DOWNREGULATION OF CD155 RESULTS IN HIV-1 RESTRICTION BY KIR2DL5+ NK CELLS

305

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BACKGROUND

- HIV-1 downregulates CD155
- CD155 serves as a NK cell receptor ligand for
  - the inhibitory KIR2DL5
  - the activating DNAM-1

HYPOTHESIS

- HIV-1 downregulates CD155 to escape DNAM-1 dependent NK cell recognition
- CD155 downregulation → loss of inhibition of KIR2DL5+ NK cells
- Enhanced antiviral activity of KIR2DL5+ NK cells

METHODS

Interactions between KIR2DL5 and CD155 were analyzed using KIR-IgG fusion proteins. In addition, NK cell degranulation in response to CD155-expressing target cells was assessed. CD155 surface levels during HIV-1 infection were determined by infecting CD4+ T cells with eight wild type HIV-1 strains or respective Nef-deficient mutants and quantified by flow cytometry. Antiviral activity of KIR2DL5+ NK cells was assessed by co-cultivation of NK cells with HIV-1 infected cells (wild-type or Nef-deficient) and quantified as inhibition of viral replication.

RESULTS

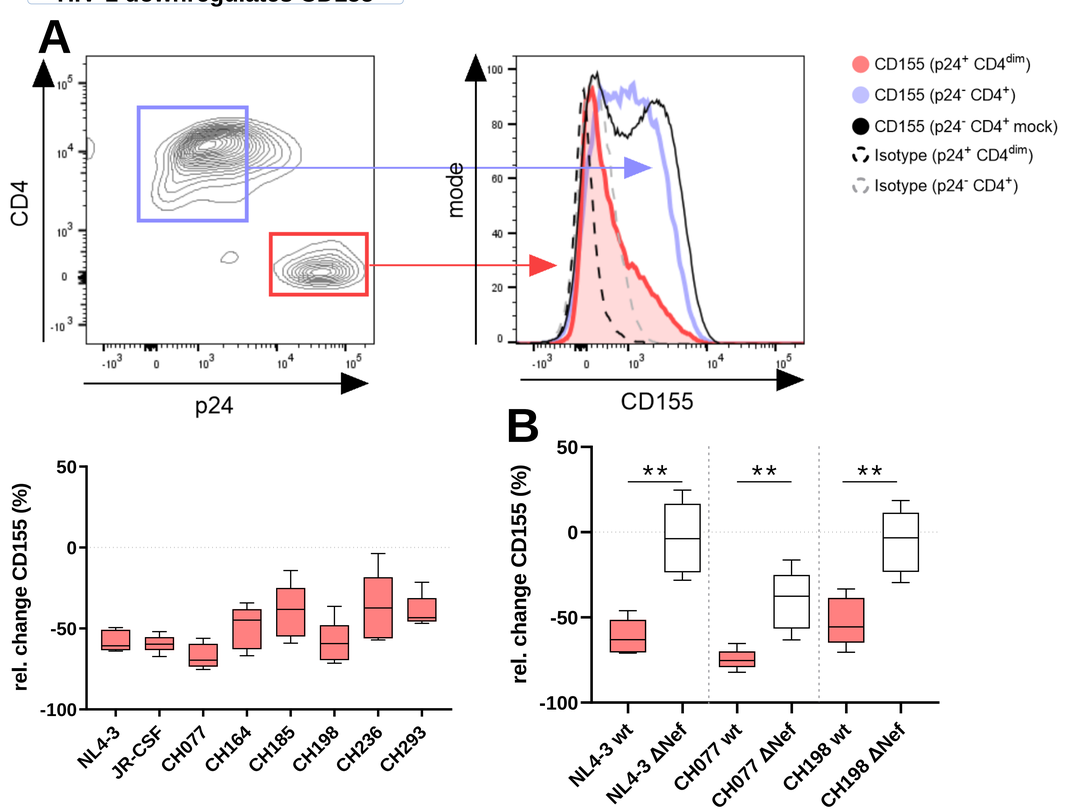
Binding of KIR2DL5 to CD155 was observed after incubation with CD155-coated beads. Primary human KIR2DL5+ NK cells exhibited lower degranulation levels after incubation with CD155-positive target cells compared to CD155-negative target cells, and this difference was abrogated by blocking CD155. Furthermore, all tested HIV-1 strains downregulated CD155 from the surface of infected cells in a Nef-dependent manner. In agreement with this, co-culture of infected CD4+ T cells with NK cells revealed increased inhibition of wild-type versus Nef-deficient HIV-1 by KIR2DL5+ NK cells.

CD155 suppresses the antiviral activity of **KIR2DL5+ NK cells** and is **downregulated by HIV-1 Nef** to counteract activating NK cell receptors, resulting in **enhanced antiviral activity of KIR2DL5+ NK cells.**

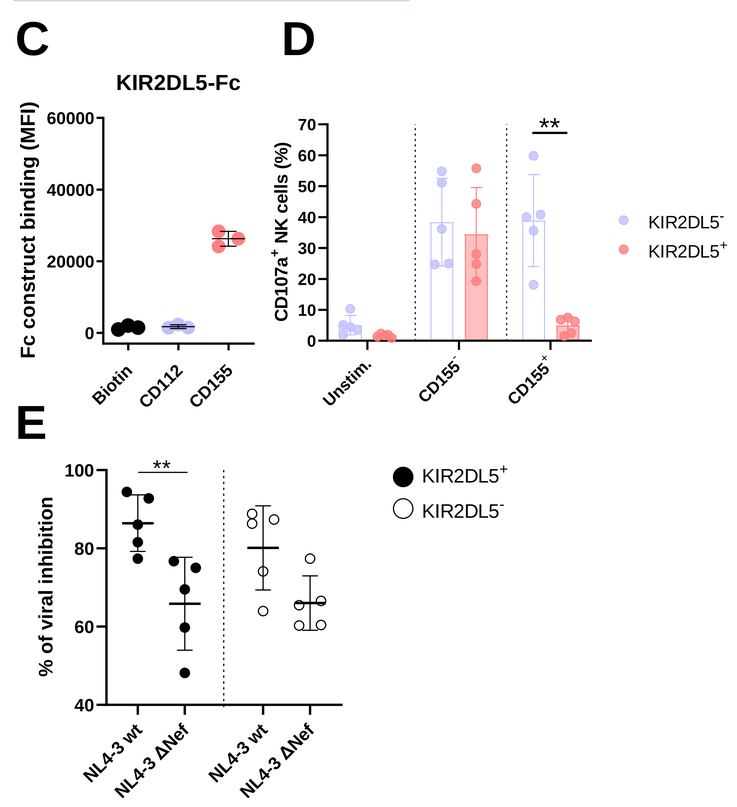
CONCLUSIONS

These data confirm that CD155 serves as a functional ligand for the inhibitory NK cell receptor KIR2DL5, suppressing the antiviral activity of KIR2DL5+ NK cells. CD155 is downregulated by HIV-1 Nef to counteract activating NK cell receptors, such as DNAM-1. However, HIV-1-mediated downregulation of CD155 renders infected cells more vulnerable to recognition by KIR2DL5+ NK cells.

HIV-1 downregulates CD155



CD155 inhibits KIR2DL5+ NK cells



A CD155 levels on HIV-1 infected ($CD4^{low}$ $p24^{high}$) and uninfected ($CD4^{high}$ $p24^{-}$) CD4+ T cells analyzed by flow cytometry. Relative change of CD155 levels was assessed for cell line-adapted (NL4-3, JR-CSF) and primary (CH077, CH164, CH185, CH198, CH236, CH293) HIV-1 strains.
B Downregulation of CD155 by HIV-1 wild-type and Nef-deficient mutant viruses.
C KIR2DL5-Fc fusion protein binding to CD155 coated beads determined as median fluorescence intensity (MFI).
D CD107a expression of KIR2DL5+ and KIR2DL5- NK cells in response to CD155 expressing or non-expressing target cells.
E Viral inhibition of wild-type vs. Nef-deficient HIV-1 by KIR2DL5+ and KIR2DL5- NK cells.

Acknowledgements

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