Psychiatric risk peptide of DISC1 inhibits kinase GSK3β, Structural investigation using crystallography

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Disrupted in Schizophrenia 1 (DISC1) is a candidate risk gene in several major mental illnesses, e.g. depression, bipolar disorder, and schizophrenia. The full-length DISC1 protein comprises of 854 amino acids, consisting of many dynamic and disordered regions. DISC1 acts as a scaffold protein. It interacts with a large group of proteins, forming a sizeable protein-protein-interaction network. This interaction network has been implicated in coordination of various stages of the brain development. One of those important interactors is the enzyme, glycogen synthase kinase 3β (GSK3β). As a target for lithium, GSK3β itself is implicated in bipolar disorder. The interaction of DISC1 and GSK3β was discovered at the cross-section of the canonical Wnt/β-catenin signalling, which controls the proliferation of neural progenitors. DISC1 specifically inhibits GSK3β's function in this pathway via a direct physical interaction. The most potent GSK3b inhibitory region has been mapped to a small region in the N-terminus (residue 195-238) of DISC1. This 44-amino acid region (hD1) can inhibit GSK3b in an ATP non-competitive manner. We have obtained different crystal forms of GSK3b bound to hD1 and another peptide that partially shares binding site with hD1 based on biochemical and biophysical data. As obtaining crystallographic data of these new crystal forms is put on hold due to Covid-19, we are also evaluating whether negative stained electron microscopy can be used to identify large conformational changes of GSK3b induced by hD1 binding

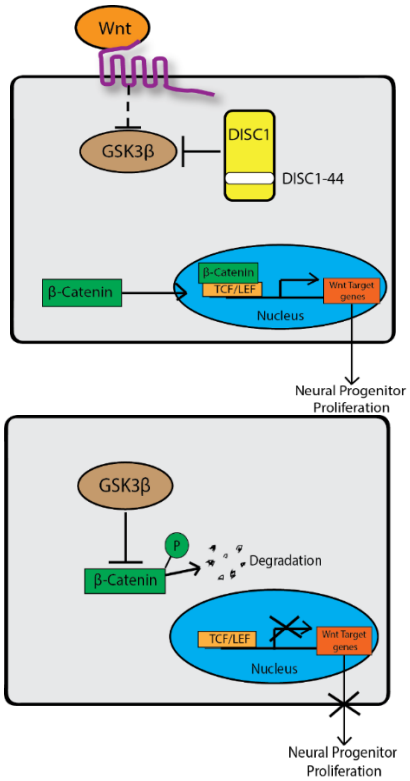

Figure 1