Discovery and Characterization of Blood-Brain Barrier Modulating Peptides based on E-cadherin

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Abstract

The delivery of pharmaceutical agents to the central nervous system is hindered by the Blood-Brain Barrier (BBB), a network of inter-cellular interactions of the epithelium. Here, we present a search for novel peptides able to modulate the BBB, focusing on the E-cadherin protein, which is involved in the formation of these intercellular junctions. Previously, two classes of peptides, HAV and ADT, were known to modulate BBB permeability *in vitro* and *in vivo*. Here we use computational methods to perform a systematic search for novel peptides which can effectively interfere with E-cadherin interactions. Employing protein-protein and peptide-protein docking methods with varied levels of flexibility, we propose 115 different peptides with a high binding affinity for E-cadherin as candidates for disrupting the BBB. Several strongest binders have been selected for experimental validation and further sequence optimization. Additionally, conformations of selected peptides in aqueous solution were explored with molecular dynamics simulations, showing a general preference for extended structures and fast conformational equilibria, on the 10-100 ns time scales. Thus, this work presents a systematic computational approach for generating novel peptides with high potential for disrupting the BBB and enabling drug delivery to the central nervous system.

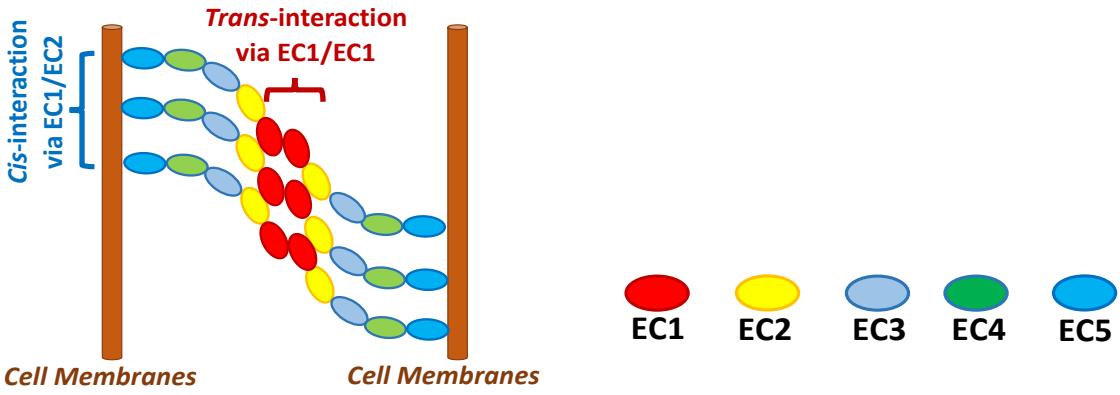

Fig. 1. Schematic view of E-cadherin interactions in intercellular junctions. The five extracellular domains of E-cadherin, EC1-EC5, are colored as shown. [1]

[1] Farokhi et al. Mechanism of the Blood-Brain Barrier Modulation by Cadherin Peptides, *Exploration of Drug Science, in press*, **2024.**