

# PSGL-1 regulates CD8+ T Cell Exhaustion



In a recent study, researchers described the role of a protein called PSGL-1 in the regulation of T cell exhaustion. The study found that PSGL-1 acts upstream of PD-1 and requires co-ligation with the T cell receptor (TCR) to attenuate activation of mouse and human CD8+ [T cells](#) and drive terminal T cell exhaustion. PSGL-1 directly restrains TCR signaling via Zap70 and maintains expression of the Zap70 inhibitor Sts-1. The study also found that PSGL-1 deficiency empowers CD8+ T cells to respond to low-affinity TCR ligands and inhibit the growth of PD-1-blockade-resistant melanoma by enabling tumor-infiltrating T cells to sustain an elevated metabolic gene signature supportive of increased glycolysis and glucose uptake to promote effector function. Additionally, pharmacologic blockade of PSGL-1 curtails [T cell exhaustion](#), indicating that PSGL-1 represents an immunotherapeutic target for PD-1-blockade-resistant tumors.

The highlights of the results are:

- PSGL-1 regulates T cell exhaustion by acting upstream of PD-1 and requires co-ligation with the T cell receptor (TCR) to attenuate activation of mouse and human CD8+ T cells and drive terminal T cell exhaustion.
- PSGL-1 directly restrains TCR signaling via Zap70 and maintains expression of the Zap70 inhibitor Sts-1.
- PSGL-1 deficiency empowers CD8+ T cells to respond to low-affinity TCR ligands and inhibit the growth of PD-1-

blockade-resistant melanoma by enabling tumor-infiltrating T cells to sustain an elevated metabolic gene signature supportive of increased glycolysis and glucose uptake to promote effector function.

- Pharmacologic blockade of PSGL-1 curtails T cell exhaustion, indicating that PSGL-1 represents an immunotherapeutic target for PD-1-blockade-resistant tumors.

The limitations of this study are that it primarily uses a model of genetic PSGL-1 deficiency, which may have developmental alterations in PSGL-1 À/À CD8+ T cells that contribute to the phenotype observed. Additionally, the study did not find that addition of recombinant PSGL-1 protein to in vitro T cell assays impacts T cell responses. Future studies investigating how recombinant PSGL-1 effectively limits T cell exhaustion will provide further insight into the in vivo interactions of PSGL-1 expressed on T cells with potential ligands.

The paper suggests that further studies are required to determine whether PSGL-1 blockade affects the responses of other PSGL-1-expressing cells in their models. The results highlight that a key, highly conserved function of PSGL-1 is that of a negative regulator of T cell responses and suggest that targeting PSGL-1 could enhance the potential of achieving more sustained antitumor T cell responses.

**Journal article: Hope J.L., et al., 2023. [PSGL-1 attenuates early TCR signaling to suppress CD8+ T cell progenitor differentiation and elicit terminal CD8+ T cell exhaustion](#). *Cell Reports*.**

*Summary by Gaurang Telang*