P1193 / #3790

Topic: AS08 Diseases of The Nervous System (including, infective and psychiatric)

IDENTIFICATION OF THERAPEUTICS FOR NEUROLOGICAL DISORDERS THROUGH DEVELOPMENT OF A NOVEL MACHINE LEARNING SYSTEM FOR PREDICTING DRUG-GENE INTERACTIONS IN THE GLYMPHATIC SYSTEM

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Neurological disorders affect millions of people worldwide. The glymphatic system - the brain's waste clearance system - has been recently identified as a likely origin for a wide array of neurological disorders including stroke, Alzheimer's Disease, and epilepsy. Since few drugs are known to treat irregularities in the glymphatic system, drug discovery in this area has the potential to make a meaningful impact on treatment of neurological disorders. In the past decade, machine learning has emerged as a tool to aid chemists and biologists in the field of drug discovery; however, currently, databases of glymphatic-related genes and drugs do not exist. The first stage of this research developed GlymDS, a new database of genes with a related function to the glymphatic system and drugs that interact with their proteins. This was done by compiling information from Gene Ontology, AlphaFold, DGIdb, and DrugBank and includes 400 newly assembled protein and drug structures. The second stage developed GlymRx, a novel machine learning system to predict which drugs would interact with genes regulating the glymphatic system. GlymRx contains three custom machine learning models based on a K-nearest-neighbors (KNN) algorithm, an XGBoost algorithm, and a deep neural network. In stage three, 11,575 FDA-approved drugs were evaluated by all three models to identify drug-gene pairs with significant enough interactions to suggest potential medical use. Of these, 273 drugs were identified by all three models as having strong interactions with glymphatic-related proteins. GlymRx trained on GlymDS may save as much as six years of drug development time.

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TOLL LIKE RECEPTOR 4 (TLR4) AND DEMYELINATION

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TLRs (Toll Like Receptors) promote the inflammatory response. Regarding TLR4, its activation increases the production of proinflammatory cytokines. For this reason, the focus has been placed on TLR4 in different diseases. Multiple sclerosis (MS) is among these pathologies. MS is a chronic, inflammatory neurodegenerative disease characterized by the death of oligodendrocytes and loss of CNS myelin. In this study we identified TLR4-positive elements in demyelinating lesions: human cerebral MS lesions, and animal models of the disease, as well as primary cell cultures. We have used immunohistochemical techniques and Western blot. We have observed the presence of TLR4+ elements in various demyelinating lesions of human MS patients. Furthermore, we have identified two distinct CNS cell types that express TLR4: i) microglia cells (and/or macrophages) and ii) oligodendrocyte precursor cells (OPCs). In the context of demyelinating damage, TLR4 influences the response of microglial cells (and/or macrophages). Thus, in the experimental autoimmune encephalomyelitis (EAE) model, TLR4 inhibition reduces the number of CD68+ cells and increases the number of CD206+ cells. That is, TLR4 inhibition implies a lower number of activated microglia (and/or macrophages) cells and a greater number of cells with a repair phenotype. Our preliminary studies suggest that TLR4 in OPCs interacts with the intracellular pathways involved in myelin formation and the thickness of myelin sheaths. In the inflammatory environment of the demyelinating lesion (EAE), we observed a decrease in ERK1/2, which prompted us to hypothesize that TLR4 activation in the OPC interrupts the myelin formation. In conclusion, the presence of TLR4 is verified in various cell types and the function of this receptor goes beyond the amount of proinflammatory cytokines released.

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