Perturbation of Cell-Subtype Specific Active Kinome Networks in Schizophrenia

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Background: We deployed the PamGene kinome array platform for use with postmortem brain samples and iPSCs from schizophrenia (SZ) and Alzheimer's dementia (AD). The kinome array platform provides a read-out of protein kinase activity across hundreds of peptide substrates, measuring global protein kinase activity across serine/threonine and tyrosine subkinomes. We used this omics-based platform to generate novel hypotheses for the pathophysiology of severe neuropsychiatric disorders with cognitive dysfunction.

Methods: We used the PamGene kinome array platform to assess protein kinase activity in disease (AD, MDD, and SZ) and control (SZ) samples. We also evaluated protein kinase activity in stem cell cultures for these disorders. We used R programs (KRSA and UKA) to deconvolve the generated kinome array datasets to identify specific protein kinases altered across these disorders. Information for deconvolution of datasets was supplemented with recombinant kinase and kinase perturbation studies.

Results: A joint hit for AD and SZ was adenosine monophosphate kinase (AMPK), a master regulator of insulin signaling pathways. Subsequent studies of AMPK in AD and SZ reveal subunit-specific deficits in the frontal cortex in AD, with changes in the regulatory subunits for AMPK. Bioinformatics analyses revealed several novel pathways and several candidate drugs that might be repurposed for treating cognitive deficits in these disorders.

Conclusion: We used a hypothesis-free, kinome-based approach to extend our understanding of the pathophysiology of SZ and AD and provide novel leads to advance the diagnosis and treatment of these often-devastating illnesses.

