Overexpression, purification of GSK3β and it's interaction with an inhibtory fragment of the psychiatric risk protein DISC1

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Disrupted in Schizophrenia 1(DISC1) is a candidate risk gene in a number of major mental illnesses, e.g. depression, bipolar disorder and schizophrenia. DISC1 is a scaffold protein that interacts with a myriad of proteins, forming a large protein-protein-interaction network that coordinates various stages of brain development. Our lab is interested to understand how the structure of DISC1 facilitates its function in brain development. One of DISC1's interactors is the enzyme glycogen synthase kinase 3β (GSK-3β). As a target for lithium, GSK3β is itself implicated in bipolar disorder. Through physical interactions, DISC1 inhibits GSK3β's function in the canonical Wnt/β-catenin signalling pathway, which controls the proliferation of neural progenitors. The full length DISC1 protein is composed of 854 amino acids. The most potent GSK3β inhibitory region has been mapped to a short region in the N-terminus (residue 195-238). This 44 amino acid region (DISC1-44mer) can inhibit and bind GSK3β in *in vitro* experiments. To understand the mechanism of how DISC1 inhibits GSK3β, we are pursuing structural studies of GSK3β in complex with different truncations of DISC1. We will present our progress towards the structural studies of this important complex that is relevant to the pathophysiology of psychiatric diseases.

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