What's Hot in Schizophrenia Research?

Cynthia Shannon Weickert, PhD[a,b,c,*], Thomas W. Weickert, PhD[a,b,c,*]

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• Schizophrenia • Psychosis • Inflammation • Biomarkers • Cytokines
• Ultra-high risk • Microglia

KEY POINTS

- Evidence and interest are increasing for the role of inflammation in at least some people with schizophrenia.
- Inflammatory markers can be found in the peripheral blood of people at risk to develop psychosis and at the first episode of psychosis.
- Increased cytokines and microglia have been reliably reported in the brains of people with schizophrenia.
- Evidence from ultra-high-risk, brain imaging, post-mortem, animal models and genetic studies (genome-wide association studies) have converged to implicate neuroinflammation in the pathogenesis of at least some form of schizophrenia.

As schizophrenia research emerges halfway through the second decade of the twenty-first century, there have been some exciting findings that have confirmed and united 2 major lines of evidence regarding the cause of schizophrenia that were reported in the twentieth century. One line of evidence was that drugs that blocked the *N*-methyl D-aspartate receptor (NMDAR) could trigger a temporary delusional and/or hallucinatory state in otherwise healthy people.[1] The other line of evidence was that maternal infection during gestation or infection during postnatal life increased the risk of developing schizophrenia or psychosis by 2- to 3-fold in offspring.[2,3] The most recent lead into the mysteries of what causes schizophrenia could be viewed

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[a] Schizophrenia Research Institute, Barker Street, Randwick, New South Wales 2031, Australia; [b] School of Psychiatry, University of New South Wales, Hospital Road, Randwick, New South Wales 2031, Australia; [c] Neuroscience Research Australia, Barker Street, Randwick, New South Wales 2031, Australia
* Corresponding authors. Neuroscience Research Australia, Barker Street, Randwick, New South Wales 2031, Australia
E-mail addresses: cyndi@neura.edu.au; t.weickert@unsw.edu.au

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as a fusion of the 2 lines of evidence referred to above. Indeed, an aberrant immune system response can cause NMDAR downregulation in the brain, which can lead to psychosis (hallucinations and delusions). Thus, what is considered to be really "hot" is the new awareness that anti-NMDAR encephalitis can result in a clinical manifestation that presents with psychosis[4] and can mimic schizophrenia. Furthermore, anti-NMDAR encephalitis can be "cured" by plasma immunotherapy, which can essentially eliminate psychotic symptoms. Observations like these are critical to the field because they demonstrate that schizophrenia symptoms or psychosis has a neurobiological basis and provides proof of principle that the psychotic symptoms can be abolished when treatment is aimed more directly at the underlying cause. Although some may argue that anti-NMDAR encephalitis is not "true" schizophrenia and that many of those cases can progress to paralysis and possibly death, milder or alternate forms of anti-NMDAR encephalitis may exist in a more chronic or relapsing and remitting fashion in some people with schizophrenia.

WHAT'S "HOT" IN BLOOD BIOMARKER STUDIES

Blood biomarker studies in general are a "hot" research area for schizophrenia. Blood is relatively easy to collect, and assays of thousands of different quantifiable factors can be performed fairly quickly and easily. Although some studies have focused on attempting to find blood biomarkers to distinguish Diagnostic and Statistical Manual of Mental Disorders (DSM)- or International Classification of Diseases (ICD)-defined schizophrenia compared with controls, or compared with bipolar illness or depression,[5] determining probability-based diagnostic categories is only one use of biomarkers.[6] Biomarkers can also be used to predict change over time, that is, prognosis (prognostic biomarkers). An important use of a prognostic biomarker is to predict who is more likely to transition to psychosis before they reach clear diagnostic criteria. Currently, the estimates of conversion to DSM-V/ICD-10 schizophrenia or psychotic bipolar illness from a prodormal state are around 22%.[7] In a recent paper from the North American Prodromal Longitudinal Study (NAPLS) group, increases in blood levels of several interleukins (IL), IL-1, IL-7, and IL-8, and molecules capable of modulating the blood-brain barrier (BBB) function could be used as part of a panel to predict conversion to psychotic illness, with blood levels of cytokines correlating with positive symptom severity (eg, delusional ideas), attentional dysfunction, and dysphoric moods.[8] Although an increase in inflammatory markers was also found concurrently with changes in markers of the hypothalamic-pituitary-adrenal axis dysregulation, these findings suggest that peripheral factors typically monitored by endocrinologists and immunologists may be useful for psychiatrists in monitoring risk for developing a psychotic mental illness.

Although predicting who will develop psychotic symptoms before manifestation of the illness is critical if the onset of major mental illness is to be prevented, many of the blood biomarker studies have been conducted in those that have already reached diagnostic criteria. One of the most highly cited meta-analyses on this topic is from Miller and colleagues,[9] which analyzes data combined from 40 studies and demonstrates clear increases in at least 9 proinflammatory cytokines (IL-1 beta, IL-6, IL-8, IL-12, IL-1RA [receptor antagonist], and tumor necrosis factor-α, transforming growth factor-β, interferon-γ, soluble IL-2 receptor) and decreases in an anti-inflammatory cytokine (IL-10) in chronically ill people with schizophrenia or people during a first psychotic episode relative to controls. Although this important analysis also suggests that antipsychotics can significantly decrease blood cytokine levels,[9] it is important to consider that although these peripheral cytokine levels may be reduced to some