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**Crystal Structure of an NK Cell Immunoglobulin-Like Receptor in Complex with its Class I MHC Ligand**

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**ABSTRACT:** Target cell lysis is regulated by natural killer (NK) cell receptors that recognize class I MHC molecules. Here we report the crystal structure of the human immunoglobulin-like NK cell receptor KIR2DL2 in complex with its class I ligand HLA-Cw3 and peptide. KIR binds in a nearly orthogonal orientation across the alpha1 and alpha2 helices of Cw3 and directly contacts positions 7 and 8 of the peptide. No significant conformational changes in KIR occur on complex formation. The receptor footprint on HLA overlaps with but is distinct from that of the T-cell receptor. Charge complementarity dominates the KIR/HLA interface and mutations that disrupt interface salt bridges substantially diminish binding. Most contacts in the complex are between KIR and conserved HLA-C residues, but a hydrogen bond between Lys 44 of KIR2DL2 and Asn 80 of Cw3 confers the allotype specificity.