Background: Preclinical and clinical studies have suggested the involvement of the endocannabinoid system in schizophrenia pathobiology. In addition, in vitro studies have shown the molecular pathways and biological processes associated with cannabinoids’ effects in some cell types, such as glial cell cultures. Thus, the effects of cannabinoid drugs on these cells may contribute to our knowledge about the pathobiology of schizophrenia. Specifically, oligodendrocytes are associated with white matter deficits in schizophrenia. The modulation of their function, survival, and differentiation can result in new approaches to treat schizophrenia’s white matter-associated deficits. Here we have investigated the effects of cannabidiol (CBD) on a human oligodendrocyte culture (MO3.13). In another experiment, we pretreated the MO3.13 with MK801, an in vitro model of study schizophrenia proposed by our group, in terms of protein expression.

Methods: MO3.13 oligodendrocytes were treated with CBD (1 μM), or MK801 (50 μM) followed by CBD (1 μM). After 8 hours, proteins were extracted from these cells, digested, and processed in a state-of-the-art LC-MS/MS system. Quantitative proteomics approaches were then employed in a label-free fashion. Differentially expressed proteins were analyzed using systems biology in silico tools.

Results: Analyses identified that several proteins were up- or down-regulated in response to CBD treatment. These proteins were analyzed in terms of biological processes, pathways, and functions. CBD affected the expression of 136 proteins. Some proteins such as the transient receptor potential channel, microtubule-associated proteins, Rho GTPase activating proteins, 1H subunit, among others possibly involved in myelination process, were increased by CBD. Additionally, the MK801-treatment decreased proteins of cytoskeleton, microtubule and RHO GTPases activate KTN1. MK801 also increased proteins involved in glycolysis and eukaryotic translation initiation and CBD attenuated these changes.

Discussion: Studies have shown the effects of CBD on the treatment of schizophrenia; but the mechanisms involved in its antidepressant properties are not fully understood. Herein, we observed that CBD modulated the expression of proteins that can be implicated in schizophrenia pathobiology. For instance, MAPs functions are related to cytoskeleton organization, differentiation, and migration of oligodendrocytes. Studies have shown a decrease of MAPs in schizophrenia patients; thus, increasing MAP2 and MAP4 by CBD may be an interesting mechanism to treat and prevent cytoskeleton impairments in oligodendrocytes and neurons in schizophrenia. Moreover, CBD increased the voltage gated channel that is involved in cannabionid retrograde signaling and glutamate and GABAergic neurotransmission. CACNA1H modulates Ca2+ levels and the synaptic vesicle cycle. To note, we also found effects of CBD on pathways and biological processes involved with schizophrenia pathobiology, such as glucose metabolism, axon guidance, and inflammation mediated by cytokine signaling. In relation to MK801-treatment, we observed that affected proteins involved in glycolysis and CBD attenuated this change, like antidepressants (as demonstrated in Cassoli et al., 2016). Moreover, MK801-treatment affected the RHO GTPases family that has been implicated in schizophrenia, and CBD increased these proteins. In summary, these proteomic findings may provide an integrated picture of the role of endocannabinoid signaling in oligodendrocyte cells and possible implications for schizophrenia’s pathobiology.

Discussion: Given that the mRNA study used samples of dorsolateral prefrontal cortex (DLPFC) while our protein-level measures were from STG, it is not inconceivable that potential O-GlcNAc dysregulation could arise from upregulated OGT in one brain region, but downregulated OGA in another. To elaborate on these findings, we will investigate OGT and OGA expression in the DLPFC and will assess total O-GlcNAcylated in both brain regions to determine functional consequences of altered enzyme expression.
depressive disorder, bipolar disorder, autism spectrum disorder, Alzheimer’s disease and Parkinson’s disease. The interactome is constructed with experimentally determined PPIs from BioGRID and HPRD databases and novel PPIs predicted using our High-confidence PPI Prediction (HiPPIP) model. We previously presented Schizophrenia Interactome constructed using HiPPIP and also showed that novel PPIs are highly accurate based on computational and experimental validations. We validated additional PPIs of cilia interactome here. We computed how closely connected cilia is to genes associated with neuropsychiatric diseases, through interactome and pathway analysis. Additionally, we analyzed drugs that proteins in the cilia interactome, and found that majority of these drugs are nervous system associated drugs.

**Results:** The ciliary protein interactome consists of 165 ciliary proteins with 1,011 known PPIs and 765 novel PPIs. We found the overlap between cilia and neurotrophin interactomes to be statistically highly significant. For e.g., cilia interactome has an overlap of 125 genes with schizophrenia interactome of which 26 are novel interactors of cilia, and has significant overlap with pathways relevant to schizophrenia. About 184 genes in the cilia interactome are targeted by 548 FDA approved drugs, of which 103 are used to treat nervous system diseases.

**Discussion:** Ciliary genes like DRD1 and DRD2 are implicated in neurotransmission and associated with schizophrenia. DRD1 has 4 novel interactors and DRD2 has 12 novel interactors that may have significant role in the pathology of mental disorders. Neuronal pathways associated with cilia interactome with high statistical significance such as dopamine signaling, eNOS signaling, synaptic long-term potentiation pathways are known to be associated schizophrenia. Wnt signaling and PCP signaling are also known to be associated with cilia mediated neurodevelopmental signaling, defects in these pathways contributing to schizophrenia. Novel interactions for cilia proteins validated by experiments have functional significance in association with cilia and neuronal disorders. For e.g., IFT88, a cilia protein required for cilia assembly, is critical for SHH signaling, cell cycle regulation and cerebellar development and is also associated with schizophrenia and bipolar disorder. CACNA1I is predicted to interact with DNA4 and MKS1, both involved in transport of proteins required for ciliogenesis. GWAS studies show that CACNA1I is associated with schizophrenia. Taken together, the cilia interactome presented here provides novel insights into the relationship between ciliary protein function and neuropsychiatric diseases.

**F201. KINASE NETWORK DYSREGULATION IN SCHIZOPHRENIA: IMPLICATIONS FOR NEW TREATMENT STRATEGIES**

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**Background:** Disrupted-in-schizophrenia 1 (DISC1) is one of the most substantiated genetic risk factors for schizophrenia (SZ). A large array of animal studies supports an etiopathogenic role of DISC1, by linking it with regulation of processes such as synapse formation and neuronal development. However, much less is known regarding the involvement of DISC1 in human neurons. Induced pluripotent stem cells (iPSCs) generated from patients carrying the disease have emerged as powerful tools to study cellular dysfunction in a disease-relevant context. In this study, we investigated serine/threonine kinase networks in a human iPSC model of DISC1-related SZ.

**Methods:** PamChip arrays evaluate kinase activity by measuring phosphorylation levels of a series of immobilized peptide sequences during exposure to kinases in the sample. We employed PamChip arrays to map the serine/threonine sub-kinome of neuronally differentiated iPSCs generated from a patient with SZ presenting the frame-shift DISC1 mutation (D2-1), an unaffected family member without the mutation (C3-1), as well as of isogenic iPSC lines in which the mutation was either corrected in D2-1 (resulting in the cell line D2-R), or introduced in C3-1 (resulting in the cell line C3-M). Using a bioinformatics workflow that identifies kinase hits using a random sampling model, we identified kinases that emerged as common hits after comparing D2-1 with D2-R (changed after rescuing the mutation in the patient cell line) and C3-M with C3-1 (changed after introducing the mutation in the control cell line). We used the resulting kinase network to identify pathways, perturbagens, and drugs related to the disease phenotype.

**Results:** By comparing D2-1 to D2-R, 9 peptide sequences were identified to be differentially phosphorylated at a +/- 1.15 fold-change level. After assigning upstream kinases to these peptides and generating the random sampling model, we identified 3 kinase subfamilies which were over-represented in D2-1 vs. D2-R: TAO, KHS and 5 adenine monophosphate-activated protein kinase (AMPK). By comparing C3-M to C3-1, we could identify 13 peptide sequences differentially phosphorylated at a +/- 1.15 fold-change level. Mapping these sequences to upstream kinases and running the random sampling model, led to the identification of 9 kinase subfamilies over-represented in C3-M vs. C3-1: AMPK, TAO, BUD32, WNK, KHS, RAD53, CK1, NEK and MLK. By overlapping the results, we could identify a set of 3 kinase subfamilies (TAO, KHS, and AMPK) commonly changed between the two methods of comparison. Ingenuity pathway analysis identified post-translational modification, cell signaling, cell morphology, cell cycle, and cellular assembly and organization, as the top functions of the DISC1 kinase network.

**Discussion:** Kinases are potent modulators of intracellular signaling that control patterns of gene expression, cytoskeletal dynamics, function of neurotransmitter systems and cellular metabolism, which may be of relevance to the etiopathogenesis of mental disorders, such as SZ. Herein, we characterized the serine/threonine sub-kinome of neuronally differentiated iPSCs from a patient with SZ presenting with a 4-bp deletion in DISC1. Using gene editing we created isogenic cell lines to either rescue the mutation in the patient cell line, or introduce the mutation in iPSCs obtained from an unaffected family member, to strengthen causality for the DISC1 mutation. This approach led to the identification of 3 kinase subfamilies as common hits of the DISC1 phenotype: TAO, KHS, and AMPK. Our unbiased approach led to the novel identification of kinases implicated in DISC1-related SZ. Further validation of these findings may open new avenues for treating this highly disabling neuropsychiatric disorder.

**F202. ABNORMAL REMODELING PROCESSING IN NEURAL GPI-APS SECRETORY PATHWAY IN SCHIZOPHRENIA**

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**Background:** Abnormalities in post translational modifications (PTMs) such as glycosylation have become targets of schizophrenia (SCZ) research and are implicated in the neuropathophysiology of this illness. Glycosylphosphatidylinositol (GPI) attachment to proteins and glycoproteins events; proteins essential to cellular function, including neurotransmitter receptors, adhesion molecules, and enzymes, are all modified by GPI. Biosynthesis of GPI-APs occurs in the endoplasmic reticulum (ER). Once GPI-APs are synthesized, they are transported from the ER to the cell surface through the Golgi apparatus. Inositol deacylation of the GPI-APs by inositol deacylation of the GPI-APs by is common PTMs. The GPI-anchored proteins (GPI-APs) play an essential role in many biological PGAP1 is required for efficient export from the ER and acts a molecular mechanism for quality control of GPI-APs. The p24 complex binds specifically to GPI-APs and plays a role in their selective trafficking by sensing the status of the GPI anchor and to promote efficient ER exit of remodeled GPI-APs. In this study, we identified abnormalities of proteins associated with the ER exit of GPI-APs in SCZ. To address mechanisms of GPI-APs ER exit, we measured expression of proteins of the GPI-APs ER exit and targeting pathway. We also measured expression of GPI-APs which have been previously implicated in SCZ, including GPC1, NCAM, MDGA2 and EPHA1.