Abstract

To the PhD thesis titled
"**Molecular and structural bases of nectin-mediated cell-cell adhesion**"
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Cell adhesion molecules (CAMs) are cell-surface glycoproteins that form cell-to-cell or cell-to-matrix adhesion at sites of cellular junctions and are thus the basis of multicellular architecture. In higher vertebrates, adherens junctions are cell-to-cell contacts formed by the concerted functioning of two families of CAMs-nectins and cadherins. This work explores the molecular and structural bases of nectin-mediated cell-cell adhesion.

Nectins are a family of four single-pass type-I membrane glycoproteins belonging to the immunoglobulin superfamily of CAMs. They interact through their membrane-distal immunoglobulin-like domains to form homodimers and specific heterodimers within the family to support cell adhesion. However, the specific heterodimers are stronger and physiologically relevant, while the homodimers are weaker with no known physiological functions. **In the first objective, the molecular mechanism controlling nectin-nectin interactions was studied.** Data shows that a conserved charged residue present on the dimer interfaces dictates the specificity of nectin-nectin interactions.

Besides nectin-nectin interaction, it is well-established that nectins also recruit cadherins to adherens junction through their cytoplasmic region-associated adaptor proteins, resulting in indirect nectin-cadherin cross-talk. However, a recent study on frog neurulation showed that nectin-2 can recruit N-cadherin even when the cytoplasmic region of nectin-2 is deleted, suggesting that N-cadherin and nectin-2 may interact directly through their extracellular domains. **The second objective of this work explores the molecular and structural bases of this novel interaction between human N-cadherin and nectin-2 through their extracellular domains.** Surface plasmon resonance study demonstrates that membrane-distal ectodomain of nectin-2 can directly recognise that of N-cadherin with a K_D of 3.5 μM. Furthermore, molecular docking and complementary mutagenesis studies reveal the key residues that mediate this novel interaction.

Multicellular architecture evolved due to the emergence of cell-cell junctions. While studies suggest that adherens junction and cadherins existed in early metazoans, no such studies currently explore the evolution of the nectin family. **In the third objective, a systematic search for nectins was carried out in selected metazoans to gain better insights into how nectin-cadherin co-operative functions evolved to support the formation of adherens junction.** Results indicate that while the nectin family is predominant in vertebrates, it has pre-vertebrate origins.

Anomalies in cell-cell adhesion are predominant in several disease conditions such as tumour metastasis and developmental defects. Understanding the various mechanisms behind nectin-mediated cell-cell adhesion provides valuable insights into the fundamental processes governing cell-cell adhesion, as well as the role played by these processes on other aspects like development and signalling.

Keywords: nectin, cadherin, cell adhesion molecules, cell-cell adhesion, adherens junction, evolution of protein families, molecular cloning, expression and purification of proteins, inclusion bodies, refolding of proteins, protein-protein interaction studies, surface plasmon resonance (SPR).