Selinexor, a Selective Inhibitor of Nuclear Export (SINE), Enhances the In Vivo Efficacy of Checkpoint Blockade with Antibodies Targeting CTLA4 or PD-1/PD-L1 in Melanoma

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Abstract
Selinexor (KPT-330) is a SINE. Selective inhibitors of nuclear export (SINEs) are being evaluated in multiple late-stage clinical trials in patients with refractory hematologic malignancies and solid tumors. In KPT-330, mice, the drug exhibited an IC50 of 0.03 nM for exportin 1 (XPO1), a heat shock protein 90 (Hsp90) inhibitor, and 0.07 nM for exportin 1 (XPO1) and Hsp90 inhibitors in vitro. The pharmacodynamic profile of the drug included phosphatidyl inositol 3-kinase (PI3K) and PD-L1 inhibition, which explains the synergistic activity of the drug in multiple studies. In a large-scale in vivo study, the drug significantly decreased the number of Ki67-positive tumor cells and significantly reduced the growth of tumors in mice. The results of this study suggest that the drug could be a potential therapeutic option for patients with refractory hematologic malignancies and solid tumors.

Combining nuclear export inhibition with immunotherapy in melanoma

Immunotherapy in melanoma
- Immune checkpoint blockade (ICBs, chemokines) has clinical efficacy against metastatic melanoma, having elicited deep and sustained responses in a proportion of patients.
- While promising, majority of patients still progress following immunotherapy in ≤ 2 years.

Nuclear export inhibition in melanoma
- The nuclear export protein exportin-1 (XPO1) is upregulated during melanoma progression.
- XPO1 overexpression is associated with tumor suppression, cell cycle modulation, and immune evasion.
- Selinexor, a selective inhibitor of nuclear export, has shown promising preclinical data.
- In vitro, Selinexor effectively inhibits melanoma cell proliferation and also enhances T cell functionality.
- In addition to its antitumor activity, Selinexor inhibits nuclear export of NFκB, STAT1, and STAT3 and may have immunomodulatory properties.

Hypothesis
Selinexor lead to direct antitumor activity but also upregulate T cell checkpoint molecule expression. Thus, combination treatment with anti-PD-1 or anti-PD-L1 will synergize with selinexor to control tumor growth.

Experimental design

Experimental Design: 3.0 x 10^9 B16F10 melanoma cells were implanted subcutaneously into C57BL/6 mice. When tumors became palpable, mice were treated with 15 mg/kg selinexor (orally) and 100 mg/kg of the relevant antibody or isotype control (i.p.). All treatments were twice per week and continued until tumor diameter ≥ 10 mm. Treatment groups were euthanized, and tumor and spleen size were measured.

Results

Selinexor induces immune checkpoint molecule expression

Selinexor significantly increases the frequency of NK cells in the spleen.

Conclusions

1. Combination of selinexor + α-PD-1 or α-PD-L1 exerts considerable anti-tumor activity in an aggressive murine melanoma model.
2. This treatment combination had significant immunomodulatory activity, inducing changes in the frequency and phenotype of immune populations systemically.
3. In contrast to human leukocytes treated in vitro, selinexor did not induce PD-1 or PD-L1 expression in tumor bearing mice. There are two important differences in these models, however:
   a) The in vitro data was generated using human cells, while the in vivo data was generated in a murine setting. Immune cells from humans vs. mice are known to differentially regulate PD-1 and CTLA-4, and there may also be subtle differences in how they regulate these molecules in response to selinexor.
   b) The human in vitro data was generated using healthy donors (i.e. tumor free) leukocytes, while the murine in vivo data only examined cells from tumor bearing mice. Thus, it is likely that immune checkpoint molecules were upregulated on the murine cells, masking potential effects of selinexor on the regulation of these molecules.

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