Immune System Disturbances in Schizophrenia

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Epidemiological, genetic, transcriptome, postmortem, peripheral biomarker, and therapeutic studies of schizophrenia all point to a dysregulation of both innate and adaptive immune systems in the disease, and it is likely that these immune changes actively contribute to disease symptoms. Gene expression disturbances in the brain of subjects with schizophrenia show complex, region-specific changes with consistently replicated and potentially interdependent induction of serpin peptidase inhibitor, clade A member 3 (*SERPINA3*) and interferon inducible transmembrane protein (IFITM) family transcripts in the prefrontal cortex. Recent data suggest that *IFITM3* expression is a critical mediator of maternal immune activation. Because the IFITM gene family is primarily expressed in the endothelial cells and meninges, and because the meninges play a critical role in interneuron development, we suggest that these two non-neuronal cell populations might play an important role in the disease pathophysiology. Finally, we propose that *IFITM3* in particular might be a novel, appealing, knowledge-based drug target for treatment of schizophrenia.

Key Words: Blood-brain barrier, blood vessels, *CD14*, *CHI3L1*, IFITM, *IFITM3*, immune, meninges, pia mater, postmortem, schizophrenia, *SERPINA3*

Gene × environment interactions play a critical role in the emergence of schizophrenia pathophysiology. Epidemiological, genetic, transcriptome, postmortem, peripheral biomarker, and therapeutic studies of schizophrenia all point to a dysregulation of both innate and adaptive immune systems in the disease (1–3), and it is likely that these immune changes actively contribute to disease symptoms (1,4,5). Regardless of the abundance of data obtained to date, our understanding of the mechanism by which the immune system disturbances arise is limited: we do not have a good insight into the origin or sequence of events by which the immune dysregulation develops, and to date we have not taken full advantage of these changes as potential therapeutic targets.

Origin of Immune Changes

What is the origin of the immune transcript disturbances? Are they coincidental, lifestyle-related, of genetic origin, "immune scars" related to early life events, or representations of life-long immune system activation in the brain? Although we do not have definite answers to these questions, knowledge integrated across several research disciplines provides us with important clues.

Genetic Susceptibility Studies

Recent genome-wide association studies identified immune-related susceptibility genes for schizophrenia in the major histocompatibility complex region of chromosome 6p21.3-22.1.2 (6–10). Using long-range phasing haplotypes tagging the major alleles at the *HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1* loci, these studies revealed significant associations of single nucleotide polymorphisms in the 5-Mb region on 6p21.3-22.1 encompassing the classical human leukocyte antigen (HLA) alleles. The Rs3131296 showed substantial correlation with the classical HLA alleles DRB1*03 and HLA-B*08. In the case of both DRB1*03 and HLA-B*08, the classical HLA allele was paired with the protective allele of rs3131296, making the results consistent with previous reports of under-transmission of DRB1*03 to schizophrenic offspring (11). However, although highly significant, the odds ratio was modest, and it is still somewhat debatable which (if any) *HLA/MHC* genes directly increase risk for schizophrenia. Furthermore, these findings are clearly not sufficient to explain the immune system disturbances in the brains of subjects with schizophrenia: the dysregulation of immune system transcripts was observed in a much larger proportion of subjects (12–15) than one would expect on the bases of genetic studies.

Biomarker Studies

A recent meta-analysis by Miller *et al.* (16) reported an increase in the inflammatory cytokines interleukin (IL)-1β, IL-6, and transforming growth factor-β during acute episodes of the illness. Furthermore, high hallucination and delusion scores seem to be correlated with the dysfunction of top canonical pathways related to IL signaling (17); and in recent-onset patients, upregulation of IL-1β, IL-6, and transforming growth factor-β in peripheral blood mononuclear cells was observed (18). In addition, a study by Song *et al.* (19) confirmed increased tumor necrosis factor (TNF)-α and IL-1β messenger RNA (mRNA) and protein levels in unmedicated first-episode patients, and at least one study reported that elevated levels of pro-inflammatory cytokines are accompanied by reduced levels of γ-aminobutyric acid (GABA)-ergic markers somatostatin (SST), parvalbumin (PV) and glutamate decarboxylase 1 (brain, 67kDa) (GAD67) in a subset of subjects with schizophrenia (15). Furthermore, recent results reveal that immunoglobulin-G, immunoglobulin-A, and immunoglobulin-M antibodies against *N*-methyl-D-aspartate receptor were detected in 9.9% of patients with schizophrenia (20). These are perhaps the strongest arguments that the immune system changes are active and continuous contributors to the schizophrenia disease process and are perhaps directly related to the symptoms of the disease.

Anti-Inflammatory Treatment of Schizophrenia

Aspirin is a nonsteroidal anti-inflammatory drug and an irreversible inhibitor of both cyclooxygenase (COX)-1 and COX-2. Aspirin is known to reduce the plasma levels of inflammatory biomarkers such as C-reactive protein, IL-6, and TNF-α in patients with cardiovascular metabolic syndrome. A recent study showed that 1000 mg of daily aspirin consumption reduced the core symptoms of schizophrenia over a course of 3-month treatment and resulted in Positive and Negative Syndrome Scale score improvements [for review, see Berk *et al.* (21) and Muller *et al.* (5)].

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Furthermore, a separate double-blind, 6-week-long placebo-controlled study revealed a significantly better outcome in both positive and negative symptoms in the group treated with adjunct celecoxib (a COX-2 inhibitor) compared with the placebo group (22). However, it should be pointed out that the beneficial effect of nonsteroidal anti-inflammatory drugs has not been replicated in all clinical studies (5).

Interestingly, there is also a growing body of literature supporting the idea that antipsychotic medication reduces cytokine levels in schizophrenia patients and in various experimental models. In maternal immune activation (MIA), it seems that atypical antipsychotics suppress production of proinflammatory cytokines. Clozapine, olanzapine, and risperidone are able to suppress TNF-α and IL-6 induction in lipopolysaccharide-treated mice (23), suggesting that antipsychotic medication might act, at least partially, as a suppressor of the immune response. Furthermore, human data suggest measuring levels of inflammation-related proteins in blood might be useful in monitoring antipsychotic drug treatment responsiveness (24).

MIA

Maternal immune activation disrupts normal fetal brain development (25–27). It is estimated that >30% of schizophrenia cases would be prevented if infection could be averted in pregnant women (3). Most commonly, MIA occurs as a result of various bacterial, viral, or parasitic infections, and presence of antibodies against influenza or toxoplasmosis in maternal serum during pregnancy is associated with increased risk of schizophrenia of the offspring (28). These pathogens trigger a maternal immune response, which consists of activation of various cytokine pathways, including IL-1, IL-6, TNFα, and interferon (IFN)-γ (25). The effect of MIA on fetal brain does not require direct infection: even in the absence of the virus the cytokine induction with polyinosinic-polycytidylic acid poly[I:C] (a synthetic double-stranded RNA) is sufficient to produce long-lasting effects, suggesting that response of the mother to the infection is critical for altering fetal brain development (29). Pathological findings in patients with schizophrenia encompass alterations in multiple domains and include increased GABAA receptor α2 immunoreactivity, dopamine hyperfunction, delayed hippocampal myelination, reduced *N*-methyl-D-aspartate receptor expression in hippocampus, reduced numbers of reelin- and parvalbumin-positive cells, reduced dopamine D1 and D2 receptors in prefrontal cortex, and enhanced tyrosine hydroxlyase in striatal structures; and similar changes are present in the adult offspring of MIA-exposed mice (reviewed by [1,2,30]). Furthermore, in adulthood, MIA exposed offspring display behavioral deficits in social interaction, prepulse inhibition, and open field and novel object exploration (25) as well as heightened response to hallucinogen exposure (31). These cellular/molecular/behavioral deficits seem to be directly related to the deficits observed in schizophrenia, further emphasizing the potential role of MIA in the disease pathophysiology. In addition, stress, genetic predisposition, and MIA interact: combined exposure to prenatal immune challenge and peripubertal stress induces synergistic pathological effects on adult behavioral functions and neurochemistry (32); and *DISC1* point mutations exacerbate the outcome of MIA (33). Importantly, it seems that induction of IL-6 is both a necessary and sufficient component of MIA, because a single injection of the cytokine IL-6 in pregnant mice can recapitulate most of the deficits observed across the various models of MIA (29).

In summary, these converging findings strongly argue that immune system disturbances are the integral part of schizophrenia pathophysiology. However, schizophrenia is a uniquely human brain disease. As a result, postmortem brain transcriptome studies are of particular importance, because they can identify disturbed genes and pathways arising from the synergistic effects of diverse genetic predispositions and various environmental insults (34–36). Thus, in the absence of true animal models of schizophrenia, postmortem studies of brains of subjects with schizophrenia are essential contributors to the overall understanding of disease pathophysiology.

Transcriptome Changes in Schizophrenia

Schizophrenia is a syndrome, characterized by a considerable symptomatic diversity. It seems that the underlying molecular diversity of the disease is even more varied than the clinical manifestations (37). Transcriptome studies since the beginning of the millennium report that schizophrenic subjects show great, almost individual diversity in gene expression disturbances. Still, it seems that the overall data argue for a substratification of disease-related mRNA profiles within the affected subjects, with molecular signatures commonly encompassing synaptic (38,39), GABAergic (40,41), mitochondrial (42–44), immune (12–15), and oligodendrocyte (45–47) disturbances (Figure 1A). These signatures overlap in a complex pattern, with many subjects showing altered expression across multiple biological domains, making it challenging to classify the individual subjects with schizophrenia into a single molecular phenotype. Yet, the overall data suggest that the most distinct molecular signatures are the oligodendrocytic and GABAergic phenotypes, and the ones that show the most overlap are the GABAergic and synaptic gene expression disturbances. Unfortunately, due to the limited postmortem brain availability and less-than-ideal clinical record access, we have no clear understanding of how the molecular disturbances might relate to the behavioral phenotypes or outcomes. As a result, different brain banking methods (e.g., recruitment from chronically hospitalized patients vs. obtaining samples for the office of the coroner) might preferentially draw from different subpopulations of patients and the various "omics" analyses yield subpopulation-specific datasets that are not easily replicated (Figure 1B).

Immune Transcriptome Changes in the Human Brain

To understand the altered immune transcriptome in schizophrenia, first we have to ask a fundamental yet elusive question—how do we define an "immune system gene"? Narrowly considered, any gene that directly participates in innate or acquired immune response can be considered an immune gene. However, this definition might be too conservative, because a large number of genes do not directly participate in the immune response, yet they are potent regulators of various host responses. For example, responses that protect against excessive inflammation can be regulated through the cholinergic anti-inflammatory pathway: lipopolysaccharide-induced TNF-α release from macrophages is inhibited by selective cholinergic receptor, nicotinic, alpha 7 (*CHRNA7*) agonists (48). Furthermore, activation of GABAergic, cholinergic, and adrenergic receptors suppresses microglial responses, whereas activation of adenosine triphosphate or adenosine receptors activates them (49). In addition, many of the cell adhesion molecules also serve as viral entry receptors (e.g., neuronal cell adhesion molecule for Rabies, CD155 for Polio, nectin-1 for herpes simplex virus-1, and coxsackievirus and