AN INTEGRATED COMPUTATIONAL AND NMR STUDY OF THE FIRST PEPTIDOMIMETIC INHIBITORS OF CADHERIN HOMOPHILIC INTERACTION

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Cadherins are a large family of calcium-dependent cell adhesion molecules that are mostly expressed at intercellular junctions. They mediate cell-cell adhesion by forming homophilic 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.

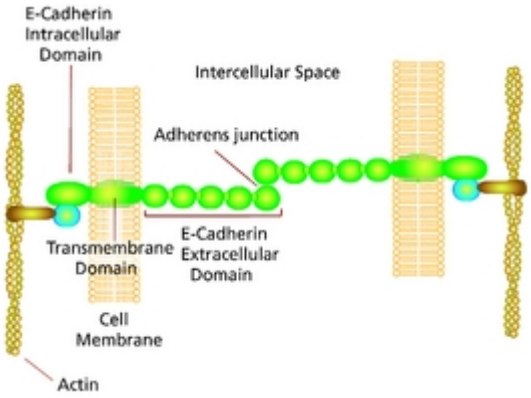

Figure 1. Cadherins as transmembrane cell adhesion receptors (taken from www.sigma-aldrich.com)

Despite a growing interest in the field, the rational design of small ligands targeting cadherin protein-protein interactions is still in a very early stage. So far, only a N-cadherin antagonist cyclic peptide, ADH-1, has entered clinical trials in patients with advanced solid tumors, including epithelial ovarian cancer (EOC), where both N- (neuronal) and E (epithelial)-cadherin are expressed [3, 4].

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 adhesion arm were achieved (by replacing the central dipeptide Trp2-Val3 with several scaffolds developed in our laboratories) and proved to inhibit adhesion of EOC cells with improved efficacy compared to the ADH-1 peptide, although still with millimolar potency [5].

The STD (Saturation Transfer Difference) bioaffinity NMR technique was applied in order to detect and study the binding epitopes of these compounds with the EC1-EC2 construct of the epithelial E-cadherin and to determine the K_D value of the complexes. NMR data and Molecular Dynamics 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

1) D. Leckband, S. Sivasankar, Curr. Opin. Cell Biol. 2012, 24, 620.
2) G. Berx, F. van Roy, Cold Spring Harbor Perspectives in Biology 2009, 1, a003129.
3) G. De Santis, S. Miotti, M. Mazzi, S. Canevari, A. Tomassetti, Oncogene 2009, 28, 1206.
4) N. Yarom, D. Stewart, R. Malik, J. Wells, L. Avruch, D. J. Jonker, Curr. Clin. Pharmacol. 2013, 8, 81.
5) F. Doro, C. Colombo, C. Alberti, D. Arosio, L. Belvisi, C. Casagrande, R. Fanelli, L. Manzoni, E. Parisini, U. Piarulli, E. Luison, M. Figini, A. Tomassetti, M. Civera, Org. Biomol. Chem. 2015, 13, 2570.