Targeting sphingosine kinase-1 enhances anti-melanoma immune response and improves efficacy of immune checkpoint blockade

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Purpose: Treatment of advanced melanomas has been recently revolutionized thanks to immune checkpoint inhibitors (ICI). However, to extend the proportion of responders and prevent cancer recurrence, current treatments still need to be improved. Our study aims at analyzing whether inhibition of Sphingosine Kinase-1 (SK1), which is over-expressed in melanoma cells as a result of BRAF and NRAS mutations, improves anti-tumor immune response as well as ICI efficacy.

Experimental Design: Tumor Infiltrating Lymphocytes (TILs) content, melanoma growth as well as mice survival were analyzed using mice harboring melanomas with BRAFV600E mutation, in which SK1 expression was inhibited by genetic or pharmacological approaches.

Results: Our data show that the downregulation of tumor SK1 by shRNA resulted in a reduction of melanoma growth in vivo. Importantly, this phenomenon was associated with alterations of lipid metabolism as well as cytokine and chemokine expression profiles leading to a significant decrease in the percentage of CD4+FoxP3+ regulatory T cells (Treg) and, conversely, to an increase in CD8+ effector T cells into the tumors. Moreover, our data reveal that inhibition of SK1 greatly improved the the efficacy of ICI treatment, such as anti-CTLA-4 or anti-PD-1, leading to tumor rejection and greatly improved animal survival.

Conclusion: Here, we show that: i) the targeting of SK1 in melanomas led to an increase in the intratumoral CD8+/Treg ratio and ii) the combination of SK1 inhibition with ICI has greatly enhanced mice survival. Altogether, our data identified SK1 as a new lipid checkpoint kinase that could be target to enhance ICI response.

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