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Thesis title: Aging impairs CD8 T cell responses in adoptive T-cell therapy against solid tumors

Research aim:

Aging of immune system is associated with decrease in T cell function and recognition of new antigens. This could be connected to an increased tendency of cancer incidence in people over 65 years old. Despite the advancement in cancer immunotherapy there is a lack of knowledge on how aging of immune system affects the efficiency of cancer immunotherapy. Here, we report that aging of immune system significantly decreases the efficiency of CD8+ T cell response to B16 melanoma in a mouse model of ACT. In addition, we found that it is due to age-induced cell-intrinsic changes which play as a negative factor in anti-tumor response of CD8+ T cells in ACT model.

Material and method:

Young (8-16 weeks old) and aged (68-96 weeks old) C57BL/6 mice were obtained from Jackson Laboratory. OT-I mice (CD45.1+CD45.2+) were obtained from breeding of OT-I mice (CD45.1-CD45.2+) (Jackson, 003831) and B6SJL mice (CD45.1+CD45.2-) (Jackson, 002014). Total murine CD8+ T cells were isolated and activated. Further retroviral transduction was used to overexpress OTI-TCR which specifically recognizes ovalbumin (OVA) antigen on mouse melanoma cell line (B16-OVA) to be used in mouse melanoma ACT model. The cell numbers and viability were analyzed by using Muse Count and Viability kit. Specific T cell cytotoxicity was analyzed by co-culturing OTI-TCR-T cells with B16-OVA. The cells were stained with Annexin V and ZombieNIR and viability of target cells (B16-OVA) was analyzed by flow cytometry. The cytokine expression was analyzed by flow cytometry. The aging-mediated changes to T cells were investigated by performing single-cell RNA-sequencing analysis. For in vivo characterization of anti-tumor efficiency of aged cells, melanoma cells were subcutaneously injected on the right flank of mice. Fur was removed from the injection site to improve accurate measurement of tumor size. After the tumor was established, OTI-TCR-T cells were adoptively administered. Tumor size was measured every other day. We also evaluated the T cells from tumor site after day 18. Finally, flow cytometry was used to evaluate exhaustion markers on OTI-TCR-T cells after adoptive transfer.

Result:

Aging of immune system decreases the anti-tumor activity and it is due to cell-intrinsic aging of CD8+ T cells. Cell-intrinsic aging leads to a decrease of ratio of progenitor exhausted cells and terminally exhausted cells. Cell-intrinsic aging also decreased DNA-damage repair and Myc hallmark pathways. Further, single-cell RNA-sequencing demonstrated important genes for survival and infiltration of CD8+ T cells to tumor site. Supplementation of these genes will benefit largely the efficiency of cancer immunotherapy.

Conclusion:

Cell-intrinsic aging of CD8+ T cells significantly reduces the anti-tumor response and enhancing the activity of CD8+ T cells in elderly patients will increase the efficiency of cancer immunotherapy.