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**IMSUT International Joint Usage/Research Center Project <International>**

**Joint Research Report (Annual/Project Completion)**

**Annual Report**

**Report**

In this research project, we focus on states of exhaustion of CD8+ T cells and NK cells during disease progression of viral infection and cancer development. We particularly investigate CD8+ T cell and NK cell exhaustion in hematopoietic malignancies progressed by EBV infection and HTLV1 infection.

Although CD8+ T cells are important immune cells for the clearance of virus-infected cells and cancer cells, NK cells also play major roles for host protection against infectious pathogens and cancer cells. Nevertheless, the states of exhaustion of NK cells are relatively elusive compared to CD8+ T cells. Therefore, we examined the states of NK cells in patients or mouse models with viral infection or cancer, including hematopoietic malignancies from public databases and previous studies in accordance with our research plan1. We then found that exhausted NK cells highly express PD-1, TIGIT, TIM-3, and LAG-3 like exhausted CD8+ T cells and that production of IFN$\gamma$, granzyme B, TNFa, CD107a, etc from exhausted NK cells are decreased (Sean J. Judge et al. *Front. Cell. Infect. Microbio*l., 2020). In addition, their cytotoxicity including antibody dependent cell-mediated cytotoxicity (ADCC) against target cells is decreased. Interestingly, continuous IL-15 exposure induces exhaustion of NK cells with altered metabolism (Felices et al. *JCI Insight*, 2018). Both IL-2 and IL-15 are important for proliferation and activation of CD8+ T cells and NK cells and both cytokines induce phosphorylation of STAT5. As shown in our previous study (Fei Mo et al. *Nature*, 2021), engineered IL-2 partial agonist doesn't induce phosphorylation of STAT5 and show different metabolism from WT IL-2. Therefore, we expect that engineered IL-2 partial agonist will inhibit NK cell exhaustion as same as CD8+ T cells (our research plan3).

To investigate states of exhaustion of CD8+ T cells and NK cells in mice with hematopoietic malignancies, we have constructed retro virus vectors expressing LMP1/LMP2A and HBZ/Tax that mimic EBV infection and HTLV1 infection, respectively (our research plan2). Then, we plan to transduce those virus vectors into murine bone marrow cells and transplant them into sublethally irradiated mice to establish mouse models. Moreover, to compare those mouse models with hematopoietic malignancies caused by mutations in the endogenous genes, we have established several mouse models with acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and acute lymphoblastic leukemia (ALL).