HPK1 Inhibition Relieves Suppression Downstream of TCR Activation to Drive Enhanced Cytokine Production, an Effect that is Further Enhanced by Immune Checkpoint Blockade


HPK1 (Hematopoietic Progenitor Kinase 1) is a member of the MAP4K family whose activity restrains T cell activation through phosphorylation of SLP-76 (SLP-76) at Serine 376, leading to disassembly of the TCR complex. Thus, genetic deletion and kinase dead mutants of HPK1 have been shown to enhance T cell activity and combine with immune checkpoint inhibition.

Here, we sought to demonstrate that inhibitors of HPK1 activity can increase T cell activation and combine with immune checkpoint blockade to amplify anti-tumor T cell responses.

**RESULTS**

HPK1 is Broadly Expressed in Immune Cells and Correlates with Immune Infiltration in Normal Human Tissue

**CONCLUSIONS**

- HPK1 (MAP4K6) is the most abundantly expressed member of the MAP4K family in CD8+ T cells and genetic deletion of HPK1 in human CD8+ T cells increases cytokine secretion.
- HPK1 inhibition shows immune selectivity and reproduces the phenotype of genetic deletion in CD8+ T cells, decreasing IL-12 (37%) and increasing IL-2 (3.2 fold).
- HPK1 inhibition enhances cytokine secretion in OT-1 splenocytes with the most enhanced effect observed in high-affinity antigen activated splenocytes.
- HPK1 inhibition combines with PD-L1 blockade to further enhance T cell activation in response to SEA or antigen recall.
- These data highlight HPK1 as an attractive target for immunotherapy as inhibiting HPK1 augments T cell activation.

**METHODS**

- T cell activation is critical in the initiation and polarization of effective immune responses.
- Hematopoietic Progenitor Kinase 1 (HPK1/MAP4K1) is a member of the MAP4K family whose activity restrains T cell activation through phosphorylation of SLP-76 (SLP-76) at Serine 376, leading to disassembly of the TCR complex.
- HPK1 is a member of the MAP4K family whose activity restrains T cell activation through phosphorylation of SLP-76 (SLP-76) at Serine 376, leading to disassembly of the TCR complex.