Do KIR3DL1/HLA-B Combinations Influence ADCC Responses of HIV-1 Infected Slow Progressors?

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BACKGROUND:

The "h"y+B57 genotype, which encodes high expression Killer Immunoglobulin-like Receptor (KIR)/3DL1 variants, and HLA-B*57 is the KIR/HLA combination with the strongest effect on slowing time to AIDS and controlling HIV viral load, as compared to Bw6 homozygotes (Bw6hmz). The interaction of 3DL1 with HLA-B*57 is a potent natural killer (NK) cell licensing combination. The percentage of functional NK cells induced by HLA-null or autologous HIV-infected CD4 cells is higher when from "h"y+B57 carriers than from Bw6hmz or carriers of several other 3DL1hmz/HLA-Bw4 combinations. Using cells from HIV-infected slow progressors (SP) we investigated whether KIR3DL1/HLA genotypes that support licensing (3DL1+Bw4) generate NK cells with higher ADCC activity than those that do not (3DL1+Bw6hmz).

METHODS

We studied 48 3DL1hmz SP with plasma VL<3000 cells/mm³, including carriers of HLA-Bw4+HLA-B*57. (n=34), Bw6hmz (n=12) and "h"y+B*57 (n=6) genotypes. Anti-HIV ADCC was measured using a GranToxiLux (GTL) assay, which assesses the ability of NK cells (effectors) to deliver granzyme B (gZB) to HIV gp120-coated CEM.NkrCCR5 targets (%gZB+ cells) in the presence of a common pooled source of anti-HIV IgG. The significance of between-group differences was assessed using the Mann-Whitney test.

RESULTS

Figure 3. NK cells from HIV-infected SP subjects mediate ADCC.
A. NK cells from 3DL1hmz mediated significantly higher levels of ADCC in the presence versus absence of pooled plasma Ig (p=0.0001). B. Matched pairs test showing %GTL activity in the presence versus absence of Ig in the 48 subjects tested (p=0.0001).

Figure 4. HLA-Bw4+ and Bw6hmz 3DL1hmz individuals exhibited similar levels of ADCC.
A. NK cells from 3DL1hmz who were HLA-Bw4+ or Bw6hmz mediated equivalent levels of ADCC (21.1 ± 13.8 vs 24.05 ± 20.7 %GZB cells+, p=0.87). NK cells from "h"y+B*57 carriers also mediated similar levels of ADCC activity (20.7 ± 16.1) as those from Bw6hmz (p=0.96) and carriers of other Bw4 alleles (p=0.85).

CONCLUSIONS

- NK cells from HIV-infected SP mediate ADCC.
- Carrying KIR/HLA combinations that play a role in NK cell licensing through 3DL1 ligation does not influence the potency of ADCC activity of NK cells from HIV-infected SP.
- This analysis is being replicated in HIV seronegative subjects to assess whether HIV infection may abrogate the influence of licensing on ADCC even in this well controlled population.

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Model for anti-HIV control by NK cells from subjects positive for *h/*y+B*57