Structural Basis of Ligand-Receptor Pairing Between Members of Two NK Gene Complex Encoded Families

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Natural killer (NK) cells utilize diverse surface receptors to monitor surrounding cells for signs of pathology. We have observed that Nkrp1 family receptors specifically recognize members of the structurally related Clr family encoded in the same genetic locus. Nkrp1 molecules are expressed on NK cells and some T cells, while the Clr proteins are predominantly found on antigen presenting cells. Herein we present the crystal structure of Nkrp1f both alone and in complex with Clrg, which is the first example of receptor-ligand pairing between two C-type lectin-like proteins. We find that soluble Nkrp1f and Clrg associate with micromolar affinity and rapid kinetics, similar to other lymphocyte surface proteins. The Nkrp1f/Clrg complex reveals a head-to-head orientation in which both proteins utilize the same interface associated with MHC-binding by other NK gene complex-encoded receptors, a finding we support by site-directed mutagenesis. We also demonstrate that the Clrg protein can both form homodimers and also heterodimers with another Clr family member, the Clrb protein. Our results provide a general framework for understanding Nkrp1/Clr family interactions that is highlighted by our successful re-engineering of Nkrp1f into a promiscuous binder of both Clrg and Clrb as well as a selective binder of Clrb. Thus, future experiments directed at deciphering the regulatory roles of individual Nkrp1 and Clr members in innate immunity can now proceed based on a solid biochemical foundation.