Importance of receptor geometry for signalling initiation by the mincle family receptors

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The mincle receptor family consists of the structurally similar C-type lectins, mincle, dectin-2 and BDCA-2. Constellation of amino acids around the primary Ca^{2+}-binding site of these receptors confers affinity for mannose, glucose and *N*-acetylglucosamine. Via association with FcRγ, mincle and dectin-2 stimulate macrophages in response to pathogen glycans, while BDCA-2 tapers production of type I interferon caused by TLR signalling followed by pathogen infection or cell death in autoimmunity. In this work, the oligomeric states of these receptors and the orientations of their CRDs have been investigated to elucidate how extracellular ligand binding initiates cytosolic signalling. We show that dimers of mincle are stabilized by disulfide bonds between cysteine residues in the neck sequence. BDCA2 forms noncovalent dimers, although a naturally occurring variant can form an interchain disulfide bond. Cysteine residues in the transmembrane portions of these receptors are not required for dimer formation or association with FcRγ, but may facilitate trafficking to the cell surface. We investigated how CRDs are positioned in receptor dimers using fusion protein of receptor extracellular domains and N-terminal dimerization domains. Analysis of these constructs showed limited interaction of the CRDs in the dimers, but interactions can be stabilized by the presence of the neck region. The resulting orientation of sugar-binding sites in the dimers would favour crosslinking of multiple dimers by oligosaccharide ligands, causing clustering of FcRγ to initiate signalling.