Stearoyl-CoA desaturase 1 blockade promotes immunogenic clearance of tumors

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Abstract

Metabolic reprogramming plays a critical role in carcinogenesis, in part due to its ability to promote immune suppressive properties within tumors. Agents that specifically target crucial metabolic enzymes utilized by cancer are being actively investigated. However, it is unclear whether inhibition of fatty acid metabolism in tumors affects their immunogenicity. Here, we show for the first time that inhibition of stearoyl-CoA desaturase 1 (SCD1), a key enzyme involved in fatty-acid synthesis and a potential prognostic marker for human cancers, increases the immunogenicity of poorly immunogenic tumors. The enhanced immune activation is accompanied by upregulated endoplasmic reticulum (ER) stress and is dependent on the translocation of ER protein calreticulin to the tumor cell surface. Inhibition of SCD1 increased both recruitment and activation of immune cells in vivo, which when combined with PD-1 blockade resulted in potent and durable anti-tumor T cell responses in models of HER2-overexpressing breast cancer. Together, our results indicate that inhibition of tumorigenic de novo lipogenesis represents a novel approach to enhance T cell based cancer immunotherapy.

Discussion

• SCD1 is a broad spectrum anti-cancer target that is overexpressed in numerous aggressive malignancies including breast, renal, lung, ovarian, prostate, thyroid, and colon cancer
• SSI-4 treatment demonstrates activation of the adaptive immune response in vitro and in vivo
• SSI-4 treatment synergizes with anti-PD-1 checkpoint blockade resulting in complete tumor regression, where SSI-4 monotherapy delays tumor progression and anti-PD-1 monotherapy demonstrates no anti-tumor activity

Conclusions

• Aberrant de novo lipogenesis is linked to tumor immunogenicity
• SCD1 inhibitors such as SSI-4 are immunosensitizing agents, and prime the tumor microenvironment towards a pro-inflammatory phenotype
• SSI-4 may be used as an adjuvant therapy with other immunotherapies including checkpoint blockade

References


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