INVESTIGATING THE INTERACTION OF PEPTIDOMIMETIC LIGANDS WITH E-CADHERIN USING NMR AND COMPUTATIONAL STUDIES

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Classical cadherins are versatile calcium-dependent cell–cell adhesion proteins, differentially and specifically expressed in different tissues. Cadherins form homophilic cell–cell interactions by forming dimers between the N-terminal extracellular domains of two cadherins on adjacent cells (Figure 1). Cadherins are known to play a key role in important physiological processes, such as tissue morphogenesis and stability, as well as in the immune system regulation [1]. Over the past 20 years,the expression and/or the dysregulation of several cadherins have been shown to correlate with tumor progression [2]. Thus, cadherins are becoming valuable diagnostic indicators as well as potential therapeutic targets.

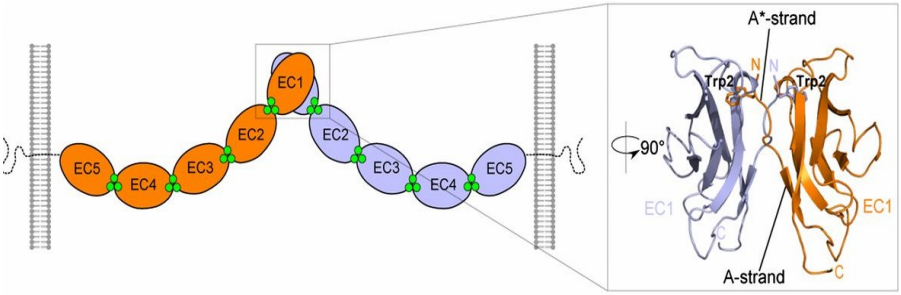

Figure 1. Cadherins as transmembrane cell adhesion receptors (taken from J. Vendome et al. PNAS 2014;111:E4175-E4184)

Recently, our group set up a docking protocol to rationally design small peptidomimetic ligands mimicking the N- and E-cadherin adhesive homodimer interface. Accordingly, the first mimics based on the tetrapeptide sequence Asp1-Trp2-Val3-Ile4 (DWVI) of the N-terminal EC1 domain were achieved (by replacing the central dipeptide Trp2-Val3 with several scaffolds developed in our laboratories) and proved to inhibit adhesion of epithelial ovarian cancer cells with millimolar potency [3]. Molecular Dynamics (MD) simulations were performed starting form the most representative docking poses to discriminate between the stable and unstable docked poses and to equilibrate the system to achieve a stable conformation. MD trajectories have been analyzed according to the experimental information on ligand-cadherin interaction obtained by STD (Saturation Transfer Difference) NMR experiments in the presence of EC1-EC2 construct of the epithelial E-cadherin. NMR data and MD simulations suggest a highly dynamic behavior of both the ligand and the protein and prompt towards an integrated computational and experimental approach to design new small peptidomimetic molecules able to interfere efficiently with cadherin-mediated cell-cell adhesion.

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References

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