Contribution ID : **3** Type : **Oral**

Structural basis for the recognition of nectin adhesion proteins by the Natural Killer cell receptors, TIGIT, CD96 and DNAM-1

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TIGIT, CD96 and DNAM-1 constitute a family of immune receptors that regulate the activity of Natural Killer (NK) cells towards transformed targets. The capacity of these nectin receptors to mediate target cell adhesion, immune synapse formation and regulate effector function is dependent on their recognition of nectin and nectin-like (necl) adhesion molecules, which are over-expressed in a wide variety of cancers. Within this axis, DNAM-1 is a stimulatory receptor that activates NK cell-mediated cytotoxicity and is cririal for tumour immune surveillence, while TIGIT is an inhibitory receptor that counteracts DNAM-1 activity. Whether CD96 functions as an activating or inhibitory receptor is unclear. Here, we have determined the crystal structures of all of the human nectin receptors in complex with their cognate ligands, including TIGIT:nectin-2, CD96:necl-5 and DNAM-1:necl-5. In addition, we have performed a comprehensive binding and mutational analysis of these receptors to fully characterise their ligand binding affinity and specificity. Our findings indicate that TIGIT, CD96 and DNAM-1 recognise their ligands with similar (low-micromolar range) affinity using a conserved docking topology that is reminiscent of that observed for nectin-nectin homo/heterodimer assembly. Structural and mutational analysis highlighted the important role that the 'lock and key' motifs within the first extracellular immunoglobulin domain (D1) of each receptor play in ligand binding. Moreover, we demonstrated that the C-C' loop of TIGIT dictates its ligand binding hierarchy, identified a novel motif in CD96, termed the 'ancilliary key', that is critical for necl-5 recognition, and interrogated the role of the second Ig domain of DNAM-1 in necl-5 binding. Altogether, these data significantly broaden our understanding of nectin-nectin receptor interactions and has implications for understanding the molecular basis for tumour recognition and escape.

Speakers Gender

Male

Travel Funding

No

Level of Expertise

Experienced Researcher

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No

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