KIR B haplotype modulates susceptibility to cHL in an EBV dependent manner

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Introduction

Recognition of HLA class I ligands by killer cell immunoglobulin-like receptors (KIRs) expressed on NK cells plays a key role in immune surveillance against virally infected cells and tumor cells. The highly polymorphic KIR locus can be divided into haplotype A alleles containing at most one activating gene and haplotype B alleles containing multiple activating KIR genes. The HLA locus is the strongest genetic factor associated with cHL susceptibility, but the potential role of KIR genes remains largely unexplored. In this study, we investigated the effect of KIR on susceptibility and tumor cell HLA expression in overall cHL and EBV-stratified subgroups.

Methods

KIR and HLA type were determined by direct typing for 210 cHL cases. EBV status and HLA class I expression data of patients were retrieved from previous studies. SNP data of the Dutch GoNL controls (n=498) were used to impute HLA types and predict KIR types. Chi square and Fisher's exact tests were used in association analyses.

Results

The KIR haplotype B frequency was not different in cHL overall compared to controls (72% vs 67%), and also not in EBV-stratified subgroups compared to controls. However, direct comparison between EBV+ and EBV- cHL did reveal a significant difference (62% vs 77%, p=0.04). A similar difference between EBV+ and EBV- cHL was observed for two out of five haplotype B specific activating genes. Loss of HLA class I expression in KIR haplotype B carriers was observed more frequently in EBV- than EBV+ cHL (84% vs 24%, p<0.0001), whereas it was not different in non-carriers (64% vs 52%, p=0.56).

Conclusion

KIR haplotype B carriers are less likely to develop EBV+ cHL, but when they do develop EBV+ cHL they are more likely to retain HLA class I expression. In contrast, KIR haplotype B carriers who develop EBV- cHL more frequently lose HLA class I expression. Based on these findings we hypothesize that tumor cells in KIR B+ EBV+ cHL need to retain HLA class I expression to avoid killing by NK cells, while tumor cells in KIR B+ EBV- cHL need to lose HLA class I expression to avoid killing by cytotoxic T cells.