iPSC-derived gdT with novel combinatorial KO demonstrated significant anti-tumor activity and extended longevity without cytokine support

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Abstract

Induced pluripotent stem cell (iPSC)-derived cell treatment offers several competitive benefits, including consistency, homogeneity and unlimited dosage, in contrast to autologous and allogeneic donor-derived cell therapies. These attributes improve affordability and accessibility of medicines worldwide. Noteworthy, the effectiveness of T cell therapy is constrained by factors such as cell potency and persistence. Our research on iPSC-derived gamma-delta T (gdT) cells has identified a novel combinatorial KO to overcome these challenges.

IL-2 administration has been approved by FDA for durable, complete, and apparently curative regressions in cancer patients. Previous studies demonstrated that IL-2 receptor beta (IL-2Rb) chain-mediated signaling pathway is critical for killing potency and cell persistence. The suppressor of cytokine signaling (SOCS) family helps control cytokine signaling by blocking the JAK/STAT pathway. For example, cytokine-inducible SH2-containing protein (CISH) is a member of the SOCS protein which is essential for managing cytokine signaling, cell growth, differentiation, and immune system activities. Our findings indicated that igdT cells deficient in both CISH and another SOCS family protein exhibited increased persistence and enhanced cytotoxic capabilities compared to cells with only one of the knockouts. Notably, we demonstrated the proliferative advantage of double SOCS protein KO by using PBMC humanized mouse model.

Cytokine withdrawal- and activation-induced cell death were key factors that diminish effector cell persistence post perfusion. For prolonging cell survival, we identified a mediator of mitochondrial apoptotic pathway and found that this proapoptotic protein is necessary for extending the survival of igdT cell post IL-15 withdrawal. In addition, FAS-FASL signaling was recently identified as auto-regulatory circuit for CAR-engineered lymphocyte persistence. We presented biochemical data and performed gain-of-function experiments to elucidate the mechanisms by which this proapoptotic protein contributes to the extended survival of effector cells. Furthermore, we demonstrated FAS deficiency protects functional enhanced igdT cells from FASL-induced apoptosis and then enhances its durable killing ability against HepG2 cells.

Altogether, we identified a novel combination of gene knockouts that extends longevity and profound anti-tumor efficacy without cytokine support. We achieved the goldilocks signaling balance could strengthen the efficacy and longevity of igdT cell, while avoid the possible dysfunction, such as exhaustion, caused by introducing constitutively active cytokine receptors as many others have attempted. Building on this engineering platform, we could incorporate tumor-targeting receptors for treating different indications in the near future.