Title: Recombinant CD155 promotes tumor proliferation as well as IL-13 expression in cutaneous T-cell lymphoma

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Introduction:
CD155, also known as poliovirus receptor, has recently drawn much attention because of its immunoregulatory role in tumor microenvironment. CD155 expressed in varieties of tumors has various effects on cytotoxic T cells dependently on its ligands. It downregulates immunoreaction against tumor cells through its binding with T cell immunoreceptor with Ig and ITIM domain (TIGIT) expressed on cytotoxic T cells. On the other hand, interaction between CD155 and CD226, also known as DNAX-associated molecule 1, activates cytotoxic T-cell-mediated anti-tumoral activity. We have reported that CD155 is expressed in CTCL lesional skin and that the molecule is the target for soluble CD226, suppressing proliferation of tumor cells. However, the effect of CD155 on CTCL tumor cells themselves is not well-documented. Here we investigated the function of CD155 in CTCL.

Methods:
Peripheral blood mononuclear cells (PBMC) were obtained from patients with Sezary syndrome (SS) and healthy controls. CD155 expression on $CD4^+CD7^-$ T-cells and $CD4^+CD7^+$ T-cells was analyzed using flow cytometry. CTCL cell lines (Myla, SeAX, HH, Hut78) were cultured and the expression of CD155, TIGIT, and CD226 was analyzed by flow cytometry and quantitative real-time reverse-transcription (RT)-PCR. The effect of recombinant CD155 (rCD155), anti-CD155 monoclonal antibody (αCD155), or anti-TIGIT antibody (αTIGIT) on viable cell counts of Myla and SeAX cells was evaluated on day 3. Expression of IL-13 by Myla and SeAX was also analyzed by quantitative RT-PCR.

Results:
CD155 was expressed higher on $CD4^+CD7^-$ T-cells in PBMC from SS patients than on those from

healthy doners, whereas there was no significant difference in CD155 expression levels on $CD4^+CD7^+$ T-cells between SS patients and healthy donors. CD155 was expressed on all CTCL cell lines, while no cell lines expressed CD226. TIGIT was expressed by Myla and SeAx. Those cells showed increased cell numbers by addition of rCD155, and αCD155 significantly reduced their proliferation. Contrary to our expectation, αTIGIT did not change cell numbers of these cells, suggesting that the ligand of CD155 may be different from TIGIT. Addition of rCD155 also increased IL-13 mRNA expression in SeAX.

Conclusion:
We have demonstrated that rCD155 increases proliferation of CTCL tumor cells as well as IL-13 expression. These findings suggests that CD155 is a promising target molecule for the treatment of CTCL.