In Silico Design of Blood-Brain Barrier Modulating Peptides Based on E-cadherin: Classical vs. AI Approaches

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Abstract

The delivery of pharmaceutical agents to the central nervous system is hindered by the Blood-Brain Barrier (BBB). We present an extensive *in silico* search for novel peptides able to modulate the BBB, focusing on the E-cadherin protein, which is involved in formation of intercellular junctions. Initially, two classes of peptides, HAV and ADT, discovered in E-cadherin crystal structures, were found to modulate BBB permeability *in vitro* and *in vivo*, enabling delivery of drugs and imaging agents to the brain. Previously, we employed interfaces identified in domain-domain docking to propose 115 different peptide sequences with a high binding affinity for E-cadherin in linear form, as candidates for disrupting the BBB. Based on preliminary experimental data, we focus here of cyclic peptide forms of six-residue (6aa) length due to their favorable pharmaceutical properties. We have used different cyclic peptide docking tools to predict ability to form stable complexes with E-cadherin for all of the 23 6aa peptides found among the 115 novel sequences in N-to-C cyclic form. Further expansion of the number of potential BBB modulators is achieved with Artificial Intelligence (AI) approaches. Docking of 103 6aa E-cadherin EC1 domain fragments to the parent domain was performed using AlphaFold3, allowing identification of several further cadherin-based BBB modulators. Next, the DiffPepBuilder AI diffusion tool was employed to predict 462 new potential 6aa peptide sequences with high affinity for the E-cadherin EC1 domain. Our progress indicates that the computational side of peptide drug design is progressing quite quickly. However, due to the limited amount of test data, the large sets of potential active molecules being generated require experimental validation. Overall, this work presents a systematic computational approach for generating novel peptides with high potential for disrupting the BBB and contributing to the treatment of diseases of the central nervous system, such as Alzheimer's and other neurodegenerative illnesses.

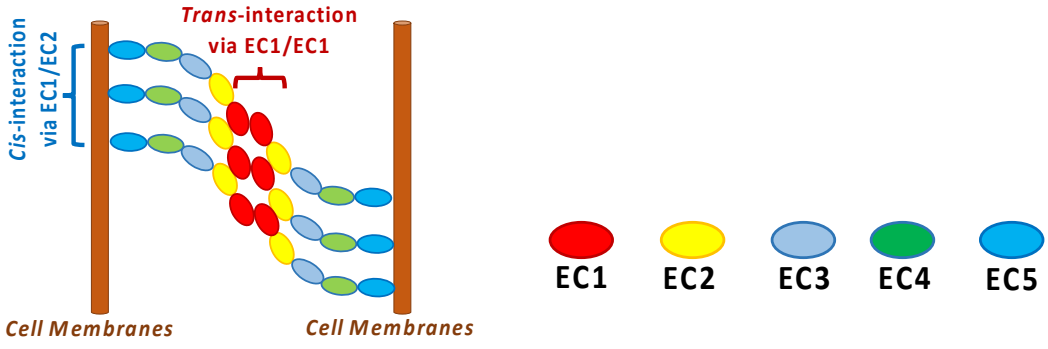

Fig. 1. Schematic view of E-cadherin interactions in intercellular junctions. The five extracellular domains of E-cadherin, EC1-EC5, are colored as shown. [1]

[1] Elinaz Farokhi, Ahmed Alaofi, Vivitri D. Prasasty, Filia Stephanie, Marlyn D. Laksitorini, Krzysztof Kuczera and Teruna J. Siahaan. Mechanism of the Blood-Brain Barrier Modulation by Cadherin Peptides, *Exploration of Drug Science,* **2024,** 2:322-338. doi: 10.37349/eds.2024.00049.