Targeting the inflammatory component of schizophrenia

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Abstract
Schizophrenia is a heterogeneous disease characterised by an array of clinical manifestations. A large number of studies over the last 20 years have pointed towards immune system abnormalities in patients suffering from this condition. In addition, the psychosis and cognitive dysfunction associated with schizophrenia have been shown to be linked with autoimmune diseases. Here, we review the evidence, which suggests that a pro-inflammatory status of the immune system induces psychopathologic symptoms and may be involved in the pathophysiology of this major mental illness. We also propose that future preclinical and clinical studies should take such pre-defined causes and the dynamic status of the inflammatory component into account. Patient stratification and personalised medicine strategies based on targeting the inflammatory component of the disease could help in alleviation of symptoms and slowing disease progression. Ultimately, this could also lead to novel concepts in schizophrenia target/molecular identification and drug discovery strategies.

Keywords: Schizophrenia, inflammation, immune system, biomarkers.

Introduction
Schizophrenia is a complex psychiatric disorder which affects approximately 1% of the world population. Although considerable progress has been made in the search for contributing factors, the aetiology of the disease is still far from understood. Heterogeneity throughout the onset and progression of schizophrenia is a major factor slowing down scientific progress in the field. Another complicating factor is the overlap of symptoms with other psychiatric and neurological disorders and it remains unclear whether the different manifestations reflect subtypes with different aetiologies or whether diverse clinical syndromes may have overlapping pathologies. These factors have led to a high rate of misdiagnosis using the current subjective clinical rating systems1. For this reason, there is now intensive effort to identify more empirical measures based on molecular fingerprints underpinning the disease aetiology. One problem is the need to identify peripheral biomarkers which can be measured easily in the clinic. Previously the main focus of schizophrenia research has been to identify pathophysiological changes in the brain, a biomaterial which is largely unavailable to the clinician for diagnostic purposes. Thus aspects of the disorder that are reflected in peripheral tissues are an important focus for biomarker discovery.

Here, we review the advances made in elucidating the potential role of the immunological component of schizophrenia. There has been considerable evidence indicating the significance of neuroinflammation and immunogenetics in schizophrenia2. This has been characterized by an increased serum concentration of several pro-inflammatory cytokines. The brain physiological interactions between the brain and immune systems have also been well established3,4. In response to environmental insults, subjects with schizophrenia can develop a compromised immune system5. There is also a genetic contribution to schizophrenia with estimates of heritability ranging from 30% to 85%6-8. However, the exact genetics of these disorders are far from being elucidated. Previous studies suggest that several genetic, endogenous and environmental factors are involved and these may interact to bring about specific disease manifestations7. The precise interaction between the genetic vulnerability to develop schizophrenia and environmental factors is still unclear. However, linkage and association studies have been conducted in an attempt to identify candidate susceptibility genes for schizophrenia and other psychiatric disorders9. Genetic studies have identified an association of polymorphisms related to inflammation. The interleukin 1 (IL-1) gene cluster in schizophrenia was suggested recently9,10. However, the increased risk of developing the disorder is unlikely to be accounted for by a single gene and is most probably a combination of several different genes. For even the most promising gene polymorphisms such as neuregulin-1, the additional risk is low at approximately 2% instead of the 1% risk seen in the general population10.
Brain studies

The pro-inflammatory status associated with neuropsychiatric diseases has been extensively investigated and well established. The activation of the brain immune system has been suggested by the increased levels of IL-1β in the cerebrospinal fluid in first-episode schizophrenia patients. Brain development is also known to be regulated by pro-inflammatory agents. Maternal infection in pregnancy can increase the risk of developing schizophrenia by impacting the neuro-developmental stage in the foetus. This is due to the fact that the balance between pro and anti-inflammatory agents may influence brain development and behaviour.

Transcriptomic profiling of post-mortem brain or peripheral tissues can provide useful insights into the perturbed biological processes in central nervous system disorders. The gene expression level of pro-inflammatory cytokines in preclinical models of schizophrenia and human subjects have been shown to be increased in the prefrontal cortex region of the brain. Several transcriptomic studies have shown that inflammation-related genes which are increased in schizophrenia brains are also associated with oligodendrocyte and endothelial cells. In these cells, transcription can be induced by the inflammatory cytokines tumour necrosis factor alpha (TNF-α), interferon alpha (IFN-α) and interferon gamma (IFN-γ) (15). However, these effects are likely to be confounded by psychotropic drug treatment, poor diet or unhealthy life styles, which are often associated with chronic stages of the disease.

The availability of tissues which are more accessible is necessary to apply these approaches clinically. A recent study carried out data analysis from the transcriptomic profiling of 33,698 genes in 79 human tissues. The results suggested that while whole blood cells share significant gene expression similarities with central nervous system tissues, the correlation between transcripts present in both of these was around 0.5, which was less than immune tissues (0.64) and comparable to a somatic tissues (0.57). The authors concluded that gene expression in whole blood cells is only partially correlated with that seen in brain tissues.

There are also numerous reports of immune abnormalities in the central nervous system and in the periphery of patients with schizophrenia. Cytokine levels have been measured in brain and body fluids such as cerebrospinal fluid (CSF) and blood serum of patients with schizophrenia and a decreased inflammation response has been linked with decreased production of T helper (Th)-1 cytokines. The pituitary gland is known to be involved in regulation of the central nervous system and peripheral tissues by release of hormones involved in vital body functions. Thus, the pituitary provides a regulatory link between the blood and brain. Furthermore, the pituitary is controlled by inflammatory stimuli, as the production of adrenocorticotropic hormone (ACTH), growth hormone (GH) and thyroid stimulating hormone (TSH) appears to be regulated by IL-6 (16). One of the first direct evidence reflecting a pro-inflammatory status at the brain in the disease onset was provided by Van Berckel et al. Using PET imaging techniques Van Berckel et al. have shown microglial activation in the brain of schizophrenic patients within the first five years of the disease onset. Further pre and clinical studies are needed to unravel the causality of blood and brain pro-inflammatory status in neuropsychiatric diseases such as schizophrenia. Nevertheless, in the past decades scientists have stipulated that infectious agents (e.g. herpes simplex virus, Epstein-Barr virus and toxoplasma) as a possible cause of schizophrenia and such a phenomenon may be explained by chronic infections or compromised immune status. Finally, a large set of data have also stipulated that environmental factors such as oxidative stress plays a major role causing or exaggerating the inflammatory component of schizophrenia.

Peripheral studies

Inflammation has been associated with schizophrenia for decades and studies of changes in inflammatory molecules may lead to a means of patient stratification prior to antipsychotic treatment. A previous study which carried out a meta-analysis revealed alterations in cytokines in blood and cerebrospinal fluid from patients with schizophrenia. Numerous studies have reported that inflammatory and cellular pro-inflammatory alterations are associated with schizophrenia. Analysis of the transcriptome pattern in circulating monocytes isolated from patients suffering from schizophrenia and bipolar disorder showed a pro-inflammatory status associated with monocyte and T-cell activations. However, some of these studies have provided an inconsistent picture, which is most likely due to differences in the number or type of cytokines measured or the presence of confounding factors such as different disease subtypes, co-morbidities, illness duration and the fact that patients had been treated with antipsychotics. In addition, many of these studies have been performed using peripheral blood mononuclear cells (PBMC) which may have led to inconsistencies related to differences in the isolation procedures used. The “macrophage-T cell theory of depression and schizophrenia” postulates an aberrant inflammatory state of monocytes, macrophages and T cells in patients with mood disorders or schizophrenia is contributing to the illness. Aberrant levels of inflammatory cytokines can destabilize function of the brain and the hypothalamic-pituitary-adrenal (HPA) axis, which can lead to changes in mood and behaviour. Most studies have focused on serum levels of neopterine or other cytokines in targeted approaches and these demonstrated the presence of an aberrant inflammatory state in psychiatric patients. However, this has led to inconsistent results as single determinations are not precise or robust enough to consistently measure alterations in immune function.

In a study aimed at identifying proteomic signatures and molecular pathways underlying schizophrenia, we carried out multiplex immunoassay analyses of serum samples from first-episode, drug naive schizophrenia patients which resulted in identification of a disease signature. Interestingly, many of these molecules have been implicated previously in patients with auto-immune or metabolic diseases. Further study of these pathways may result in important breakthroughs in schizophrenia research as this could lead to a means of stratifying patients prior to treatment. It could also lead to the development of new supplemental therapies which target the inflammatory aspects of the disease. Recent studies have explored the possibility of using immuno-modulatory drugs such as cyclooxygenase-2 (COX-2) inhibitors and these have been reported to have beneficial effects on schizophrenia symptoms. In addition, anti-diabetic compounds such insulin-sensing agents have already been used in targeting the cognitive deficits in Alzheimer’s disease patients and could equally be tested for improvement of similar symptoms in schizophrenia.

Inflammatory/autoimmune diseases and schizophrenia

Activation of certain immune system cells in response to an infection, or on an ongoing low level of inflammation, may contribute to mental illness. It is known that psychosocial stress can contribute to the onset of autoimmune disease or affect its course by impairing the regulation of the immune reactivity. Eaton and co-workers suggested that the correlation between various autoimmune diseases and some cases of schizophrenia may contribute to the disease development. Moreover, other studies have already linked dysfunctional immune status to some of the clinical features of schizophrenia. It has also been hypothesised that schizophrenia shares clinical, epidemiological and genetic characteristics with classical autoimmune diseases. A recent study carried out an analysis of the comprehensive records of Denmark’s health system, which has tracked a Danish cohort (n = 7,704) comprised of subjects diagnosed with schizophrenia between 1981 and 1998. The results showed that subjects who developed any of nine different autoimmune disorders had a 1.45 fold increased risk for developing schizophrenia. The link between inflammatory diseases, such as systemic lupus erythematosus (SLE), and psychiatric conditions has been well-documented. For example, cognitive dysfunctions and psychoses which are associated with schizophrenia can also be found in patients suffering from SLE.
Moreover, autoimmune mechanisms may play a role in the aetiology of schizophrenia as shown by the presence of elevated levels of auto-antibodies in blood, cerebral spinal fluid and brain of schizophrenia patients. More recently, we reported that several pro-inflammatory molecules are elevated in first onset schizophrenia patients. Interestingly, these same molecules are also elevated in SLE patients.

It is well established that obstetric complications and perinatal trauma are associated with an increased chance of the offspring later developing schizophrenia, although overall these associations are more likely to be contributory factors. Viral infection during pregnancy has been linked to an increased frequency of schizophrenia in the offspring. Studies using a rodent model of schizophrenia have led to the suggestion that maternal infection during embryogenesis contributes to microglial activation in the offspring, which may represent a contributing factor to the pathogenesis of schizophrenia.

Also, the occurrence of schizophrenia is more common in those born in winter to early spring, when infections are more frequent.

Imaging studies of the brain, using positron emission tomography have also suggested that the neuropathology of schizophrenia is associated with altered immune system function. Doorduin et al. used the benzodiazepine receptor ligand isoxiquinoline (R)-N-11C-methyl-N-1(1-methylpropyl)-1-2-chlorophenyl) as a positron emission tomography (PET) imaging ligand and found that neuro-inflammation characterized by increased microglia cells activation is associated with schizophrenia-related psychosis. Moreover, the mild anti-inflammatory properties of antipsychotics are thought to be involved in targeting the inflammatory component of schizophrenia by acting as anti-inflammatory agents. Moreover, inflammatory modulating agents have been linked to damage of the vascular system in schizophrenia and patients with schizophrenia have an average reduction in life expectancy of approximately 15 years which may be related to the development of cardiovascular conditions.

Modelling the inflammatory component of Schizophrenia

Although neuropsychiatric disorders are thought to be manifested mainly as dysfunction of the central nervous system, many alterations have also been found in peripheral tissues. This is not surprising considering the role that the blood plays in the transport of key regulatory factors such as hormones, nutrients and immune-related molecules which can affect brain function. For example, various immune system alterations have been reported in major depressive disorder and schizophrenia including a shift from type 1 (cellular) to type 2 (humoral) immune responses. We have conducted extensive studies on cellular function in schizophrenia which suggests that immune system changes are also seen in antigen-stimulated T cells from patients. We have shown that an in vitro challenge of peripheral blood mononuclear cells (PBMC) from schizophrenia and control subjects resulted in identification of altered signalling and metabolic pathways. The changes included a schizophrenia-specific alteration in proliferation rate, glucose metabolism and an imbalance of different T cell subpopulations. The finding of impaired glycolysis in PBMCs isolated from first onset and drug naïve schizophrenic patients was consistent with previous studies of post-mortem brain tissue and cerebrospinal fluid samples with regards to changes in glucose regulation and energy metabolism. Interestingly, these changes were not apparent in non-stimulated cells.

PBMC express the glucose transporter 1 (GLUT1) and various neurotransmitter receptors such as dopamine D2, 5-Hydroxytryptamine (HT) 2A, 5HT2C, 5HT1A and nicotinic acetylcholine receptors, which are similar to those found in the brain. This makes culture of these cells a potentially useful model for investigating mechanisms involved in metabolic abnormalities in schizophrenia and/or antipsychotic drug action. Interestingly, the schizophrenia-related molecular changes appear to be normalized in PBMC in response to treatment, and this was associated with remission of the disease.

Other studies have shown that peripheral lymphocytes of patients with schizophrenia had decreased expression of the receptor for reelin, a serine protease associated with schizophrenia pathology. In addition, membrane fatty acid abnormalities including elevated levels of phospholipase A2 and impaired prostaglandin signalling have been identified and linked to the reduced niacin skin flush response in schizophrenia patients.

We have recently applied multiplex immunoassay in combination with mass spectrometry proteomic profiling to provide dynamic readouts that are likely to lead to deeper molecular insights into the cellular dysfunction associated with schizophrenia. We used a novel ex vivo whole blood system (TruCulture) in the presence or absence of an immune challenge to investigate the differential release of molecules from blood cells at the onset of the disease. This cellular model more closely approximates in vivo conditions of immune cell activity compared to isolated PBMC models. Nine molecules showed a compromised immune status in schizophrenia blood cells compared to those from controls and this was replicated in an independent cohort. In silico pathway analysis showed that these molecules had roles in endothelial cell function, inflammation, acute phase response and fibrinolysis pathways.

Immune/metabolic dysfunction in schizophrenia

There is evidence that there are functional associations between the peripheral and central immune systems. For example, alterations in the calcium-binding protein S100B associated with blood-brain barrier function have been linked with schizophrenia at both the peripheral and central levels. A recent study has shown that S100B secretion by human CD8+ T cells activates monocytes and granulocytes, suggesting crosstalk between cells of the adaptive and innate immune systems in mediating such inflammatory responses.

Recent studies suggest that the perturbations in immune system function seen in psychiatric disorders may result from failure to mount an appropriate inflammatory response and could be related to impaired metabolism. This is likely to be the case as inflammatory responses consume large amounts of energy. In support of this, we have shown recently that glycolysis may be impaired after stimulation of PBMC taken from schizophrenia patients. This is also consistent with other studies showing that drug-naive schizophrenia subjects may have impaired insulin signalling, which regulates most metabolic pathways in the body.

The observation that metabolic disorder has been associated with low grade systemic inflammatory conditions has led to studies linking these two pathways. For example, the excessive adipose tissue often associated with metabolic syndrome produces elevated levels of proteins such as adipokines which have been implicated in the pathogenesis of metabolic diseases including diabetes, hypertension and cardiovascular disease. In the case of psychiatric disorders, it is still not clear whether such peripheral effects on metabolism or on immune function are a cause or consequence of central nervous system disturbances. The central nervous system responds to inflammatory processes through activation of the HPA axis and production of the stress hormone cortisol. Indeed, the HPA axis provides a functional link between central and peripheral control of metabolism.

Most studies have identified an abnormal HPA axis response in schizophrenia, including elevated basal plasma cortisol and a blunted cortisol response to psychosocial stress. Cortisol antagonises the effects of insulin, inducing gluconeogenesis. Chronically elevated cortisol levels may therefore lead to symptoms of metabolic syndrome including hyperglycaemia, insulin resistance and increased visceral fat deposition. Alterations in cortisol in schizophrenia patients have been considered to be a confounding factor in studies of metabolic features due to the high levels of psychosocial stress experienced by psychiatric patients. However, abnormalities in glucose tolerance have also been found independent of changes in cortisol levels. Moreover, HPA axis dysfunction may be mechanistically linked to the balance of energy substrate distribution between the central and peripheral systems.

One of the major contributing factors to schizophrenia comorbidities which could lead to an inflammatory response includes an increased risk for metabolic syndrome, weight gain and type II diabetes.
diabetes. These effects have been attributed mainly to side effects of atypical antipsychotic medications such as clozapine and olanzapine81. However, impaired fasting glucose tolerance has also been reported in first onset antipsychotic-naïve schizophrenia cases, suggesting that disease-inherent abnormalities in glucose metabolism may already be present in the earliest stages of the disease82,83. Also, effects on changes in the inflammatory response have been reported for first onset patients86. Interestingly, not all schizophrenia subjects develop such effects, suggesting that an empirical means of predicting treatment responses would be a major benefit.

Recently, we carried out a system biology analysis combining a comprehensive literature search and large in-house database on peripheral biomarkers associated with schizophrenia84. This analysis has shown categorically that “immunological disease”, and “inflammatory responses” are the top diseases associated with these molecular lists and significantly associated with schizophrenia. Moreover, the top canonical pathway analysis of schizophrenia sera proteome biomarkers studies provided further evidence for altered immunological and/or inflammatory signalling in schizophrenia85.

Clinical need

There is now agreement that there is a fundamental lack of understanding of the biological abnormalities associated with severe mental illnesses, which are still defined by vague symptomatic descriptions that do not address the etiological heterogeneity of these conditions. The available therapeutic regimes are aimed largely at relieving symptoms and may only slow or halt disease progression at an early stage. Thus early and accurate diagnosis is essential. Many patients with neuropsychiatric diseases such as schizophrenia remain unrecognised or have received incorrect or late diagnoses. The recognition rate of schizophrenia in primary care settings is less than 50%. The main reason for this is that the current diagnosis of schizophrenia is subjective. This is a result of the complex spectrum of symptoms, the overlap of these symptoms with those in other mental disorders, and the current lack of empirical markers specific for these diseases. Moreover, less than 50% of schizophrenia patients respond favourably to an initial treatment with antipsychotic medication86,87. This is most likely a result of the insufficient understanding of the underlying pathophysiology of schizophrenia to inform diagnosis or guide treatment selection. Furthermore, traditional pharmacotherapy for schizophrenia using “blockbuster” drugs usually leads to administration and switching of drugs multiple times until an adequate response is achieved. It is perhaps not surprising that there is a low treatment response rate and that relapse is common88.

The idea of personalized medicine approaches in psychiatric could be realized using molecular biomarkers which target subgroups of patients based on inflammatory, metabolic or HPA axis status. A molecular test that recognizes such subtypes may also be used for identifying those patients who are most likely to respond to a particular treatment89. The development of empirical immuno- or neuroendocrine markers and objective diagnostic and prognostic blood tests for psychiatric disorders, based on an integral approach of proteomics would be a major breakthrough in the field of schizophrenia. The discovery of novel diagnostic or therapeutically useful biomarkers involves profiling of biological samples in search for disease related qualitative and quantitative changes of molecules. Biomarkers which target alterations in the immune system, for example, could form the basis of novel empirical tests for patient stratification at the onset and throughout disease progression. This will ultimately pave the way for personalised medicine strategies with a focus on the inflammatory component of the disease. Nevertheless, environmental effects (seasonal illnesses) could be targets of future investigation. These effects on changes in the inflammatory response have been reported for first onset patients86. Interestingly, not all schizophrenia subjects develop such effects, suggesting that an empirical means of predicting treatment responses would be a major benefit.

There is a need for clinicians to employ multiple strategies to minimize the inflammatory risk in schizophrenia patients at all stages of the disease. Alternative treatment strategies have also been attempted for central nervous system disorders associated with metabolic perturbations81. For example, peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists with anti-inflammatory and anti-diabetic properties have been used to treat behavioural symptoms in autism92 and cognitive deficits associated with neurodegenerative disorders93. In addition, this approach has also been employed as an anti-inflammatory and neuroprotective agent94. This includes the use of anti-diabetics such as dipeptidyl peptidase IV (DPP-IV) inhibitors or PPAR-γ agonists95.

The inflammatory component of the disease could be targeted by existing or novel anti-inflammatory agents as add on or stand-alone therapies to alleviate the symptoms or contribute to schizophrenia treatment. Recent studies have already tested the potential of using anti-inflammatory agents to target the inflammatory component of schizophrenia and improve the clinical rating96. More, recently acetylsalicylic acid given as adjuvant therapy to regular antipsychotic treatment was used to reduce the symptoms associated with schizophrenia spectrum disorders97. Such a strategy has shown that these anti-inflammatory agents were beneficial in treating or managing mental disorders with schizophrenia as the reduction in symptoms were more pronounced in those subjects with more pronounced alterations in immune function98. This could be of major importance since recent studies have found that alterations in the inflammatory response may contribute to early development of schizophrenia99 with the possibility that certain infectious agents can contribute to the disease onset100.

A proof of concept study has already been conducted in humans and Cox-2 inhibitors have been tested as an alternative treatment for schizophrenia101. Similar strategies could also be applied in future therapeutics by using existing humanised monoclonal therapy or biopharmaceuticals on schizophrenia patients. It has already been found that targeting amyloid peptide oligomers by passive immunization with a conformation selective monoclonal antibody improves learning and memory in a mouse model of Alzheimer’s disease102. Also, an IL-6 receptor-inhibiting monoclonal antibody, a tumour necrosis factor alpha (TNF-α) antibody (Infliximab) and etanercept (a soluble TNF-receptor-Fc fusion protein) are already in use in the clinic for treatment of rheumatoid arthritis patients103. These could be tested on patients suffering from mental disorders such as schizophrenia, however one drawback of this strategy would be the occurrence potential side effects such as increased rates of infection104. This could potentially contribute to symptom exacerbation rather than alleviation. Therefore, well designed clinical trials are essential for future research.

A successful outcome of biomarker-based studies should assist clinicians in stratifying schizophrenia patients for selection of the most appropriate therapeutic regimens. This will reduce incidence of inflammatory effects, improve patient compliance and increase the proportion of patients that respond favourably to therapy with regards to psychopathology.

Conclusion

It is has been established that central and peripheral pro-inflammatory status is a significant component of schizophrenia. As ongoing
and future studies aim to investigate the relationship between the cause and effect of the inflammatory component of schizophrenia, advances in molecular profiling platforms have given us the possibility to understand the disease at a more fundamental level. This should pave the way for designing biomarker-based tests for stratification of the patients based on their molecular profile at different stages of the disease. Targeting the inflammatory component of a multi-factorial disease such as schizophrenia requires well-designed preclinical and clinical studies to correlate molecular data with clinical ratings. This comprehensive strategy (Figure 1) should enable us to understand schizophrenia aetiology and, more precisely, the role of the inflammatory component in this disease. It will also allow us to develop a flexible and progressive personalised medicine strategy based on patient stratification from the onset to late stage of the disease. The proposed paradigm change targeting the inflammatory component of schizophrenia at different stages of the disease might lead to alleviation of some symptoms, preventing the disease onset and/or slowing progression. Further studies in this area could also lead to the development of a novel target discovery strategy based on patient stratification at the molecular level. More importantly, there are conflicting reports in regards to the nature of pro-inflammatory agents as well as their directional changes that are associated with schizophrenia. As the immune system is ever changeable/adaptable, a personalised medicine strategy based on targeting the inflammatory component of schizophrenia should be tailored throughout the disease progression to suit the patient inflammatory status.

Figure 1. Schematic diagram representing personalised medicine strategy based on targeting the inflammatory component of schizophrenia.

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References


