Title

59.4 Networks of Blood Analytes are Collectively Informative of Risk of Conversion to Schizophrenia

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Authors

Jeffries, Clark
Perkins, Diana
Addington, Jean
et al.

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Background: Schizophrenia is a neurodevelopmental disorder with risk factors of both genetic and environmental origins. Several neurodevelopmental animal models have been developed in which a genetic manipulation or an environmental insult is introduced to alter the normal trajectory of the developing brain. Certain features of schizophrenia pathology, such as deficits in parvalbumin interneurons, have been recapitulated in such animal models. The present study aimed to compare transcriptional alterations in neurodevelopmental animal models to post-mortem schizophrenia brain.
Methods: We first analyzed prefrontal cortex, hippocampus, and striatum from subjects with schizophrenia by microarray. We than collected tissues from several developmental rodent models, including the MAM rat, neonatal ventral hippocampal lesion rat, the Df1/+ model of 22q11 microdeletion syndrome, a truncated DISC1 mouse model, and a prenatal poly I:C mouse model. Animal model tissues were analyzed by RNAseq, and select pathways significantly enriched in the schizophrenia data were examined across animal models.
Results: Increased expression of numerous genes involved in inflammatory pathways was observed in schizophrenia, including pro-inflammatory cytokines (e.g., IL-6 and IL-2). Several signaling pathways were enriched based on genes that were reduced in schizophrenia, but the pathway with the largest burden of down-regulated transcripts was oxidative phosphorylation. The oxidative phosphorylation pathway was significantly enriched in the Df1/+ mouse, though changes in select redox related genes could be observed across models. While several models showed enrichment in select inflammatory pathways, the MAM rat showed the greatest number of these. Several inflammatory pathways enriched in schizophrenia PFC were enriched in MAM rat PFC, such as IL-6 signaling, acute phase response signaling, and nF-kB signaling.
Conclusion: Transcriptional profiling of post-mortem schizophrenia brain samples suggested an increased inflammatory state and an altered state of redox homeostasis. Several neurodevelopmental animal models showed signs of altered inflammatory pathways and some alterations in redox-related genes at ages when loss of cortical parvalbumin has been reported. The MAM rat, in particular, showed a significant overlap in pathways found to be enriched in schizophrenia. Taken together, these data suggest that some elements of schizophrenia molecular pathology can be recapitulated in neurodevelopmental animal models.

59.4 NETWORKS OF BLOOD ANALYTES ARE COLLECTIVELY INFORMATIVE OF RISK OF CONVERSION TO SCHIZOPHRENIA

Clark Jeffries*[,1], Diana Perkins[2], Jean Addington[3], Carrie Bearden[4], Kristen Cadenhead[5], Tyrone Cannon[6], Barbara Cornblatt[7], Daniel Mathalon[8], Tom McGlashan[6], Larry J. Seidman[9], Ming Tsuang[5], Elaine Walker[10], and Scott Woods[6]
[1]University of North Carolina, Chapel Hill; [2]University of North Carolina; [3]University of Calgary; [4]University of California, Los Angeles; [5]University of California, San Diego; [6]Yale University; [7]Zuker Hillside Hospital; [8]University of California, San Francisco; [9]Massachusetts Mental Health Center, the Beth Israel Deaconess Medical Center, Harvard Medical School; [10]Emory

Background: The presence and severity of attenuated-psychosis symptoms define a clinical high risk (CHR) population at elevated risk for psychotic disorders. The NAPLS project is a prospective study of mechanisms contributing to psychosis vulnerability in persons at CHR. Here we investigated a hypothesized role for the highly-integrated immune and redox systems in the development of psychosis.
Methods: We examined expression of 143 plasma analytes from a subgroup of the NAPLS2 cohort, including 32 CHR with subsequent psychosis conversion, 40 CHR followed for 2 years without psychosis, and 35 unaffected subjects. We used a Luminex platform with analytes chosen to reflect immune, redox, hormonal, and metabolic system status, including many analytes previously associated with schizophrenia and psychosis risk. We applied correlation network analysis to discover potentially co-regulated networks associated with later development of psychosis.
Results: Several robust ($r > .75$) and highly significant ($P < .0001$ after correction for multiple testing) correlation networks were found in all groups, including a network involving IL3, IL5, IL7, and IL13, and a network involving CCL5, BDNF, TSH, and PDGF. There were significantly fewer nodes in CHR-converters compared with CHR-nonconverters and unaffected subjects. In unaffected subjects, plasminogen activator inhibitor-1 (PAI-1) was highly correlated with matrix metallopeptidases (MMP) 7, 9 and 10 and CD40LG, this network was absent in CHR subjects, and in CHR-converters PAI-1 was robustly and significantly correlated with TIMP1, CCL13, and TIMP1.
Conclusion: A pattern of robust and highly significant correlation networks in plasma analytes suggests shared regulatory mechanisms for the inter-correlated analytes. The lower number of correlated analytes in CHR subjects who converted to psychosis suggest a shift in regulation, as does the change in the correlation network involving PAI-1. PAI-1 is of interest given studies linking schizophrenia with reduced tissue plasminogen activator (tPA) and increases in negative regulators of tPA, including activation of both PAI-1and TIMP1 with oxidative stress. In addition, a recent study links toxoplasmosis infection and schizophrenia risk to a pathway involving PAI-1 and TIMP1.
Patricio O'Donnell, Pfizer Inc.

60. THE ROLE OF GABA IN THE NEUROBIOLOGY OF SCHIZOPHRENIA: A PRECLINICAL, CLINICAL, AND NEUROPATHOLOGY UPDATE

Lawrence Kegeles
Columbia University & New York State Psychiatric Institute

Overall Abstract: Animal models of psychosis indicate a new focus on altered GABAergic neurotransmission as the source of subcortical dopamine dysfunction in schizophrenia. While neuroimaging research allows testing the relevance of these models in humans, the extent to which GABAergic neurotransmission is altered in patients with psychosis and people at clinical high risk for psychosis (CHR) is less clear. This symposium will address this issue by integrating findings from state-of-the-art preclinical research, neuropathology studies in schizophrenia, and human neuroimaging studies before and after the development of psychosis. Tony Grace (Pittsburgh) will describe preclinical evidence for a central role of prefrontal and hippocampal GABA interneuron dysfunction in the neurobiological cascade driving subcortical dopamine dysfunction and will show new data on the prevention of schizophrenia-like GABA cell loss by pharmacologically intervening on the GABAergic system. Francine Benes (Harvard) will report new neuropathological data on reduced hippocampal GABA interneurons in schizophrenia, which allow for a detailed understanding of corticolimbic GABAergic changes in the disorder and show specificity with regard to other psychotic disorders. Hilleke Hulshoff Pol (Netherlands) will present new findings on reduced prefrontal GABAergic function in patients with schizophrenia through magnetic resonance spectroscopy research, and its relationship with cognitive functioning. Finally, these data will be complemented by novel multimodal imaging evidence of alterations in prefrontal GABA levels and their relationship to hippocampal perfusion in CHR subjects, presented by Gemma Modinos (London). Philip McGuire, who leads one of the world's largest groups working with neuroimaging in psychosis and high-risk groups, will integrate this set of complementary findings from different disciplines.