学位論文抄録

Control of HIV-1 by NK cells via KIR2DL2

(KIR2DL2 を介した NK 細胞による HIV-1 の感染制御)

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Abstract of the Thesis

[Background and purpose] Killer cell immunoglobulin-like receptors (KIRs) play an important role in the regulation of NK cell anti-viral functions and influence the clinical outcome of HIV-1 infection. In the present study, we studied the effect of KIR-HLA interaction on NK cell reactivation and eradication of HIV-1 infection in the Japanese population.

[Methods] We analyzed the correlation between the clinical outcomes of HIV-1 infection and the presence of different KIR genes or KIR-HLA combinations in a cohort consist of 504 treatment naïve HIV-1 chronically infected Japanese patients. In order to clarify the mechanisms of the protective effect of KIR genes or KIR-HLA combinations, we then performed viral suppression assay, NK cell functional assay, peptide-HLA binding assay and pHLA-KIR binding assay.

[Results] The genetic analysis identified two KIR/HLA combinations, KIR2DL2/HLA-C*12:02 and KIR2DL2/HLA-C*14:03, with synergistic effect on suppression of HIV-1 replication. Viral suppression analysis showed that KIR2DL2^{+} NK cells inhibited viral replication significantly stronger than KIR2DL2^{-} NK cells in HLA-C*14:03^{+} or HLA-C*12:02^{+} cells infected with the WT HIV-1 or the virus with an escape mutation. Binding assay suggested that the reduced peptide-HLA binding and the lower pHLA surface expression level directly influences NK cell recognition of the target cells and reactivation via KIR2DL2.

[Discussions] We showed that peptide-HLA binding and surface expression directly influence KIR2DL2^{+} NK cell reactivation which is different from previous studies on Caucasian and African cohorts suggesting that the binding affinity of inhibitory KIRs to the pHLA influences NK cell activity.

[Conclusions] We demonstrated the synergistic effect of KIR2DL2/HLA-C*12:02 and KIR2DL2/HLA-C*14:03 on HIV-1 control as well as the role of NK cells via KIR recognition in HIV-1 infection.