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Neuroimmune biomarkers in schizophrenia

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ABSTRACT

Schizophrenia is a heterogeneous psychiatric disorder with a broad spectrum of clinical and biological manifestations. Due to the lack of objective tests, the accurate diagnosis and selection of effective treatments for schizophrenia remains challenging. Numerous technologies have been employed in search of schizophrenia biomarkers. These studies have suggested that neuroinflammatory processes may play a role in schizophrenia pathogenesis, at least in a subgroup of patients. The evidence indicates alterations in both pro- and anti-inflammatory molecules in the central nervous system, which have also been found in peripheral tissues and may correlate with schizophrenia symptoms. In line with these findings, certain immunomodulatory interventions have shown beneficial effects on psychotic symptoms in schizophrenia patients, in particular those with distinct immune signatures. In this review, we evaluate these findings and their potential for more targeted drug interventions and the development of companion diagnostics. Although currently no validated markers exist for schizophrenia patient stratification or the prediction of treatment efficacy, we propose that utilisation of inflammatory markers for diagnostic and theranostic purposes may lead to novel therapeutic approaches and deliver more effective care for schizophrenia patients.

1. Introduction

Schizophrenia affects about 1% of the population but the understanding of its aetiology remains incomplete. At present, schizophrenia is not considered a single disorder but a group of conditions with manifestations common to other psychiatric and non-psychiatric disorders. Those manifestations include clinical symptoms, such as hallucinations, delusions, disturbed emotions and social withdrawal, and involve biological mechanisms, in particular perturbations of the immune, metabolic and endocrine systems. In the absence of a biological marker, the current diagnosis of schizophrenia and its treatment are mainly based on clinical questionnaires and it is not surprising that the response rate is unsatisfactory, in particular after multiple treatment attempts, and relapse is common for those patients who discontinue medication (Emsley et al., 2013). For decades, pathophysiological studies relating to schizophrenia were focused on disturbances of dopaminergic and glutamatergic neurotransmission with limited clinical breakthroughs. Current antipsychotic drugs primarily alleviate the neurotransmitter imbalances, but most patients continue to experience residual symptoms on current treatment regimens (Chakos et al., 2001; Leucht et al., 2009, 2013). Furthermore, the rate of novel compounds coming to the market is far from satisfactory. However, recently there has been a greater focus on the identification of molecular changes in central and peripheral tissues obtained from schizophrenia patients to unravel the molecular signatures underpinning schizophrenia pathophysiology as a means of improving and accelerating this process (Guest et al., 2013).

A link between inflammatory diseases and schizophrenia has been proposed over decades. The evidence suggests that some clinical, epidemiological and genetic features may be shared between schizophrenia and certain autoimmune diseases (Wright et al., 1996; Brey et al., 2002; Benros et al., 2011). The co-prevalence between various autoimmune disorders and some cases of schizophrenia may contribute to the disease development (Eaton et al., 2006). For example, Graves' disease (thyrotoxicosis) has been shown to share similar aetiological features with schizophrenia (Bianco and Lerro, 1972; Ogah et al., 2009). In addition, a relationship between perinatal and adulthood infections and schizophrenia is supported by various lines of evidence (Maurizi, 1984; Buka et al., 2001a; Leweke et al., 2004; Brown et al., 2005;

Abbreviations: AP, antipsychotic; CD, cluster of differentiation; CNS, central nervous system; COMT, catechol-O-methyltransferase; COX, cyclooxygenase; CSF, cerebrospinal fluid; CSF2RA, colony stimulator factor receptor 2 alpha; DISC, disrupted in schizophrenia; GWAS, genome-wide association study; HER2, human epidermal growth factor receptor 2; HLA, human leukocyte antigen; HSV, herpes simplex virus; IFITM, interferon-induced transmembrane protein; IFN, interferon; IL, interleukin; KYNA, kynurenic acid; MHC, major histocompatibility complex; NAC, N-acetylcysteine; NK, natural killer; NMDA, N-methyl D-aspartate; NRG, neuregulin; PANSS, Positive and Negative Syndrome Scale; PET, positron emission tomography; RA, rheumatoid arthritis; SERPINA3, alpha-1-antichymotrypsin; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TGF, transforming growth factor; Th, T helper; TNF, tumour necrosis factor; TSPO, translocator protein.

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Brown, 2006; Khandaker et al., 2012). More recently, genome-wide association studies (GWAS) have substantiated these findings by indicating a strong relationship between genes regulating immune response and schizophrenia (Corvin and Morris, 2013).

In the past years, a significant proportion of clinical and molecular studies have attempted to unravel the role of immune dysregulation in schizophrenia and explore the possibility of targeting these pathways especially as add-on intervention to existing therapies (Muller and Schwarz, 2010; Meyer et al., 2011; Keller et al., 2013; Kirkpatrick and Miller, 2013; Najjar et al., 2013; Smyth and Lawrie, 2013; Feigenson et al., 2014; Girgis et al., 2014; Kroken et al., 2014). As the immune system is dynamic and sensitive to changes, the research into the relationship between schizophrenia and immune system abnormalities has yielded contradictory results. This is most likely due to a complex interplay between genetic predisposition, environmental risk factors, disease stage and side effects of antipsychotic medication. Recent findings from our group indicate that molecular changes in schizophrenia patients show an overlap with certain inflammatory as well as metabolic disorders (Chan et al., 2011). The utility of the immunological markers for diagnosis and prognosis of schizophrenia is yet to be established.

In this review we will evaluate findings of neuroimmune changes in schizophrenia. We will discuss the evidence of central and peripheral immune findings in schizophrenia, their potential causes, and effects of immunomodulatory therapies on symptoms and outline potential applications of these markers in managing the disease.

2. Neuroimmune alterations and schizophrenia features

2.1. Central nervous system markers

Imaging studies have shown that the brains of schizophrenia patients display characteristic structural changes at the onset of the disease, which cannot be attributed to drug effects or other confounding factors. Most often, decreased hippocampal and cortical volumes, accompanied by enlarged ventricular spaces, have been identified (Harrison, 1999). Contrary to the findings in Alzheimer's disease, the changes in schizophrenia do not result from an ongoing neurodegenerative processes or neuronal death, but are related to changes in the organisation and size of neurons and other brain cells (Harrison, 1999). Although central nervous system (CNS) changes show only low sensitivity and specificity for identification of patients compared to controls, they have improved our understanding of the mechanisms underlying schizophrenia symptoms (Allen et al., 2009). It has been postulated that psychotic symptoms, at least in part, are due to impaired dopaminergic and glutamatergic neurotransmission in the extended limbic system (hippocampus, dorsolateral prefrontal cortex and cingulate gyrus). However, the exact underpinning processes remain largely unknown.

Molecular profiling studies have suggested that molecules related to oxidative stress and immune regulation are implicated in the pathophysiology of certain brain regions in schizophrenia. However, their relation to the structural changes is not clear. These studies have repeatedly shown altered expression of immune-related markers in prefrontal (Arion et al., 2007; Saetre et al., 2007; Martins-de-Souza et al., 2009; Fillman et al., 2013) and temporal (Wu et al., 2012) cortices as well as in the hippocampus (Hwang et al., 2013) of schizophrenia patients. Since brain profiling studies can be performed only in post-mortem brain tissue, and as most patients have been treated long-term before death, these results suggest that current treatment approaches are not effective in alleviating the immune manifestations of the disease. Some studies have found that only about 40% of schizophrenia patients display signs of immune activation, e.g. changes in IL1B, IL6, IL8 and alpha-1-antichymotrypsin (SERPINA3) transcript levels (Fillman et al., 2013; Fillman et al., 2014). These findings are consistent with the proportion of schizophrenia patients displaying structural abnormalities (Allen et al., 2009), but further studies are required to assess precisely the association between immune activation and brain volume. Also, changes in other cytokines related mostly to the innate immune system have been observed in brains of schizophrenia patients, including tumour necrosis factor alpha (TNF-α) (Rao et al., 2013), and interferon-induced transmembrane proteins 1 and 2 (IFITM2/IFITM3) (Saetre et al., 2007); as well as the microglia marker CD11b (Rao et al., 2013) (Table 1). In line with these findings, immunohistochemical studies have shown that the density of microglial cells and their marker, HLA-DR, are higher in post-mortem schizophrenia brains, in particular in those patients who committed suicide (Bayer et al., 1999; Radewicz et al., 2000; Steiner et al., 2006b; Fillman et al., 2013). Microglia are the equivalent of macrophages in the brain and one of their main roles is immune defence of the CNS. Therefore, activation of these cells indicates ongoing immunological processes in the CNS.

Signs of immune dysregulation in schizophrenia have also been observed using in vivo brain imaging. Activated microglia express the 18 kDa translocator protein (TSPO) on the mitochondrial membrane. This protein has been targeted in positron emission tomography (PET) studies by measuring binding of the radiolabeled ligand, PK11195. Studies have shown increased binding of PK11195 in total grey matter of recent onset patients with schizophrenia (van Berckel et al., 2008) and in hippocampus of recovering patients (Doorduin et al., 2009), suggesting activation of microglial cells in these regions at different stages of the disease. Also, astrocytes have been reported to show signs of activation in schizophrenia, as indicated by an increased release of S100B protein into the cerebrospinal fluid (CSF). S100B is a marker of nervous system damage and increased levels have been observed in the CSF of schizophrenia patients at disease onset and in drug-naïve patients (Rothermundt et al., 2004; Steiner et al., 2006a). This protein induces the production of several other immune markers by microglia cells, including cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) (Najjar et al., 2013), which are considered to be potential novel drug targets for the treatment of schizophrenia (Laan et al., 2010; Weiser et al., 2012).

Interestingly, many other cytokines showing changes in schizophrenia brains and CSF can be linked to microglia activation (IL-1β, IL-12, TNF-α) or are secreted by activated astrocytes [IL-6, IL-10, transforming growth factor beta (TGF-β)]. It is hypothesized that the interaction between these two glial cell types increases the production of quinolinic acid by microglia and kynurenic acid (KYNA) by astrocytes (Kroken et al., 2014). These metabolites activate N-methyl D-aspartate (NMDA) receptors (Muller and Schwarz, 2006), which provides a direct link between immune activation and hypoglutamatergic neurotransmission in schizophrenia. KYNA has been found to be elevated in the CSF of drug-naïve first episode schizophrenia patients (Erhardt et al., 2001), as well as in chronically ill patients (Linderholm et al., 2012), consistent with findings from post-mortem studies (Schwarcz et al., 2001). Drugs targeting the kynurenine pathway have shown positive effects on cognitive function in animal models (Wu et al., 2014), but have not yet been tested in schizophrenia patients.

2.2. Peripheral markers

Several studies have suggested that immune alterations in the CNS may originate from peripheral immune activation, crossing the blood–brain barrier in a subgroup of patients (Kirch et al., 1985; Kirch et al., 1992). Peripheral cytokines can cross the blood–brain barrier and are known to perturb brain function through the hypothalamic–pituitary–adrenal (HPA) axis, precipitating changes in mood, behaviour and cognition (Watanabe et al., 2010). Although this causality is not well-established, characteristic immune imbalances are observed in the blood of schizophrenia patients (Table 1). The majority of studies have focused on cytokine changes in serum of schizophrenia patients and have been extensively reviewed in several meta-analyses (Potvin et al., 2008; Miller et al., 2011; Tourjman et al., 2013). Importantly, a review from 2008 (Potvin et al., 2008) challenged the previous hypothesis of blunted Th1 and enhanced Th2 responses in schizophrenia, reporting increased IL-1RA levels in both unmedicated and treated patients,