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KIR-HLA footprints and NK cell-mediated recognition of HIV-1

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Background

Increasing data suggest an important role of KIR+ NK cells in the control of HIV-1, however the precise mechanisms on how NK cells recognize HIV-1-infected cells remain poorly understood. KIRs can bind to HLA class I molecules, but the binding affinity of these interactions is dependent on the HLA class I presented epitope. Recent reports have suggested that sequence variations within HIV-1 epitopes presented by HLA class I can affect the binding of inhibitory KIRs expressed on NK cells, potentially modulating NK cell responses to infected cells. Here we investigated whether HIV-1 might adapt to the combined KIR/HLA genotypes on a population level to identify areas within HIV-1 that might be targeted by KIR+ NK cells.

Methods

HIV-1 Gag was sequenced in 390 untreated chronically clade C infected individuals from KwaZulu-Natal, South Africa. All study subjects were HLA class I and KIR typed. Phylogenetically-corrected logistic regression analysis of KIR/HLA associated Gag sequence polymorphisms was performed and q-values were used for multiple test correction.

Results

A total of 93 sequence polymorphisms significantly associated with the combined HLA/KIR genotypes were identified ($p<0.05$), 6 of them with a false-positive rate of less than 20% ($q<0.2$). These significant associations were independent of previously identified KIR or HLA-linked polymorphisms.

Conclusion

This study identified several sequence polymorphisms within HIV-1 Gag that were significantly associated with the expression of combined KIR/HLA genotypes at the population level, indicating adaptation of HIV-1 to NK cell mediated immune pressure. KIR/HLA class I binding studies in the context of the sequence polymorphisms and studies for NK cell function are ongoing to determine the consequence of these sequence changes for NK cell-mediated recognition of HIV-1-infected cells.

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