Targeting Innate Immune Cells for the Treatment of Cancer

Introduction

- Innate immune cells contribute to tumor immunosuppression by expressing immune checkpoint protein ligands, depleting essential amino acids such as arginine, and producing immune suppressive cytokines such as IL-10.
- Multiple signaling pathways contribute to maintaining the immunosuppressive phenotype of intra-tumoral innate immune cells:
  - Adenosine, found in high concentrations in tumors, suppresses immune cell activation by acting on adenosine receptors, A2aR/A2bR, expressed on innate immune cells and lymphocytes.
  - PI3Kγ signaling is central in the decision between an anti-inflammatory pro-tumor M2 macrophage and a pro-inflammatory anti-tumor M1 macrophage.

Methods

- Monocyte-derived dendritic cells (moDC) and macrophages: moDC were differentiated from CD14+ monocytes with IL-4/GM-CSF +/- adenosine +/- AB928.
- Macrophages: Macrophages were differentiated from CD14+ monocytes with M-CSF. Macrophages were polarized into M1 macrophages with LPS+IFN-γ +/- IPI-549 +/- adenine +/- AB928. M2 macrophages were polarized with IL-4 +/- arginase I inhibitor. All compounds were synthesized by Arcus Biosciences.

Expression of Adenosine Receptors, PI3Kγ, and Arginase I in Myeloid Cells

- Adenosine Suppresses the Enhanced M1 Polarization Phenotype Induced by PI3Kγ Inhibition
  - AB928, a dual A2aR/A2bR antagonist, inhibits the immunosuppressive effects of adenosine on innate immune cells.
  - PI3Kγ inhibition enhances macrophage M1 polarization and T cell co-stimulatory function.
  - Cross-talk between PI3Kγ and A2R receptor signaling observed in M1 polarized macrophages.
  - Adenosine upregulates PI3Kγ expression.
  - PI3Kγ inhibition upregulates A2aR expression.
  - Dominant effects of adenosine-mediated inhibition of IL-12 expression even in the presence of PI3I-549 is reversible through the addition of AB928.

Conclusions

- AB928, a dual A2aR/A2bR antagonist, inhibits the immunosuppressive effects of adenosine on immune cells.
- PI3Kγ inhibition enhances macrophage M1 polarization and T cell co-stimulatory function.
- Cross-talk between PI3Kγ and A2R receptor signaling observed in M1 polarized macrophages.
- Adenosine upregulates PI3Kγ expression.
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