ENHANCED CYTOLYTIC EFFECTOR FUNCTION AND ANTI-TUMOR EFFECTS OF EXHAUSTED CD8 T-CELLS BY THE KLF4 EXPRESSION

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Background Antigen-specific CD8 T-cells reach an unresponsive state during chronic inflammatory responses against viral infections and cancer, which is described as exhaustion. Exhausted CD8 T-cells are phenotypically and functionally heterogeneous. It has been reported that the number of progenitor exhausted CD8 T-cells increases in response to anti-PD-1 immunotherapy, which appears to be a critical factor for the successful control of chronic viral infection and cancer. Effective immune responses exerted by the progenitor exhausted CD8 T-cells imply that cells with effector functions may develop from the progenitor cells. Indeed, CD8 T-cells with effector characteristics in the exhaustion context have recently been identified.

Methods Using in vitro CD8 T-cell exhaustion model and mouse tumor model, we analyzed the expression of Klf4 and single cell RNA sequence during the exhaustion process. We also combined retroviral transduction of Klf4 on CD8 T-cells with the models to figure out the role of Klf4 on anti-tumor immunity. To investigate whether Klf4 expression could reinvigorate exhausted CD8 T-cells, we used modified in vitro exhaustion model in which Klf4 could be induced after the exhaustion process, not during the activation stage. Lastly, to apply the results to human cancer patients, we used analytical tools to examine the correlation between gene expression and tumor prognosis.

Results We found that Klf4 is a hallmark of the cytolytic transitory effector CD8 T-cells during the exhaustion process. Klf4 is required for the differentiation and function of transitory effector CD8 T-cells. In consequence, Klf4 expression in CD8 T-cells enhances anti-tumor immunity and provides great advantage in controlling tumor growth in mice. Importantly, we demonstrated that Klf4 expression could reinvigorate the effector function of exhausted CD8 T-cells, in part by restoring epigenetic status of genes related to effector function. In addition, Klf4 expression blocked the exhaustion of human CD8 T cells expressing the GD2 CAR construct, and our TCGA data analysis suggested that KLF4 expression correlates well with the prognosis of cancer patients. We also found that upregulation of KLF4 expression by anti-PD-1 therapy increased the survival rates of melanoma patients.

Conclusions Klf4 promotes the differentiation of CD8 T-cells into cytolytic transitory effector cells and blocks reaching into terminal exhaustion. Klf4 expression could reinvigorate the effector function of terminally exhausted CD8 T-cells, Thus, the potential effects of Klf4 on CD8 T-cell exhaustion can be highlighted in terms of anti-tumor immune therapy.

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