

# Cytokines in Schizophrenia

Subjects: Cell Biology

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## Definition

Schizophrenia is a chronic mental disorder with a complex etiopathogenesis, which involves both congenital and environmental factors. It leads to neurodegenerative changes in the central nervous system (CNS) and a significant impairment of social functioning. Its lifetime incidence has been estimated at 7.1 per 1000 people, and the male to female risk ratio is 1.4:1.

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## 1. Introduction

Recent research indicates that subclinical inflammation in the CNS and immune dysregulation may play a role in the etiopathogenesis of schizophrenia, which is supported by immunogenetic evidence and a higher incidence of autoimmune diseases in patients with schizophrenia relative to the general population [1][2][3]. Neuroinflammation can lead to white matter pathology, dysconnectivity, and thus to the onset of schizophrenia symptoms [3].

Numerous studies, including many meta-analyses, demonstrate alterations in blood cytokine levels in schizophrenia patients compared to healthy controls (HC) [4][5][6][7][8]. Additionally, they tend to manifest the increased mRNA expression of cytokine genes in lymphocytes relative to HC [9]. This may stem from epigenetic mechanisms underlying the relationship between schizophrenia and stress in early childhood [10][11]. A known risk factor for schizophrenia, early childhood trauma is associated with poorer responses to treatment and symptom characteristics [10][12][13][14][15]. Elevated peripheral and cerebrospinal fluid (CSF) cytokine levels are hypothesized to partially result from disturbed gut microbiome composition, which were observed in patients with schizophrenia and may be caused by both maternal and developmental stress [16][17][18][19][20].

Schizophrenia research is typically conducted on a small patient population. The most extensively researched cohort is patients with first-episode psychosis (FEP), whose functioning is monitored prior to the initiation of antipsychotic treatment (first episode antipsychotics naive, FEAN). The second group consists of patients showing subsequent psychotic episodes, who receive treatment due to relapse (acute relapsed chronic, ARCh), while the third includes those in remission (stable chronic, SCh). Some other, far less studied patient populations include those with early onset psychosis (EOP) and patients at clinical high risk (CHR) or ultra-high risk (UHR) of psychosis.

## 2. Cytokines and Schizophrenia

A positive correlation has been found between peripheral levels of IL-10 and negative symptom severity, general psychopathological presentation, attention deficits and incidence of aggressive behaviors, and a negative correlation with cognitive deficits [21].

Meta-analyses of the effect of antipsychotics on IL-12 peripheral levels where no stratification by population or administered pharmacotherapy is applied seem to yield inconsistent results, suggesting their elevated [4][6][22] or unaltered values [23]. In addition, in their meta-analysis including the largest sample, Romeo et al. described no changes in IL-12 peripheral levels in ARCh patients, and their elevated values in those treated with risperidone [23].

To date, no effect of antipsychotics on peripheral IL-17 levels has been demonstrated [4][23][24][25].

A correlation between peripheral levels of IL-18 and the severity of depressive symptoms was found in EOP, which is probably related to the increased cortisol level [26].

### 3. Immunogenetics of Cytokine Alternations in Schizophrenia

The role of immunological dysfunction in the etiopathogenesis of schizophrenia is also demonstrated by its association with disorders of known autoimmunological underpinnings [27]. Schizophrenia has been shown to be associated with major histocompatibility complex A gene (MHC-A) polymorphisms [28], and with rheumatoid arthritis through major histocompatibility complex class II (MHC-II) or DRB1 $\beta$  chain gene (HLA-DRB1) [2].

Schizophrenia has also been shown to be associated with polymorphisms of numerous genes responsible for the synthesis of such cytokines as IL1A, IL1B, IL10 and IL6, which are genes for, respectively, IL-1 $\alpha$ , IL-1 $\beta$ , IL-10 and IL-6 [27][28]. The polymorphism of the IL6 (-174G/C) gene does not elevate the level of IL-6 in the serum, but it has been shown to be associated with the occurrence and severity of positive symptoms in the course of schizophrenia [29]. Polymorphisms of TGFB1, which encodes TGF- $\beta$ , along with its additional overexpression [30] were also associated with schizophrenia [31]. Quite remarkably, polymorphisms of the TNFR2 gene encoding the TNF- $\alpha$  receptor, depending on the variant, may be associated with an increased risk of schizophrenia, or may have a protective effect [32].

### 4. Gut Microbiome Dysbiosis in Schizophrenia

Gut microbiome dysbiosis affects behavior as well as the functioning and maturation of microglia [33][34]. Dysbiosis may also influence the activity of astrocytes with the participation of type I interferons and tryptophan metabolites [35]. Disturbances in the composition of the intestinal microbiome are associated with an increased permeability of the intestinal epithelium for bacteria, their antigens, and pathogen-associated molecular patterns (PAMPs), e.g., LPS. Greater permeability, in turn, correlates with elevated peripheral cortisol levels and could lead to the activation of the immune system related to the secretion of pro-inflammatory cytokines, activation of the HPA axis and the creation of a positive feedback loop [36][37][38][39].

In schizophrenia, there are differences in the composition of the microbiome compared to healthy controls, both in the oropharynx and in the intestines [18][19][40]. Gut microbiome biodiversity is greater in patients with schizophrenia, and shows a negative correlation with the number of CD8+ memory T cells in the blood [20]. The population size of individual bacterial species in the microbiome also correlates with symptom severity, and disturbances in its composition may be a marker of response to pharmacotherapy in FEP [41]. Moreover, an altered composition of gut microbiota persists despite treatment with olanzapine, which does not appear to have a significant effect on it [42]. Although there is no evidence of a beneficial effect of probiotic supplementation on schizophrenia symptom severity, it seems possible to use microbiome tests as an auxiliary tool in the diagnosis of the disease [19][43]. Further research is required to establish whether and to what extent dysbiosis may be responsible for the disturbances in the cytokine system present in patients with schizophrenia.

### 5. The Role of Nuclear Factor- $\kappa$ B and Human Endogenous Retroviruses

Nuclear factor- $\kappa$ B (NF- $\kappa$ B), which mediates the increase in the secretion by microglia of such cytokines as IL-1 $\beta$  and IL-18 and is activated by IL-1 $\beta$ , TNF- $\alpha$ , PAMP, adrenal cortex hormones and adrenaline, may play an important role in the potential pathological feedback loop associated with disturbances in the cytokine network in schizophrenia [44]. The increased expression of NF- $\kappa$ B and related receptors and kinases in the cerebral cortex compared to HC is confirmed by autopsy studies of the brains of people diagnosed with schizophrenia [45][46]. Elevated levels of IL-1 $\beta$  and TNF- $\alpha$ , well documented in meta-analytic data, could therefore partially result from or be the cause of increased NF- $\kappa$ B activity [6][8][44]. Other factors influencing the increased activation of NF- $\kappa$ B could also include the well-confirmed increased blood cortisol levels in patients with schizophrenia [47], the indirect dysbiosis of the intestinal microbiome [48], and, with the participation of epigenetic mechanisms, early childhood trauma [49].

Human endogenous retroviruses (HERVs) are a group of viruses that infected germinal cells of mammals many millions of years ago and were permanently integrated into their genome [50]. Under the influence

of viral infections, for example, with Epstein-Barr viruses (EBV) and Herpes simplex type 1 (HSV-1), some HERVs may reactivate, the role of which has been proposed, for example, in the etiopathogenesis of multiple sclerosis [51][52]. HSV-1 infections, similarly to other infections during pregnancy and birth in the fall and winter, when such infections are more frequent, are a confirmed risk factor for the development of schizophrenia in the offspring [53]. HSV-1 exposure is also associated with greater cognitive deficits in the course of schizophrenia [54]. It has been suggested that HERVs reactivation may be mediated by NF- $\kappa$ B with the involvement of TNF- $\alpha$  and INF- $\gamma$ , whose peripheral levels are elevated in schizophrenia [6][55][56]. In turn, the increase in HERVs expression may be associated with both an increase in the expression of pro-inflammatory cytokines and the activation of microglia, thus creating another pathological positive feedback loop [57][58]. Moreover, one of the HERVs, HERV-W, increases the expression of TNF- $\alpha$  and IL-10 in glial cells by inhibiting MyD88s, which is a splice variant of the activator NF- $\kappa$ B (MyD88), which in turn is activated, inter alia, by IL-1 $\beta$  [59][60][61]. It has been proposed that the activation of microglia and peripheral myeloid cells caused by HERVs reactivation could lead to an increase in oxidative stress, and thus damage to astrocytes, disturbance of their function, and abnormal myelination [50].

A study by Karlsson et al. demonstrated HERV-W expression in FEP patients, which is absent in HCs [62]. Similarly, although based on a rather small sample, a post-mortem study by Frank et al. indicated an increased expression of HERV-K10 in the brains of schizophrenia patients [63]. HERV-K methylation in the genetic material obtained from peripheral blood leukocytes is also significantly lower in both FEP and ARCh patients compared to HC [64]. In addition, the increased expressions of HERV-K and HERV-W are also correlated with increased expressions of DISC1, PRODH, BDNF and D3 genes, which are associated with susceptibility to schizophrenia [50][65][66]. Interestingly, the presence of HERV-W antigens in the peripheral blood was also associated, in at least a certain subpopulation of schizophrenic patients, both with elevated peripheral levels of IL-6 and a higher incidence of early childhood trauma resulting from emotional abuse [67].

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## Keywords

schizophrenia;cytokines;antipsychotics;psychosis;neuroinflammation

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