Salt-inducible kinase 3 facilitates tumor cell resistance against cytotoxic T cell attack by shifting TNF signaling from apoptosis to survival

Introduction

Immune checkpoint blockade has in long-lasting patient survival. However, majority of patients do not benefit from current immunotherapies because tumors employ an arsenal of evasion mechanisms. We used the iTarg RNAi screening platform to discover targets and pathways in tumor cells that induce immune resistance. Here we report that desensitization to immune cell–derived TNF is a key immune evasion strategy of tumor cells, which is tightly regulated by the tumor-intrinsic activity of salt-inducible kinase 3 (SIK3). SIK3 potentiates NFκB activity in a TNF-rich environment, thereby regulating its pro-apoptotic effect. Using small molecule inhibitors, we show that specific abrogation of SIK3 results in broad anti-tumor activity against multiple human tumor cell lines in vitro as well as in a significant tumor growth inhibition in MCB3 syngeneic mouse model. Taken together, targeting SIK3 to re-sensitize tumors to immune attack is a compelling therapeutic strategy for cancer treatment.

Results

iToTarg identifies and validates SIK3 as an immune checkpoint in multiple solid tumors

- SIK3 potentiates NFκB in the paraneoplastic ovarian cancer cell line.
- Knockdown of SIK3 sensitized multiple other tumors to T cell-mediated killing.
- Conversely, SIK3 overexpression restored TNF-mediated killing.

iToTarg screening overview

- Discovery of novel immune checkpoint in paraneoplastic ovarian cancer.
- Blockade of SIK3 rescues SIK3-dependent tumor cells from apoptosis.
- SIK3-induced immune resistance in TNF-deprived conditions.

Blockade of TNF rescues SIK3-dependent tumor cells from apoptosis

- SIK3 promotes NFκB transcription of pro-survival genes by inhibiting HDAC4.
- SIK3-inhibited NFκB-mediated gene expression in tumor cells upon TNF treatment.
- Furthermore, SIK3 regulates NFκB activity at an epigenetic level.
- Abrogation of HDAC4 is linked to SIK3-mediated immune suppression.

SIK3-mediates intrinsic resistance of tumors against TNF

- SIK3-specific inhibitors sensitize tumor cells to TNF by counteracting NFκB activity.
- SIK3-specific inhibitors significantly restored tumor cells to TNF-mediated killing.

SIK3 inhibition reduces tumor growth in vivo

- Novel SIK3 inhibitors exhibit in vivo efficacy in cancer models.
- SIK3 inhibition facilitates tumor cell death with less toxicity than TNF.

Conclusion

- iTarg platform identifies SIK3 as a novel tumor-associated immune checkpoint.
- SIK3 sensitizes tumor cells to TNF-mediated apoptosis.
- Intratumoral SIK3 activity strongly increases chromatin accessibility and expression of NFκB-regulated genes by preventing HDAC4 from inhibiting the NFκB signaling cascade.
- SIK3-specific inhibitors alone sensitize a wide array of human and murine cancer cell lines to TNF-induced apoptosis by engaging the HDAC4/NFκB pathway.
- Our novel SIK3 inhibitor demonstrates significant anti-tumor effect in MCB3 syngeneic mouse model combined with an improved anti-tumor immune profile.

References


Statistic information

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