8.4 GUT DYSBIOSIS AND AUTOIMMUNE FEATURES IN SCHIZOPHRENIA FUEL BROKEN BARRIER HYPOTHESES

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Background: The blood-gut and blood-brain barriers represent highly regulated and dynamic cellular interfaces that when dysfunctional set into motion neuropathological sequelae relevant to schizophrenia. The recognition of gastrointestinal (GI) comorbidities has a long history in schizophrenia and predates the advent of currently utilized antipsychotic agents. In particular, inflammatory bowel diseases are over-represented in schizophrenia and may be the combined result of genetic predispositions and environmental insults. Exposure to stress, food-derived antigens and infection all serve to unsettle the balance of a resident community of gut microbes, a collective functional unit that determines the blood-gut barrier integrity and modulates the immune system to minimize autoimmune responses. Here we focus on the blood-gut barrier as the genesis for ensuing systemic processes that ultimately impact the blood-brain barrier and function of the central nervous system. Toward this end, we present translational work regarding the gut microbiome and inflammatory autoimmunity phenotypes based on data from clinical studies of schizophrenia and modeling of this pathological process in rodents.

Methods: We examined biomarkers of endothelial barrier integrity, microbial translocation, GI inflammation and autoimmunity in biological samples from individuals with schizophrenia and controls. We then evaluated these same markers in an experimental mouse model of inflammatory bowel disease induced by a neurotropic pathogen, Toxoplasma gondii. Analysis of variance and multi-variate regression models were used to detect differences in levels of blood biomarkers amongst experimental groups.

Results: In individuals with schizophrenia, the measurement of diverse biomarkers of intestinal dysbiosis demonstrates a pro-inflammatory gut environment that is associated with gut barrier breakdown. In mice, infection with T. gondii, a gut pathogen, resulted in the increased prevalence of markers of a breached blood-gut and blood-brain barrier, compared to uninfected controls. Similarly, in T. gondii-positive individuals with schizophrenia, the same set of markers of barrier compromise were elevated compared to controls. Intriguingly, this loss of gut-gut and blood-brain barrier integrity was accompanied by elevated levels of autoantibodies to the NMDA (NR2) receptor in both humans and mice.

Conclusions: Infection and intestinal inflammation lead to an environment that is conducive to the concurrent generation of autoimmunity pathologies and endothelial barrier dysfunction. NMDA receptor hypofunction is a leading hypothesis concerning the etiology and pathophysiology of schizophrenia. Of note, the enteric nervous system hosts an array of neurotransmitter receptors and thus may serve as a location where autoantibodies against important brain proteins are formed. Mechanistically, GI inflammation may expose novel immunogenic triggers composed of neurotransmitter receptors in association with other intestinal cellular, dietary or microbial antigens. Breached endothelial barriers would enable the transference of antibodies directed against these novel targets in the gut to reach the brain. The precise timing and interactions of these key elements across the gut-brain axis is complex. As our understanding of the relevant mechanisms progresses, suitable diagnosis and treatment strategies related to the gut-brain axis in psychiatric disorders can be identified and refined.

Plenary Session

9. MODELLING THE IMPACT OF RARE AND COMMON VARIANTS IN SCHIZOPHRENIA USING STEM CELLS

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Schizophrenia (SZ) is a debilitating psychiatric disorder for which the complex genetic mechanisms underlying the disease state remain unclear. Whereas highly penetrant variants have proven well-suited to human induced pluripotent stem cell (hiPSC)-based models, the power of hiPSC-based studies to resolve the much smaller effects of common variants within the size of cohorts that can be realistically assembled remains uncertain. Overall, we consider the successes and limitations in applying human induced pluripotent stem cell (hiPSC)-based models to study the impact of rare and common variants in SZ risk. To explore the neuronal impact of rare variants, we investigated the relationship between heterozygous 2p16.3 deletions, alternative splicing of NRXN1, and perturbations in neuronal activity, finding some commonalities with idiopathic SZ. We identified ~100 NRXN1 isoforms in control hiPSC neurons; patient-derived 2p16.3 neurons show perturbed NRXN1 isoform repertoires, reduced neuronal branching and decreased neuronal activity, which unexpectedly can be partially ameliorated by overexpression of a single NRXN1 isoform. Second, we present a genetics-driven hiPSC-based CRISPR-mediated approach for the functional validation of common variants and genes associated with SZ, evaluating the impact of one putative causal SZ SNP (FURIN rs4702) and two SZ-associated genes (SNAP91 and TSNARE1) on global gene expression patterns and synaptic function. We predict a growing convergence between hiPSC and post-mortem studies as both approaches expand to larger cohort sizes. We demonstrate a systematic and scalable strategy to interpret and evaluate the growing number of SZ-associated variants and genes across neural cell types and genetic backgrounds. Altogether, our objective is to dissect the genetic origins of SZ while developing a precision medicine approach to screen for novel therapeutics with which to prevent or reverse disease course.

Concurrent Symposia

10. NEW PARADIGMS FOR DISCOVERY

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Schizophrenia conceptualized as a specific disorder has resulted in substantive knowledge but has not been validated as a disease entity. An alternative concept of schizophrenia as a heterogeneous clinical syndrome requiring deconstruction. Syndrome status and implications was proposed over 40 years ago and is formally stated in DSM-5. The modest progress in understanding pathophysiological mechanisms and limited progress in therapeutics has resulted in the development of new paradigms for discovery. Four paradigms sensitive to heterogeneity and to across diagnostic boundaries are currently engaged in opening new views and scientific approaches to understanding psychopathology and will be represented in the panel presentations. Each has the potential to increase knowledge on psychopathology and guide future modifications in nosology and diagnostic concepts [think DSM-5.1, DSM-5.2, etc.]

1. Roman Kotov will present on reconceptualization of schizophrenia from the HiTOP perspective including continuity with normal functioning, heterogeneity within the disorder, and its relations to mania, schizotypy, and other conditions. This new paradigm has immediate implications for research and clinical care. New data will be presented from an epidemiologic study of psychosis.

2. Aristotle Vlameskos will illustrate the RDoC paradigm with the study of social cognition as a single dimension including deficit schizophrenia, non-deficit schizophrenia and non-ill participants. Several emerging findings from an ongoing RDoC initiative show that a dimensional approach coupled with multivariate analytics, can be successfully used to identify brain-behavior subtypes related to social impairment cutting