World Academy of Science, Engineering and Technology
International Journal of Chemical and Molecular Engineering
Vol:17, No:08, 2023

A Computational Investigation of Potential Drugs for Cholesterol Regulation to Treat Alzheimer's Disease

Authors : Marina Passero, Tianhua Zhai, Zuyi (Jacky) Huang

Abstract : Alzheimer's disease has become a major public health issue, as indicated by the increasing populations of Americans living with Alzheimer's disease. After decades of extensive research in Alzheimer's disease, only seven drugs have been approved by Food and Drug Administration (FDA) to treat Alzheimer's disease. Five of these drugs were designed to treat the dementia symptoms, and only two drugs (i.e., Aducanumab and Lecanemab) target the progression of Alzheimer's disease, especially the accumulation of amyloid-b plaques. However, controversial comments were raised for the accelerated approvals of either Aducanumab or Lecanemab, especially with concerns on safety and side effects of these two drugs. There is still an urgent need for further drug discovery to target the biological processes involved in the progression of Alzheimer's disease. Excessive cholesterol has been found to accumulate in the brain of those with Alzheimer's disease. Cholesterol can be synthesized in both the blood and the brain, but the majority of biosynthesis in the adult brain takes place in astrocytes and is then transported to the neurons via ApoE. The blood brain barrier separates cholesterol metabolism in the brain from the rest of the body. Various proteins contribute to the metabolism of cholesterol in the brain, which offer potential targets for Alzheimer's treatment. In the astrocytes, SREBP cleavage-activating protein (SCAP) binds to Sterol Regulatory Element-binding Protein 2 (SREBP2) in order to transport the complex from the endoplasmic reticulum to the Golgi apparatus. Cholesterol is secreted out of the astrocytes by ATP-Binding Cassette A1 (ABCA1) transporter. Lipoprotein receptors such as triggering receptor expressed on myeloid cells 2 (TREM2) internalize cholesterol into the microglia, while lipoprotein receptors such as Low-density lipoprotein receptor-related protein 1 (LRP1) internalize cholesterol into the neuron. Cytochrome P450 Family 46 Subfamily A Member 1 (CYP46A1) converts excess cholesterol to 24S-hydroxycholesterol (24S-OHC). Cholesterol has been approved for its direct effect on the production of amyloid-beta and tau proteins. The addition of cholesterol to the brain promotes the activity of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), secretase, and amyloid precursor protein (APP), which all aid in amyloid-beta production. The reduction of cholesterol esters in the brain have been found to reduce phosphorylated tau levels in mice. In this work, a computational pipeline was developed to identify the protein targets involved in cholesterol regulation in brain and further to identify chemical compounds as the inhibitors of a selected protein target. Since extensive evidence shows the strong correlation between brain cholesterol regulation and Alzheimer's disease, a detailed literature review on genes or pathways related to the brain cholesterol synthesis and regulation was first conducted in this work. An interaction network was then built for those genes so that the top gene targets were identified. The involvement of these genes in Alzheimer's disease progression was discussed, which was followed by the investigation of existing clinical trials for those targets. A ligand-protein docking program was finally developed to screen 1.5 million chemical compounds for the selected protein target. A machine learning program was developed to evaluate and predict the binding interaction between chemical compounds and the protein target. The results from this work pave the way for further drug discovery to regulate brain cholesterol to combat Alzheimer's disease.

Keywords : Alzheimer's disease, drug discovery, ligand-protein docking, gene-network analysis, cholesterol regulation
Conference Title : ICCCE 2023 : International Conference on Cheminformatics and Chemical Engineering
Conference Location : Montreal, Canada
Conference Dates : August 03-04, 2023