK11 compared with that of other tumor suppressors, in cooperation with KRAS mutation, results in more frequent metastasis in lung adenocarcinoma (Ji et al., 2007). Although somatic inactivation of STK11 gene occurs in only 10% of melanomas, Dzung et al. (2021) findings suggest that reduced STK11 expression in primary melanoma may be essential for cancer progression and metastasis.

**The mechanism by which STK11 suppresses melanoma invasion**

Increased activity of STAT3/5 and FAK signaling pathways in the pathogenesis of several cancers has been described. These signaling pathways are involved in cancer cell migration and metastasis (Marcus and Zhou, 2010; Paffenberger et al., 2018). However, the activation of these signaling pathways after the loss of STK11 in cancer cells has not been previously studied. Downregulation of STAT3/5 signaling increases apoptosis in human melanoma cells (Krasilnikov et al., 2003). Enhanced STAT3 signaling, together with increased cytokine expression after heterozygous deletion of STK11 gene in T cells, is associated with polyposis formation and symptoms intensification in PJS (Paffenberger et al., 2018). Tokita et al. (2007) show that inactivation of the suppressors of cytokine signaling family...
promotes malignant behavior of melanoma by activation of STAT and FAK signaling pathways. On the basis of the work by Pei et al. (2017), the expression of FAK, Src, and STAT3 increase in human metastatic melanoma, which in combination with reduced E-cadherin promotes melanoma cell migration (Pei et al., 2017). Consistent with these findings, Dzung et al. (2021) observed increased activation of STAT3, STAT5a/b, and FAK after STK11 deletion in both BRAFV600E and NRASQ61R sequence variant melanoma cells, which was accompanied by AMPK inactivation (Figure 1).

**Clinical Implications**

- STK11 loss in cutaneous melanoma may represent a biomarker for metastasis progression.
- Inhibition of signal transducer and activator of transcription (STAT) 3/5 and FAK signaling pathways can provide a novel therapeutic strategy against metastatic melanoma.
- It is intriguing to postulate that the combination of STAT3/5 and FAK inhibition with immune checkpoint inhibitor therapy in STK11-deficient metastatic melanoma may boost the efficacy of immunotherapy for melanoma.

**SKT11 signaling pathway as a novel target for metastatic melanoma treatment**

Immune checkpoint inhibitor (ICI) therapy is widely used for the treatment of metastatic cancers. In particular, ICI therapy for malignant melanoma has been adopted as an optimal therapy in combination with BRAF/MEK inhibitors, revolutionizing the management of patients with metastatic melanoma and improving their survival (Luke et al., 2017). The predictive biomarkers for ICI response in cancer cells, such as PD-L1 expression, tumor mutational burden, and microsatellite instability, do not completely determine cancer behavior in response to ICI. Recent studies have shown that other pathways in the tumor microenvironment contribute to ICI resistance, including antigen presentation deficiency, activation of immunosuppressive signaling pathways, and mutation in tumor suppressors with immune evasion properties (Binnewies et al., 2018). Interestingly, STK11 loss-of-function mutation has been found to cause resistance to immunotherapy in lung cancer (Skoulidis et al., 2017). According to work by Rassy et al. (2021), the mutation in STK11 is significantly associated with resistance to ICI in patients with metastatic melanoma. However, the underlying mechanism linking STK11 mutation to immunotherapy resistance is unknown. Dzung et al. (2021) showed that the invasive melanoma phenotype after the loss of STK11 was reverted by STAT3/5 and FAK inhibitors in melanoma cells. Active STAT3/5 and FAK signaling pathways play critical roles in maintaining an immunosuppressive tumor microenvironment, which presents a major obstacle for cancer immunotherapy (Jiang et al., 2016). Accordingly,

![Figure 1. The effects of STK11 loss on metastatic melanoma.](image)

Activation of STAT3/5 and FAK signaling pathways caused by STK11 loss leads to melanoma metastasis and contributes to an immunosuppressive tumor microenvironment. The combination of STAT3/5 and FAK inhibitors plus ICI may be an effective treatment for STK11-deficient metastatic melanoma. Created with BioRender.com. AMPK, adenosine monophosphate–activated protein kinase; ICI, immune checkpoint inhibitor; MDSC, myeloid-derived suppressor cell; STAT, signal transducer and activator of transcription; TAM, tumor-associated macrophage; Treg, regulatory T cell.
the described effect of STK11 deletion on STAT3/5 and FAK pathway activation highlights a possible role for immune suppression as an additional detrimental impact of STK11 loss in metastatic melanoma, especially in the context of brain metastasis (Figure 1). Thus, the combination of STAT3/5 and FAK inhibitors with ICI may prove effective for melanoma immunotherapy while limiting the immune-related adverse events caused by long-term usage of ICI therapy. Future studies are needed to examine this concept.

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CONFLICTS OF INTEREST
The authors state no conflict of interest.

REFERENCES