

Gut microbiome and adaptive immunity in schizophrenia

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Over the past few years, immunopathogenesis has emerged as one of the most compelling aetiopathological models of schizophrenia (SCZ), suggesting a chronic, immune-based, low-grade inflammatory background of this devastating disorder.^{1,2} Mounting evidence points towards a prominent role of the adaptive immune system in SCZ, suggesting alterations in defense mechanisms, such as altered T-cell function and a shift towards B-cell immunity.³ Immune cells have the ability to infiltrate the brain and mediate a neuroimmune cross-talk through activation of microglia, production of pro-inflammatory cytokines and reactive oxygen species, leading to neuroinflammation, as mediator of neuroprogressive and neurodegenerative changes in SCZ.⁴ Antipsychotic drugs, commonly used to treat SCZ, are also known to affect the adaptive immune system, interfering with the differentiation and function of immune cells, towards their normalization in response to treatment.

Adaptive immunity is principally founded on T-cell and B-cell populations, but also includes the host microbiome. The gastrointestinal microbiota is a complex ecosystem with a great organism diversity and refined genomic structure that resides in the intestinal tract and has a central position in human health and disease.⁵ Neuroimmune dysregulation, relying of the highly sensitive and fine-tuned equilibrium between microbiome and adaptive immunity, can tip the scales towards neuroinflammation and disruption of higher-order brain networks.^{4,6,7}

During the last decade, the human microbiome and the microbiota-gut-brain (MGB)-axis have become a novel epicentre in mental health research as a potentially vital new determinant in the field of neuroimmunoregulation, brain development, emotions, cognition and behaviour.⁷ The MGB-axis represents a bidirectional, key communication pathway between the immune system and the brain, thus partly also mediating the regulation of cognitive and emotional processing. An imbalanced human microbiome might greatly influence proper neuroimmune reactions and neurodevelopment with long-lasting effects and could thus play a pivotal role in the susceptibility and aetiology of psychiatric illness.

Recent research offers first evidence that patients with SCZ show marked disturbances of gut bacterial taxa composition with a decreased microbiome diversity index, partly associated with specific SCZ phenotype, symptom severity and treatment response.^{8,9} As the elegant education of the adaptive immune compartment depends on the colonization niche, antigen type and metabolic property of different gut microbes, T-cell differentiation as well as a continuous diversification of B-cell repertoire is expressed through microbiome-related, antigen-specific receptors that define a unique clonotype.¹⁰ However, there is only sparse evidence on the precise role of the microbiome on the programming of T- and B-cells in the underlying neurobiological pathways of SCZ and even less findings on the association of molecular T- and B-cell receptor repertoire signature and microbiome clonal landscape with specific phenotypical features of the disease.¹¹

The latest conceptual advances in immunology urge an integrative re-evaluation of previous immunological findings in SCZ through modern approaches. High-throughput, next-generation sequencing (NGS) represents a powerful single-cell transcriptomic tool to profile the whole clonal landscape of T and B cells and human microbiome. NGS thus offers a unique opportunity for in-depth characterization of cellular and molecular signatures of adaptive immune receptor repertoires and microbiome taxonomy in SCZ and investigation of their intersection as a relevant pathway of disease progression and phenotype differentiation. SCZ patients are likely to show a diverging host-microbiome immune ho-

meostasis with disease-specific clonotypes of adaptive immune receptor repertoires associated with altered microbiome taxonomy and molecular signature differences, which, in turn, may be related to distinct symptomatic phenotypes and neurocognitive patterns.

Such sophisticated immuno-bioinformatic analyses may transform our understanding of SCZ by identification of novel neuroimmune pathways, offering us clinically accessible symptomatic and diagnostic biomarkers important for personalized medicine implications.¹² An increased understanding and better characterization of immuno-phenotypes in SCZ will better guide the development of novel immune-based treatments in this severe disease and pave the way for possible prevention options through implementation of antibody engineering, vaccine design, and cellular immunotherapy.

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