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研究課題名	Control of T cell and NK cell exhaustion to overcome viral infection and cancer development	
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IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Annual/Project Completion)

Project Completion Report

Report

We investigated which surface molecules on leukemic cells could affect the exhaustion of $CD8^+$ T cells and NK cells. We found that CD112, also known as Nectin-2, expressed on leukemic cells, inhibits the cytotoxicity of NK cells. CD112 is one of the immune checkpoint molecules expressed in both hematologic malignancies and solid tumors.

Interestingly, CD112 interacts with three ligands: CD112R, TIGIT, and CD226 (also known as DNAM-1). It is known that the functions of $CD8^+$ T cells and NK cells are suppressed through interactions with CD112R or TIGIT, whereas these cells are activated via CD226/DNAM-1.

Therefore, we utilized the CRISPR-Cas9 system to generate CD112 knockout (KO) leukemic cells and found that NK cells exhibit higher cytotoxicity against CD112 KO cells compared to wild-type (WT) CD112-expressing cells.

Additionally, we examined whether drug treatment affects CD112 expression on leukemic cells and the cytotoxicity of NK cells. We discovered that several anti-cancer drugs induce upregulation of CD112 expression. Consistently, NK cell cytotoxicity against drug-treated leukemic cells was reduced compared to untreated cells.

To further investigate this, we evaluated NK cell cytotoxicity after treating CD112 KO leukemic cells with anti-cancer drugs. We found that NK cells exhibited increased cytotoxicity compared to the control group. Furthermore, when neutralizing antibodies against CD112 were added along with NK cells to drug-treated leukemic cells, the cytotoxicity of NK cells was significantly enhanced compared to treatment with control antibodies.

As mentioned above, CD112 interacts with CD112R, TIGIT, and CD226/DNAM-1. Among these, we focused on CD226/DNAM-1 because it is an activating receptor for $CD8^+$ T cells and NK cells. We confirmed that NK cells transduced with CD226/DNAM-1 exhibit enhanced cytotoxic activity against leukemic cells compared to non-transduced NK cells.

Taken together, these results suggest that combining anti-cancer therapy with neutralizing antibodies against CD112, or adoptive cell therapy using NK cells engineered to express CD226/DNAM-1, may represent promising strategies to target leukemic cells that highly express CD112—particularly those that persist following drug treatment.