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TheStructure of the Murine CD94/NKG2A Complex Reveals Convergence With the Human Homologue

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Natural Killer cells are immune effectors that clear viruses and malignancies through the gain of recognition of “altered self (stress)” molecules or through the loss of recognition of “healthy self” molecules on the target. The heterodimeric CD94-NKG2A receptor is an inhibitory receptor that monitors global MHC class I expression levels through binding to MHC class Ia-derived leader sequence peptides presented by HLA-E (in humans) or Qa-1b (in mice). In so doing, CD-NKG2A monitors for “healthy self”. Viruses and malignancies that down-regulate MHC-Ia expression to evade recognition by the T-cell arm of the adaptive immune system are thus vulnerable to natural killer cell clearance through “dis-inhibition” of CD94/NKG2A. This system of “immune cross-checking” has made the CD94/NKG2A system a promising target for therapeutic intervention with a number of check-point inhibitor antibodies that target CD94/NKG2A currently in clinical development. In this study we determined the high-resolution crystal structure of murine CD94-NKG2A in complex with Qa-1b presenting the Qa-1 determinant modifier (Qdm) peptide, and thus provide the mode of binding in mouse. Through comparison with the human homologue we show that despite an overall similar binding mode, recognition of Qa-1b by murine CD94-NKG2A occurred via altered electrostatic complementarity. These data show how human and murine CD94-NKG2A have co-evolved with HLA-E and Qa-1b which exhibit cross-species heterogeneity yet exhibit highly similar function. This has important implications for understanding differences in the model murine system compared to the human for the clinical progression of disease.

Speakers Gender

Male

Travel Funding

No

Level of Expertise

Experienced Researcher

Do yo wish to take part in the poster slam

No

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