The role of aberrations in the immune-inflammatory reflex system (IRS) and the compensatory immune-regulatory reflex system (CIRS) in different phenotypes of schizophrenia: the IRS-CIRS theory of schizophrenia

Short title: The IRS-CIRS theory of schizophrenia

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Abstract

In this paper we propose a novel theoretical framework, which was previously developed for major depression and bipolar disorder, namely the compensatory immune-regulatory reflex system (CIRS), as applied to the neuro-immune pathophysiology of schizophrenia and its phenotypes, including first episode psychosis (FEP), acute relapses, chronic and treatment resistant schizophrenia (TRS), comorbid depression, and deficit schizophrenia. These schizophrenia phenotypes and manifestations are accompanied by increased production of positive acute phase proteins, including haptoglobin and α2-macroglobulin, complement factors, and macrophagic M1 (IL-1β, IL-6 and TNF-α), T helper (Th)-1 (interferon-γ and IL-2R), Th-2 (IL-4, IL-5), Th-17 (IL-17) and T regulatory (Treg; IL-10 and transforming growth factor (TGF)-β1) cytokines, cytokine-induced activation of the tryptophan catabolite (TRYCAT) pathway as well as chemokines, including CCL-11 (eotaxin), CCL-2, CCL-3 and CXCL-8. While the immune profiles in the different schizophrenia phenotypes indicate activation of the immune-inflammatory response system (IRS), there are simultaneous signs of CIRS activation, including increased levels of the IL-1 receptor antagonist (sIL-1RA), sIL-2R and tumor necrosis factor-α receptors, Th-2 and Treg phenotypes with increased IL-4 and IL-10 production, and increased levels of TRYCATs and haptoglobin, α2-macroglobulin and other acute phase reactants, which have immune-regulatory and anti-inflammatory effects. Signs of activated IRS and CIRS pathways are also detected in TRS, chronic and deficit schizophrenia indicating that these conditions are accompanied by a new homeostatic setpoint between upregulated IRS and CIRS components. In FEP, increased baseline CIRS activity is a protective factor which may predict favorable clinical outcomes. Moreover, impairments in the CIRS are associated with deficit schizophrenia and greater impairments in semantic and episodic memory. It is concluded that
CIRS plays a key role in the pathophysiology of schizophrenia by negatively regulating the primary IRS and contributing to recovery from the acute phase of illness. Components of the CIRS may offer promising therapeutic targets for schizophrenia.

Key words: schizophrenia, immune system, inflammation, cytokines, immune regulatory, CIRS, psychiatry, immunology, psychosis

**List of abbreviations**

TRYCAT = Tryptophan catabolite

NMDA = N-methyl-D-aspartate

Hp = Haptoglobin

Fb = Fibrinogen

C3C = complement component 3

C4 = complement 4

alpha 1S = Alpha 1-acid-glycoprotein

Hpx = Hemopexin

sIL-2R = soluble interleukin-2 receptor

IL = Interleukin

IRS = Immune-inflammatory response system

TNFα = Tumor necrosis factor-alpha

IFN-γ = Interferon-gamma

Th = T helper

iTreg = induced T regulatory
TGF = Transforming growth factor
CIRS = Compensatory immune-regulatory reflex system
FEP = First episode psychosis
TRS = Treatment resistant schizophrenia
LPS = Lipopolysaccharides
NK cells = Natural killer cells
CRP = C-reactive protein
CSF = cerebrospinal fluid
CC = Clara cell secretory protein
CXCL8 = chemokine (C-X-C motif) ligand 8
CCL = chemokine ligands
MIP = macrophage inflammatory protein
IDO = Indoleamine 2,3-dioxygenase enzyme
PANSS = The Positive and Negative Syndrome Scale
NFκB = Nuclear factor kappa B
NDEL1 = Nuclear distribution protein nudE-like 1
MBP = Myelin basic protein
COMT = catechol-O-methyltransferase
HERV = Human endogenous retrovirus
GM-CSF = Granulocyte-macrophage colony-stimulating factor
DCs = dendritic cells
1. Introduction

Schizophrenia is a major psychiatric disorder associated with meaningful disability [1-3]. The onset of schizophrenia typically occurs around late adolescent to early adulthood [4], with males having an earlier age of onset, whilst females exhibit a second post-menopausal peak [5]. A number of risk factors have emerged, including: being male [6]; an array of genetic susceptibility alleles [7-9]; immune-related processes and genes [10-12]; pre- and/or perinatal complications or exposure to environmental insults [13, 14], malnutrition [15], infections [16, 17], and exposure to neurotoxic infectious pathogens [18].

Although the role of immune dysregulation has been long investigated in schizophrenia [19], it was not until 1995, when Smith and Maes (1995) proposed the monocyte-T lymphocyte theory of schizophrenia that modern research in this area started to flourish [20]. The monocyte-T lymphocyte theory incorporated activated immune-inflammatory pathways, neurodevelopmental pathology associated with prenatal infections, activated microglia, increased nitro-oxidative stress, cytokine-induced activation of the tryptophan catabolite (TRYCAT) pathway, modulation of the N-methyl D-aspartate (NMDA) receptor and glutamate production [20]. In their studies, Maes and coworkers reported that the acute phase of schizophrenia is accompanied by an acute phase (inflammatory) response with significantly higher plasma haptoglobin (Hp), fibrinogen (Fb), complement component 3 (C3C), C4, alpha 1-acid-glycoprotein (alpha 1S), and hemopexin (Hpx) levels as compared with normal controls, with the levels of these factors being even higher in untreated patients [21]. Moreover, they also found significantly higher levels of soluble interleukin-2 receptor (sIL-2R), an indicator of T cell activation, and Interleukin 6 (IL-6) and sIL-1R antagonist (sIL-1RA), indicants of monocytic
activation, in schizophrenia patients [22]. These early data pointed to an involvement of adaptive immunity, activation of the monocytic and T cells and an inflammatory response in schizophrenic patients. Since then many more results have been published confirming these earlier findings indicating immune-inflammatory processes in the peripheral blood [23], the brain [24-26] and genome-wide association studies as well [27, 28].

In the peripheral blood of patients with schizophrenia, there are validated findings on an activation of the immune-inflammatory response system (IRS), including M1 macrophagic activation, with increased production of IL-6 and tumor necrosis factor alpha (TNF)-α, T helper (Th)-1 activation, with increased levels of interferon (IFN) and IL-2, and activation of a Th-17 response with increased levels of IL-17 [29-31]. Schizophrenia patients also show increased levels of immune products which have immunosuppressive effects, for example the sIL-2R and sIL-1RA, to name a few [32]. In addition, schizophrenia patients exhibit signs of increased activity of immune cells with negative immune-regulatory effects, namely induced T regulatory (iTreg) cells (with increased levels of IL-10 and transforming growth factor (TGF)-β) and a Th-2 shift (with increased levels of IL-4) [29, 33, 34]

Therefore, schizophrenia is accompanied by activation of IRS (immune activation) and signs of counter-regulatory immune mechanisms, which are mounted following immune activation and tend to attenuate the detrimental effects of a primary IRS [32]. For example, the release of IL-1β by activated immune cells is accompanied by an increased release of the IL-1RA, which may attenuate IL-1 pro-inflammatory signaling (see below). Thus, increased levels of the sIL-1RA indicate immune activation, but at the same time inhibit the IRS. We named the aggregate of these immune-regulatory responses the “compensatory immune-regulatory reflex
Nevertheless, no review has addressed the activity of the CIRS in relation to IRS activation in schizophrenia.

Schizophrenia is a heterogeneous phenotype and recent research showed that different phenotypes of schizophrenia may exhibit distinct immune profiles and even different IRS and CIRS profiles. For example, a series of studies conducted by Noto and colleagues between 2014-2018 (see below) reported different immune profiles in different schizophrenia subtypes, including first episode psychosis (FEP), treatment resistant schizophrenia (TRS) and chronic schizophrenia. A meta-analysis shows that acute exacerbations of schizophrenia are accompanied by activation of the IRS, with increased levels of M1 macrophagic and Treg cytokines, while Th-1 activation with increased levels of IL-12, interferon-gamma (IFN-γ) and sIL-2R, may constitute a trait marker of schizophrenia [35]. Patients with deficit schizophrenia show specific alterations in the CIRS as compared to patients with non-deficit forms of schizophrenia. However, no research has addressed whether schizophrenia phenotypes, including FEP, relapses of acute psychoses, chronic schizophrenia, treatment resistant schizophrenia and deficit schizophrenia present with different IRS and CIRS profiles.

2. Aims of the review

The aims of this narrative review are a) to summarize the immune findings in different phenotypes and dimensions of schizophrenia with reference to IRS and CIRS components in the peripheral blood and examine which component prevails in these different forms of schizophrenia; and b) to propose a new immune-pathological framework for schizophrenia based on aberrations in the IRS and CIRS.
3. Methods

We performed a narrative review by searching Google Scholar, PubMed and Scopus for articles published in English from 1991 to present, using combinations of the words schizophrenia, FEP, treatment resistant schizophrenia, chronic schizophrenia and deficit schizophrenia with immune, inflammation, adaptive immunity, humoral immunity, acute phase response, interleukins, cytokines, chemokines, M1 macrophagic, T helper (Th)-1, Th-2, Th-3, and T regulatory (Treg).

4. Basics on IRS versus CIRS

Macrophages and lymphocytes exist in distinct functional states such as inflammatory versus anti-inflammatory or negative immune-regulatory effects, including macrophage polarization into M1 (classically activated) and M2 (alternatively activated) macrophages, and T helper (Th) polarization into Th-1, Th-2, and Th-17 phenotypes [32]. Thus, M2 macrophages display immune-regulatory effects (Th-2 and Treg-like activities by producing IL-10 and TGF-β1, inhibiting IL-1 release, elevating IL-1RA production), while M1 macrophages are pro-inflammatory (produce IL-1β, IL-6 and TNF-α, activate Th-1 responses with IFN-γ production) [36, 37]. Naive T (T0) cells can be primed to differentiate into different Th phenotypes with different activities such as: a) Th-1 phenotype (immune activation, pro-inflammatory) through activation by IL-12; b) Th-2 phenotype (anti-inflammatory and producing IL-4 and IL-5) through activation by IL-4; and c) Th-17 phenotype (involved in autoimmunity and pro-inflammatory) through activation by IL-6, IL-1β and TGF-β.

**Figure 1** shows that IL-1β, IL-6 and TNF-α are predominantly produced by activated M1 (and other immune) cells and play a key role in orchestrating the immune-inflammatory response
as well as the acute phase response in the liver. The same immune cells that release IL-1β also release IL-1RA following stimulation by M1 and Th-1 products such as IL-1, IL-6 and IFN-γ. Importantly, once released in the blood, sIL-1RA inhibits IL-1β signaling by binding to the IL-1 cell receptor [36]. Therefore increased plasma levels of sIL-1RA indicate immune activation including monocytic / macrophagic activation with increased IL-1β release, but at the same time indicate increased regulation of the IL-1 signaling pathway [36].

**Figure 1.** Key immune cell phenotypes and its products belonging to the immune-inflammatory response system (IRS) and the compensatory immune-regulatory reflex system (CIRS).

IL-6 has several pro-inflammatory effects including induction of Th-17 differentiation [38]. Nevertheless, IL-6 also exhibits immune-regulatory effects for example by promoting iTreg (CD4+ CD25+ Foxp3+) activation by TGF-β and increasing sIL-1RA and sTNF-R production (both of which have immune-regulatory effects). Here, a differentiation should be made between
classical IL-6 signaling pathway and IL-6 trans-signaling [38]. IL-6 may bind to its membrane receptor, namely the IL-6R, thereby forming a complex with gp130 and activating the classical IL-6 signaling pathway, which is frequently immune-regulatory. Activated immune cells release (through shedding) the IL-6R into the plasma thereby binding to IL-6 and forming an IL-6-sIL-6R complex, which may subsequently bind to membrane gp130 and induce IL-6 trans-signaling, which has predominant pro-inflammatory activities [38].

TNF-α is another pro-inflammatory cytokine, which is produced mainly by macrophages, monocytes and T cells [39]. TNF-α and other immune signals, including increased levels of IL-1, IL-6, IL-2, IL-10 and lipopolysaccharides (LPS) may cause shedding of TNF-α receptors in the plasma leading to increased levels of sTNF-R1 and sTNF-R2 [40]. Therefore, elevated plasma concentrations sTNF-Rs can be regarded as surrogate biomarkers of an ongoing immune-inflammatory response [41]. However, both receptors concomitantly act as decoy receptors thereby attenuating TNF-α signaling and protecting against TNF-α-related toxicity [32].

Figure 1 further shows that cytokines such as IL-4 (Th-2-like), TGF-β and IL-10 (Treg) may have immune-regulatory effects and are major players of the CIRS and that iTreg cells are major components of the CIRS. iTreg cells exert immune-regulatory in part by enhancing the production of IL-10 and TGF-β thereby inducing tolerance by regulating Th-1, Th-17 and Th-2 cells [32]. IL-4 activates M2 macrophages, which also play a role in the CIRS by activating IL-10, TGF-β and the sIL-1RA and suppressing IL-1β, IL-6 and TNF-α production [32]. TGF-β and IL-10 may also induce T0 cells which in turn differentiate into iTreg cells, whilst IL-10 enhances the release of IL-1RA from macrophages and also suppresses Th-1-like, M1, dendritic, effector and cytotoxic cells, as well as B and natural killer (NK) cells [32]. TGF-β attenuates pro-inflammatory cytokine-production by M1 macrophages and proliferation of other immune cells
(e.g. B cells). As such, increased levels of IL-10, IL-4 and TGF-β occur during an immune-inflammatory response, but those actors regulate and counteract the IRS response and therefore may be key players together with Th-2 and iTreg cells in the CIRS.

Figure 1 also shows that IL-6, IL-1β and TNF-α promote the production of acute phase proteins by the liver, including C-reactive protein (CRP), Hp, alpha 1S, Hpx, alpha-1 antitrypsin and alpha-2 macroglobulin. As previously explained, Hp, alpha 1S, Hpx, alpha-1 antitrypsin (but not CRP) have significant anti-inflammatory effects through different mechanisms. For example, those acute phase proteins stimulate the production of IL-10 and heme-oxygenase-1, they have anti-protease activities, attenuate the production of IL-8 and Th-17-associated inflammation and bind hemoglobin [32]. In addition, alpha-2 macroglobulin shows potent anti-inflammatory, anti-oxidant and anti-fibrosis effects for example by capturing nearly all proteinase activity, promoting DNA repair mechanisms and binding to IL-6, IL-1β and TNF-α [42, 43]. This latter activity may induce latency of cytokines and thus exert immune-regulatory effects by protecting against the toxic effects of these cytokines and targeting these cytokines to cells bearing the alpha-2 macroglobulin-receptor, a mechanism that ultimately results in increased production of alpha-2 macroglobulin [43]. In other words, IL-6 and other pro-inflammatory cytokines induce the acute phase response in the liver and therefore increased levels of these proteins indicate the presence of an inflammatory response, but at the same time some of these proteins exert potent anti-inflammatory and anti-oxidative effects and thus are part of the CIRS.

Table 1 displays an overview of the major chemokines and cytokines and their receptors, which are reported to be altered across schizophrenia phenotypes. This table also shows the type of cells producing these molecules as well as the predominant functions of these immune products.
Table 1. Biomarkers of the immune-inflammatory response system (IRS) and compensatory immune-regulatory reflex system (CIRS) in schizophrenia.

<table>
<thead>
<tr>
<th>Cytokine / chemokine / soluble receptors</th>
<th>Predominant Type</th>
<th>IRS / CIRS function</th>
<th>Main IRS and CIRS functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin (IL)-1β</td>
<td>M1</td>
<td>IRS</td>
<td>Pro-inflammatory cytokine</td>
</tr>
<tr>
<td>Soluble IL-1 receptor antagonist (sIL-RA)</td>
<td>M2</td>
<td>CIRS</td>
<td>Attenuates IL-1 signaling; promotes tissue repair and resolution of inflammation</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF)-α</td>
<td>M1</td>
<td>IRS</td>
<td>Pro-inflammatory cytokine</td>
</tr>
<tr>
<td>sTNF-R60 (R1) and sTNF-R80 (R2)</td>
<td>-</td>
<td>CIRS</td>
<td>Act as decoy receptors and reduce TNFα bioactivity and signaling</td>
</tr>
<tr>
<td>IL-6</td>
<td>M1</td>
<td>IRS</td>
<td>Pro-inflammatory cytokine</td>
</tr>
<tr>
<td>sIL-6R</td>
<td>-</td>
<td>IRS</td>
<td>Binds IL-6 and causes IL-6 trans-signaling</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony stimulating factor (GM-CSF)</td>
<td>M1</td>
<td>IRS</td>
<td>Stimulates development of immune cells</td>
</tr>
<tr>
<td>IL-2</td>
<td>Th-1</td>
<td>IRS</td>
<td>A Th-1-like cytokine</td>
</tr>
<tr>
<td>sIL-2R</td>
<td>Th-1</td>
<td>CIRS</td>
<td>Lowsers IL-2 levels; suppresses IL-2-induced proliferation; promotes differentiation into Treg cells</td>
</tr>
<tr>
<td>Interferon-γ (IFN-γ)</td>
<td>Th-1</td>
<td>IRS</td>
<td>Th-1-like cytokine</td>
</tr>
<tr>
<td>IL-12</td>
<td>Th-1</td>
<td>IRS</td>
<td>Differentiates naïve T cells into Th-1 cells</td>
</tr>
<tr>
<td>IL-17</td>
<td>Th-17</td>
<td>IRS</td>
<td>Pro-inflammatory cytokine</td>
</tr>
<tr>
<td>IL-4</td>
<td>Th-2</td>
<td>CIRS</td>
<td>Suppresses M1 and Th-1 cytokines, promotes M2 macrophages; activates sIL-1RA and IL-10 production</td>
</tr>
<tr>
<td>IL-5</td>
<td>Th-2</td>
<td>-</td>
<td>Growth factor for B cells and eosinophils</td>
</tr>
<tr>
<td>IL-13</td>
<td>Th-2</td>
<td>CIRS</td>
<td>Regulator of IgE synthesis; has CIRS functions comparable to those of IL-4 but less potent</td>
</tr>
<tr>
<td>Transforming growth factor (TGF-β1)</td>
<td>Treg</td>
<td>CIRS</td>
<td>Inhibits Th-1 and Th-17 cells; stimulates sIL-1RA; Lowers production of IL-13, IL-12, IFN( and TNFα</td>
</tr>
<tr>
<td>IL-10</td>
<td>Treg</td>
<td>CIRS</td>
<td>Major immune-regulatory cytokine</td>
</tr>
<tr>
<td>IL-3</td>
<td>Activated T cells</td>
<td>IRS</td>
<td>Activates macrophages and granulocytes and thus immune</td>
</tr>
<tr>
<td>Cytokine</td>
<td>Source Cells</td>
<td>IRS</td>
<td>Function</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>IL-7</td>
<td>Bone marrow and thymus cells</td>
<td>IRS</td>
<td>Activates the differentiation of lymphoid progenitor cells and T and B cell development; induces Th-1 subsets; decreases TGF-β1 production</td>
</tr>
<tr>
<td>IL-15</td>
<td>Macrophages, dendritic cells, epithelium cells</td>
<td>IRS</td>
<td>Pro-inflammatory, pleiotropic cytokine; costimulates IFN-γ; expansion and survival of immune cells</td>
</tr>
<tr>
<td>IL-18</td>
<td>Antigen presenting cells</td>
<td>IRS</td>
<td>Pro-inflammatory cytokine; differentiates naïve T cells into Th-1; activates macrophages; increases IFN-γ; host defense</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source Cells</th>
<th>IRS</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uteroglobin or CC16</td>
<td>-</td>
<td>CIRS</td>
<td>Anti-cytokine and immunomodulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source Cells</th>
<th>IRS</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCL-2 or monocyte chemoattractant protein (MCP1)</td>
<td>macrophages, monocytes and dendritic cells</td>
<td>IRS</td>
<td>Recruits T cells and monocytes</td>
</tr>
<tr>
<td>CCL-3 or macrophage inflammatory protein (MIP-1α)</td>
<td>M1</td>
<td>IRS</td>
<td>Recruits mononuclear cells, activates granulocytes and induces the production of IL-1, IL-6 and TNF-α</td>
</tr>
<tr>
<td>CCL-11 or eotaxin</td>
<td>Th-2, eosinophils</td>
<td>IRS</td>
<td>Recruits eosinophils</td>
</tr>
<tr>
<td>CXCL-8 or IL-8</td>
<td>M1</td>
<td>IRS</td>
<td>Induces neutrophil chemotaxis and promotes phagocytosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Source Cells</th>
<th>IRS</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Reactive Protein</td>
<td>M1-acute phase</td>
<td>IRS</td>
<td>Acute phase reactant</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>M1-acute phase (liver)</td>
<td>CIRS</td>
<td>Captures HMGB1 and complexes hemoglobin; stimulates a Th-2 phenotype, IL-10 and heme-oxygenase-1 (HO-1); inhibits cyclooxygenase 2 and effector cells; potent antioxidant</td>
</tr>
<tr>
<td>α1 Anti-trypsin</td>
<td>M1-acute phase (liver)</td>
<td>CIRS</td>
<td>Has anti-protease activity (e.g. elastase) Inhibits the production of IL-8 Regulates neutrophil chemotaxis, T and B cell proliferation, cytokine production by monocytes and macrophages</td>
</tr>
<tr>
<td>Alpha-2 macroglobulin</td>
<td>M1-Acute phase (liver)</td>
<td>CIRS</td>
<td>Induces latency of IL-6, TNF-α and IL-1β and has immune-regulatory effects by protecting against the toxic effects of these cytokines; panprotease inhibitor</td>
</tr>
<tr>
<td>Hemopexin</td>
<td>Acute phase (liver)</td>
<td>CIRS</td>
<td>Inhibits Th-17 associated inflammation; binds haem; inhibits synergy with HMGB1</td>
</tr>
<tr>
<td>Alpha 1-acid-glycoprotein</td>
<td>M1-Acute phase (liver)</td>
<td>CIRS</td>
<td>Attenuates mitogen-induced T cell proliferation; prevents Gram-negative bacteria infections; promotes wound healing</td>
</tr>
</tbody>
</table>
5. IRS and CIRS in schizophrenia

The role of immune-inflammation in schizophrenia has attracted considerable research with data generally supporting a role for increased peripheral and central inflammatory responses in schizophrenia [35, 44-47]. The first study which attributed immune findings in schizophrenia to an ongoing inflammatory response, was published in 1997 [21]. These authors reported that patients with schizophrenia have significantly increased plasma levels of acute phase proteins, such as Hp, Fb, alpha 1-antitrypsin, alpha 1S and Hpx, as well as complement factors C3C and C4. This study also reported that aberrations in acute phase reactants were more pronounced in patients with schizophrenia than in patients with major depression. Furthermore, there was also a significant association between schizophrenia and Hp-2 gene frequency and Hp 2-2 phenotype in schizophrenia as compared with controls [48]. This is of relevance as Hp genotypes/phenotypes have different immune-inflammatory and pro-oxidant effects, which may differently influence the pathophysiology of medical conditions [49, 50]. Hence, the Hp 2 gene and 2-2 genotype is associated with increased inflammatory potential and related carotid artery intima-media thickness [51] and poorer disease outcomes [52]. This together with prior results showing increased cerebrospinal fluid (CSF) levels of IL-1, and plasma/serum levels of IL-6, sIL-1RA, IL-2 and sIL-2R indicate an immune-inflammatory (IL-6 and sIL-1RA) and Th-1-like (IL-2 and sIL-2R) response in schizophrenia [22, 53-57]. Interestingly, Maes et al. (1996) also reported lowered levels of Clara cell secretory protein 16 (CC16) or uteroglobin, an endogenous anti-inflammatory protein, which inhibits the production of pro-inflammatory cytokines and thus acts as an anti-cytokine mediator [58]. As such, already in the 1990ties it was established that schizophrenia is characterized by an immune-inflammatory response and simultaneous signs of a
CIRS as indicated by higher sIL-2R and sIL-1RA levels [22, 58] and a relative deficit in CC16, an endogenous CIRS component [58].

These early findings on IRS activation in schizophrenia are now well replicated and synthesized in meta-analytic studies. A meta-analysis suggested that changes in IL-1β, IL-6, and TGF-β to be state-related markers of schizophrenia, whilst alterations in peripheral levels of IL-12, INF-γ, TNF-α, and sIL-2R may be trait markers for schizophrenia [35]. Moreover, findings on an acute phase responses in schizophrenia were replicated for example by [59] who found elevated serum levels of CRP in schizophrenia and a positive correlation between CRP and symptom severity. Increased TNF-α levels are now established as one of the most frequently reported findings in schizophrenia [35, 45], while also its soluble receptors, sTNF-R1 and sTNF-R2, are also frequently increased in this disorder [33, 60-63]. Again, these findings show that schizophrenia is accompanied by IRS activation (increased serum levels of TNF-α and its receptors) and increased CIRS activity due to the immune-regulatory effects of sTNF-R1 and sTNF-R2.

A relatively more recent new direction in schizophrenia research is the examination of alterations in the production and signaling of chemokines, which are immune mediators that display chemotactic activity attracting various types of immune effector and inflammatory cells. Thus, the first reports that emerged in the literature pointed to a significant increase in peripheral levels of C-X-C motif ligand 8 (CXCL8) or IL-8 in schizophrenia relative to healthy controls [64-66]. CXCL8 is predominantly produced by macrophages and endothelial cells and may induce neutrophil chemotaxis and promote phagocytosis [64].

Later, schizophrenia was found to be associated with a specific chemokine profile, comprising increased plasma levels of CXCL8, chemokine ligand (CCL)-11 or eotaxin, CCL-3
or macrophage inflammatory protein (MIP)1α, and CCL-2 or monocyte chemoattractant protein (MCP)-1 [33, 67-70]. CCL-11 is an eosinophil chemotactic factor released by different cell types including eosinophils, fibroblasts, endothelial and epithelial cells, macrophages, lymphocytes, and B cells [71]. CCL-11 is induced by cytokines belonging to the Th-2 lineage, including interleukin IL-4, IL-10 and IL-13 [71]. CCL-3 is another chemokine, predominantly produced by macrophages, that recruits mononuclear cells, activates granulocytes and induces the production of IL-1, IL-6 and TNF-α thereby playing a key role in inflammation [72]. CCL-2 is secreted by macrophages, monocytes and dendritic cells and recruits T cells and monocytes at inflammatory sites [73]. Thus, the increased levels of these four chemokines in schizophrenia indicate the presence of IRS activation with macrophagic / monocyte (increased CCL-2, CCL-3 and CXCL8) and Th-2 (eotaxin) activation.

There is now also evidence that schizophrenia is accompanied by increased activity of the tryptophan catabolite (TRYCAT) pathway. This pathway is induced by IRS activation, through increased production of Th-1 (IFN-γ) and M1 macrophagic (IL-1β) cytokines, which stimulate indoleamine-2,3-dioxygenase (IDO) thereby lowering tryptophan and increasing the production of TRYCATs [74, 75]. Schizophrenia is accompanied by an activated TRYCAT pathway as indicated by lowered plasma tryptophan levels and increased levels of TRYCATs, such as kynurenine and kynurenic acid, in plasma, CSF and brain tissues [76-78]. More recently, Kanchanatawan et al. (2017) reported that schizophrenia is accompanied by increased IgA responses directed to different TRYCATs including xanthurenic acid, picolinic acid, 3-OH-kynurenine and quinolinic acid [79]. In addition, Sirivichayakul et al. [72] found highly significant associations between indicants of immune activation (increased IL-10, MIP1 and sIL-1RA plasma levels) and the activity of the TRYCAT pathway in schizophrenia. These findings
suggest that IRS activation in schizophrenia induces the TRYCAT pathway leading to an increased production of different TRYCATs. However, IDO activation is a key immune-regulatory process that has an established CIRS role in pregnancy, transplantation, cancer, infections and autoimmune conditions [80]. Indeed, decreased plasma tryptophan contributes to a tolerogenic environment, metabolic shutdown and starvation thereby attenuating T cell activation and proliferation [81]. Moreover, TRYCATs, including kynurenine and xanthurenic acid, may have immune-regulatory effects by suppressing T cell proliferation and the production of Th-1 cytokines including IFN-γ [82]. Thus, IRS activation is accompanied by over-activation of the TRYCAT pathway, which in turn exerts a negative feedback control over T cell activation thereby attenuating the primary immune response through the effects of tryptophan depletion and TRYCAT formation.

6. IRS and CIRS in patients at high risk for psychosis and first episode psychosis (FEP)

Several studies have reported biological abnormalities even before the onset of psychotic symptoms. Individuals with prodromic symptoms, who later convert to psychosis may present immune-inflammatory imbalances. Khoury and Nasrallah (2018) reviewed 15 studies and found a possible role of plasma levels of IL-1β, IL-7, CXCL-8, matrix metalloproteinase (MMP)-8 and albumin as predictors of psychotic transition [83]. Other studies found higher IL-6 and lower IL-17 levels compared to healthy controls [84] and higher IL-6 levels when comparing who convert to psychosis with those who did not convert [85]. Kappelmann et al. (2018) in a large population study with 638,213 men in Sweden found associations between erythrocyte sedimentation rate (ESR), a marker of low-grade inflammation, IQ, and subsequent psychosis, suggesting that
inflammatory abnormalities may influence schizophrenia risk by affecting neurodevelopment [86].

Patients in a first episode of psychosis (FEP) differ from their chronic psychosis counterparts in various aspects, including symptom patterns [87], cognitive impairments [88], neuroanatomical and functional changes [89, 90], and response to antipsychotic treatment as well [90, 91]. FEP also shows a specific immune-inflammatory profile. Thus, a recent study reports that FEP is associated with an increased expression of the Hp gene and that there are significant associations between the Positive and Negative Syndrome Scale (PANSS), depression, and excitement symptoms and peripheral levels of Hp, alpha-1 antitrypsin and alpha-2 macroglobulin [92]. These data show that not only schizophrenia [21] but also FEP is accompanied by an inflammatory response. These findings are further supported by results showing that the production of nuclear factor kappa B (NFκB), which is a major inflammatory regulator, is elevated in FEP [93].

There are recent reports on increased levels of IL-6, TNF-α and IL-10 in drug-naïve FEP patients, indicating monocyctic (IL-6 and TNF-α) and Treg (IL-10) activation [94]. Kubistova et al. (2012) found significantly increased plasma levels of IL-6 and TNF-alpha, suggesting a proinflammatory state in the FEP [95]. de Witte et al. (2014) measured levels of 9 cytokines in antipsychotic-naïve first-episode schizophrenia patients and age and gender-matched controls using a multiplex immunoassay and found significantly increased levels of IL-1RA, IL-10 and IL-15 in FEP patients, again indicating signs of both IRS and CIRS activation in FEP (CIRS activation being indicated by increased sIL-1RA and IL-10 levels) [96]. Zhang et al. (2013) found increased levels of IL-18, a pro-inflammatory cytokine, in FEP and a significant association between IL-18 and neurocognitive deficits in the visuospatial and constructional
domains [97]. Fu et al. (2016) reported significantly lowered IL-3 levels in FEP patients when compared with chronic schizophrenia patients and healthy controls, suggesting signs of immunosuppression [98]. Borovcanin et al. (2012) detected decreased levels of IL-17 and increased levels of IL-4 and TGF-β in FEP, indicating a suppressed Th-17 response, but elevated Th-2 and Treg responses [99]. Moreover, other studies found that, when compared to healthy controls, FEP patients show higher levels of IL-4, IL-10 and TNF-α [33, 100]. Interestingly, some studies reported significantly decreased levels of IL-10 levels in FEP [101-103]. IL-10 is a Treg cytokine which inhibits macrophage/monocyte and T-cell lymphocyte replication and the production of some inflammatory cytokines (including IL-1, TNF-α, IL-6, IL-8 and IL-12) [104], thus indicating that there is a lowered immune-regulatory potential in some patients with FEP. A recent meta-analysis shows that serum IL-6 and TNF-α are significantly higher in FEP patients than in normal controls [105].

All in all, recent studies and meta-analyses found significantly higher levels of IL-1β, sIL-1RA, IL-6, TNF-α, sTNF-R1, sTNF-R2, IL-12, IFN-γ, IL-2, sIL-2R, IL-18, IL-4, IL-5, IL-13, IL-10, and TGF-β in drug-naïve FEP patients compared to healthy controls [33, 35, 45, 99, 106, 107]. These data point towards an activation of macrophagic M1 (IL-1β, sIL-1RA, IL-6, TNF-α), Th1 (IL-12, IFN-γ, IL-2 and sIL-2R), Th-2 (IL-4, IL-5) and Treg (IL-10, TGF-β) cells during a first psychotic episode, including in drug-naive patients.

IL-6 and IL-10 may significantly contribute to the immunopathogenesis of FEP. Thus, Noto et al. (2016), in a gene expression study, found an up-regulation of protein nudE-like 1 (NDEL1) and myelin basic protein (MBP) genes in FEP, while DROSHA (which encodes a class 2 ribonulease III enzyme), catechol-O-methyltransferase (COMT), and disrupted in schizophrenia 1 (DISC1) were downregulated as compared to controls [108]. In addition, IL-6
levels in FEP were associated with lowered $AKT1$ (which encodes RAC-alpha serine/threonine-protein kinase) and $DROSHA$ expression, whereas increased IL-10 levels were associated with increased $NDELI$, $DISC1$ and $MBP$ expression [108]. Importantly, these genes play a key role in neuronal processes and therefore changes in the equilibrium between IL-6 and IL-10 in FEP may regulate miRNA machinery and neuronal functions, including intracellular signaling, neuroplasticity, neurogenesis and neuroprogression. For example, elevated levels of IL-6 in FEP may dysregulate the miRNA machinery (lowered $DROSHA$ expression) and downregulate AKT-mediated cellular functions, while increased levels of IL-10 may have neuroprotective effects by increasing $NDELI$, $MBP$ and $DISC1$ expression [108].

It should be noted that the CSF levels of kynurenic acid are increased in patients with FEP [109]. There are also reports that patients with FEP show elevated levels of human endogenous retrovirus (HERV) transcripts, which are endogenous viral elements in the human genome [110-114], as well as increased levels of antibodies against those retroviral proteins [115]. HERVs glycoproteins may contribute to neuro-inflammation and neurodegeneration, which could increase vulnerability to develop schizophrenia [116-119]. Moreover, copies of HERV elements are activated by some infectious pathogens including $T. gondii$ and influenza virus [120, 121], whilst there is evidence of increased levels of antibodies against $T. gondii$ in schizophrenia [122]. The derived hypothesis is that envelope proteins released due to pathogenic activation of HERVs may activate the innate immune system thereby inducing production of pro-inflammatory cytokines, for example by activating the CD14 / TLR4 pathway [123].
7. IRS and CIRS in acute episodes and relapses

As in FEP, recent meta-analyses indicate increased levels of IRS cytokines, including IL-1β and IL-6, during an acute episode of psychosis, which is frequently normalized with treatment [35, 45]. Indicants of Th-1 activation (including increased IFN-γ and sIL-2R levels) may be trait markers of schizophrenia [23, 35]. Kubistova et al. (2012) found increased levels of IL-6 and TNF-α in the acute phase of schizophrenia and showed that treatment with antipsychotics decreased IL-6 but not TNF-α [95]. The above-mentioned meta-analysis showed increased levels of CIRS products including TGF-β during the acute episode of psychosis, which normalized with treatment [35] and increased sIL-2R levels as a possible trait marker of schizophrenia [35].

As in FEP, Borovcanin et al. (2012) reported decreased levels of IL-17 (lowered autoimmune and anti-inflammatory potential) coupled with increased levels of two CIRS cytokines, namely IL-4 and TGF-β [99]. Another study examined T-cell subsets (CD3+, CD4+, CD8+) and NK-cells as well as the CD4+/CD8+ ratio in schizophrenia patients in an acute psychotic episode and reported signs of both IRS and immunosuppression. Thus, increased CD3+ and CD4+ cells and an elevated CD4+/CD8+ ratio were observed in schizophrenia, whereas NK-cells were decreased [124]. After treatment, all T-cell alterations returned to normal while in chronic cases the number of NK-cells remained low and the CD4+/CD8+ ratio remained high, supporting that signs of immune activation and suppression are present in the acute and chronic phases of illness.
8. IRS and CIRS in chronic schizophrenia

In patients with chronic schizophrenia, there are many signs of IRS activation including increased levels of IL-6, sTNF-R1 and sTNF-R2, CCL-11 (eotaxin) and CCL-3 (MIP-1α), while the levels of immune-regulatory CIRS cytokines, namely IL-4 and IL-10, are decreased [33, 102, 125]. Nevertheless, some of those immune markers, namely increased sTNF-R1 and sTNF-R2, also indicate increased CIRS functions in that condition [33, 125]. Fu et al. (2016) found significant increased levels of IL-3 and additionally a significant association between IL-3 levels and the PANSS score in chronic schizophrenia patients, which contrasts with their findings in FEP patients [98]. These authors suggested that lowered IL-3 in FEP patients may indicate that signs of immunosuppression are associated with developing schizophrenia and that IL-3 may increase as the disease progresses perhaps related to medication treatment or other factors that occur during chronic illness. Xiu et al. (2012) reported that serum levels of IL-18, another pro-inflammatory cytokine, are significantly higher in patients with chronic schizophrenia than in FEP patients and healthy controls and they also reported a positive correlation between IL-18 and the PANSS general psychopathology subscore [126].

Interestingly, Boll et al. (2017) performed regression analysis with different biomarkers and found that the main predictors of chronic schizophrenia were increased levels of sTNF-R1 (5-fold higher) and CCL-11 (2-fold higher) [125]. This indicates that signs of immune activation (namely the TNF-pathway with increased sTNF-R1 as biomarker) and Th-2 activation (increased CCL-11) are the best predictors for chronic schizophrenia, while in fact increased sTNF-R1 levels are part of the CIRS. Therefore, in chronic schizophrenia, the CIRS may not be activated to an extent necessary to counter-regulate the overly activated IRS.
9. IRS and CIRS in (ultra) treatment resistant SCZ

The first paper reporting an association between the IRS and treatment resistant schizophrenia (TRS) was published in 1998 [127]. These authors found that serum IL-6 is significantly higher in TRS as compared to controls and patients who responded to treatment. Interestingly, increased levels of IL-6 and sIL-6R were inversely associated with CC16, an endogenous anti-cytokine which may constitute a trait marker for schizophrenia [127].

Other signs of IRS activation in TRS are: increased levels of sIL-1RA, IL-2, IL-10, sTNF-R1, sTNF-R2, CXCL-8, CCL-3 and CCL-2 [33, 64, 66, 125, 128]. Interestingly, a significant association was found between A-2518G polymorphism (rs1024611) of the MCP-1 gene (CCL2) and TRS with resistant patients more frequently carrying the G-allele [129]. Since G-allele carriers produce significantly more MCP-1 than non-carriers [130], this polymorphism may underpin the increased levels of MCP-1 in TRS. All in all, these results indicate that TRS is characterized by: a) signs of IRS activation as indicated by increases of M1 and TH-1 cytokines and chemokines, which are released during an IRS response; and b) activation of CIRS functions as indicated by increased levels of sIL-1RA, IL-10, sTNF-R1 and sTNF-R2.

10. IRS and CIRS in schizophrenia with depressive symptoms.

Many patients (up to 61%) with schizophrenia suffer from burdensome depressive symptoms or comorbid clinical depression, which is often poorly recognized [16]. Furthermore, depression is a common and harmful dimension of schizophrenia, particularly in FEP [131, 132]. Both schizophrenia and major depression or bipolar depression share alterations in immune pathways including increased pro-inflammatory cytokines, with a M1 macrophagic and Th1 response and activation of the tryptophan catabolite (TRYCAT) pathway through IDO induction
[16]. The latter authors proposed a model whereby schizophrenia is immunologically primed for an increased expression of depressive symptoms via the adverse effects of (among other elements) Th-1 and M1 macrophagic activation and their consequences including activation of the TRYCAT pathway with an increased production of neurotoxic TRYCATs, including kynurenine [16]. Nevertheless, there is a paucity of data on immune functions in patients with schizophrenia and a comorbid depressive phenotype or depressive symptoms.

Noto et al. (2015) found higher IL-4 and TNF-α levels in FEP patients who also showed depression when compared to those without depression [33], suggesting that depression in FEP is accompanied by M1 macrophagic and Th-2 activation. These results suggest that depression in FEP is a key component that may contribute to aberrations in specific cytokines in FEP. Moreover, FEP patients with depression may have a different gene expression pattern compared to those without depression, namely a decreased expression of the NDELI gene and increased expression of COMT gene [108], further underscoring that FEP plus depression could represent a biologically different phenotype when compared to FEP without depression. Yee et al. (2017) observed that in FEP patients, there were significant associations between the severity of depressive symptoms and gene expression of acute phase proteins, including Hp, alpha-1 antitrypsin and alpha-2 macroglobulin [92]. Overall, these results show that FEP with co-occurring depression may be accompanied by a mixed profile with inflammatory signs along with Th2 and macrophagic M1 activation. As such, FEP with depression may be accompanied by signs of IRS activation (acute phase response) and possibly M1 activation and signs of CIRS activation, namely increased haptoglobin and alpha-1 antitrypsin levels (which have immunosuppressive effects) and Th-2 activation.
Recently, Kanchanatawan et al. reported that an increased production of TRYCATs (as measured using IgA responses to TRYCATs) was significantly associated with the severity of depression and anxiety symptoms in schizophrenia and that mainly picolinic acid, but also xanthurenic acid, quinolinic acid and 3-OH-kynurenine, were important in predictors of affective symptoms in schizophrenia [133].

Moreover, the same authors reported that specific changes in IgM-mediated regulatory activities with lowered IgM responses to 3-OH-kynurenine are associated with these affective dimensions. These data indicate that affective symptoms in schizophrenia may be driven by IRS activation leading to TRYCAT pathway activation and by inference increased immune regulation via increased levels of TRYCATs.

11. IRS and CIRS in deficit SCZ

A subset of patients with schizophrenia present negative symptoms (including apathy, alogia, social inhibition, flat affect, monotonous speech, lack of interest and anhedonia) and cognitive deficits (including deficits in semantic and episodic memory and executive functions) over the course of their illness [134]. This phenotype, referred to as deficit schizophrenia, differs from non-deficit schizophrenia in several aspects including poorer social functioning, worse long-term prognosis and a specific neurocognitive profile [135]. Recently, it was shown, using machine learning techniques, that this phenotype of schizophrenia is a distinct nosological entity shaped and modeled by the above-mentioned cognitive deficits and neuro-immune aberrations, including increased CCL-11, CCL-3, IL-10 and IgA responses to TRYCATs as compared to non-deficit schizophrenia [71, 79]. Therefore, deficit schizophrenia is accompanied by an activated TRYCAT pathway and patients with deficit schizophrenia patients exhibit increased
IgA responses directed to xanthurenic acid, picolinic acid, and quinolinic acid and relatively lowered IgA responses to kynurenic acid and anthranilic acid when compared to patients with nondeficit schizophrenia [79]. As such, deficit schizophrenia is characterized by signs of immune activation (increased cytokines, chemokines and TRYCATs) and increased CIRS activity as indicated by increased IL-10 and sIL-1RA levels and immune-regulatory TRYCATs as well. Moreover, deficit schizophrenia is accompanied by significant decreases in IgM autoimmune responses directed to all TRYCATs [75]. Generally, IgM responses are self-regulatory and therefore lowered IgM responses to TRYCATs may indicate lowered regulation of the TRYCAT pathway and consequently an increased vulnerability to develop TRYCAT pathway activation upon immune challenge [75]. This indicates that deficit schizophrenia is characterized by a deficit in the CIRS leading to an increased vulnerability to peripheral immune challenges.

Since the negative symptom cluster is a key in the conceptualization of deficit schizophrenia, it is also important to assess the associations between negative symptoms and cognitive deficits and aberrations in neuro-immune pathways. Thus, highly significant associations between cognitive deficits, negative symptoms and especially eotaxin (but also IL-10, sIL-1RA and MIP1) levels and neurotoxic TRYCATs, including xanthurenic acid, picolinic acid and 3-OH-kynurenine, were found in schizophrenia [71, 72, 136]. The negative symptoms of schizophrenia were also significantly correlated with IL-2, sIL-2R, CCL-11 [33, 137, 138], IL-6 [139], and the sIL1-RA [62]. Xiu et al. (2014) found an inverse relationship between IL-10 levels and negative symptoms, as well as with the PANSS cognitive factor subscores [103]. On the other hand, serum IL-4 and IL-10 concentrations are correlated with negative symptoms in drug-naive FEP patients [140]. A recent study [141] reported that serum IL-6 and CXCL-8 are strongly associated with negative and positive symptoms. Apart from associations between
eotaxin and TRYCATs with cognitive deficits, also levels of some chemokines (CXCL8 or CCL2) were associated with cognitive deficits in schizophrenia [142]. All in all, negative symptoms are strongly associated with signs of M1 macrophagic (IL-6, IL-1RA, CXCL8), Th-1 (IL-2 and sIL-2R, TRYCAT pathway activation), and Th-2 (IL-4, CCL-11) activity, whilst also increased CIRS products (sIL-2R, sIL-1RA, TRYCATs) are associated with negative symptoms.

12. Are macrophages and T helper cells polarized in schizophrenia?

One major question in schizophrenia research is whether the different phenotypes are accompanied by macrophage (M1 versus M2) or Th (Th-1 versus Th-2 versus Th-17) polarization. It is important to consider the effects of M1/M2 polarization as M1 is a key factor in host defense against (intracellular) bacterial and viral infections, whereas M2 plays a key role in tissue repair, matrix remodeling and homeostasis [37, 143]. Classical M1 activation is mainly driven by the Th-1 production of IFN-γ, LPS and GM-CSF, while the key stimuli to generate the M2 phenotype are derived from Th-2 activity via IL-4 and IL-13, and immune complexes, IL-10 and glucocorticoids [37, 143]. Nevertheless, it should be underscored that the M1 and M2 phenotype do not exclude each other and together may develop a mixed phenotype with a continuum between the two polarized extremes [37]. Likewise, Th polarization towards either Th1, Th-17 or Th2 subsets plays a critical role is host defense (Th-1 being associated with M1) and repair (Th-2 being related to M2), while prolonged Th-1 and Th-2 activation induces pathophysiological responses including chronic inflammatory and degenerative disorders (Th-1-related), autoimmune conditions (Th-17 related) and asthma and allergic disease (Th-2 related).

Previous reports concluded that schizophrenia patients may have an impaired production of Th-1 cytokines and an overactivation of the Th-2 system, leading to a dysfunction in Th1/Th2
balance and thus Th-2 polarization and consequently TRYCAT pathway activation [144, 145]. Nevertheless, this theory is not compatible with the findings of this review that M1 macrophages and Th-1 subsets as well as the TRYCAT pathway (Th-1-related) are activated in different schizophrenia subtypes. However, since no studies measured transcription factors, cell activation markers or antigen presenting molecules that may better define the macrophage and Th subsets we are confined to interpret cytokine biosignatures. In this respect, already in the 1990ties, it was described that schizophrenia is accompanied by activation of M1 (IL-6, sIL-1RA), Th-1 (sIL-2R) and Treg (IL-10) cytokines/receptors [22, 56, 146, 147]. As reviewed in previous sections, FEP is also accompanied by increased IL-1β, IL-6, TNF-α, sIL-2R and IL-10 levels indicating M1 and Th-2/Treg activation [29, 106].

Table 2 provides a summary of immune subsets in schizophrenia phenotypes as reviewed in this paper. As can be seen in Table 2, activation of M1, Th-1, Th-2 and Treg subsets is detected in the schizophrenia and its phenotypes and without a specific statistical approach it is challenging to conclude whether there is any polarization and which polarization type would prevail. Recently, a new statistical method was published to compute the ratio between various cytokines produced by Th-1 versus Th-2 cells and between M1 + Th-1 versus Th-2 + Treg by computing z unit weighted composite scores [32, 148].

Table 2. Summary on the IRS (immune-inflammatory response system) and CIRS (compensatory immune-regulatory reflex system) functions and findings in schizophrenia phenotypes.

<table>
<thead>
<tr>
<th>Schizophrenia phenotype</th>
<th>Key findings</th>
<th>IRS functions</th>
<th>CIRS functions</th>
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<td>8 M1, Pro-inflammatory effects</td>
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<td></td>
<td>8 sTNFR1 and sTNFR2</td>
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<td>9 TNF signaling</td>
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<td></td>
<td>8 IL-2, sIL-2R, IFN-γ, IL-12</td>
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<td>9 IL-2 signaling</td>
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<td></td>
<td>8 CCL-11, CCL-2, CCL-3 and CXCL-8</td>
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<td><strong>First episode psychosis</strong></td>
<td>8 TGF-β1 and IL-10</td>
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<td>8 Treg regulation</td>
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<td></td>
<td>8 TRYCATs</td>
<td>-</td>
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<td>8 CXCL-8</td>
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Comorbid depression

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<td>8 IL-4</td>
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<td>8 Th-2 regulation</td>
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Deficit schizophrenia

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Unfortunately, none of the papers described above has computed such ratios and hence no firm conclusions can be drawn. Recently, Noto et al. [141] published a paper that used z unit weighted composite scores computed on a wider array of cytokines that are predominantly produced by distinct subsets. This study reported that the most significant cytokines separating FEP from controls were granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-6 and IL-12, representing M1 and Th-1 activation, and IL-4, IL-13, IL-5 and IL-10, representing Th-2 and Treg activation. Figure 1 presents part of the results of that study focusing on M1, Th-1, Th-17, Th-2 and Treg and the ratios Th-1 / Th-2, and M1 + Th-1 + Th-17 / Th-2 + Treg. Therefore, the results suggest that M1, Th-1, Th-17, Th-2 and Treg may be functionally more active in FEP patients than in controls, whilst there were no significant differences in Th-1 / Th-2 ratio and M1 + Th-1 + Th-17 / Th-2 + Treg ratios between both groups. Moreover, all immune subsets were highly correlated with each other, namely all $r > 0.900$ ($p<0.001$, n=53), while also M1 + Th-1 + Th-17 and Th-2 + Treg were strongly correlated ($r=0.955$, $p<0.001$, n=53). Thus, these results
indicate that FEP is accompanied by a more generalized immune activation with interrelated increases in M1, Th-1, Th-2, Th-17 and Treg responses.

In fact, the cytokine biosignature in schizophrenia and FEP showing increased levels of TNF-α, IL-12, IL-4, IL-10 and IL-8 suggests that monocytes, macrophages and dendritic cells (DSs) are induced by infectious (bacterial or viral) agents (although complement factors cannot be ruled out). Moreover, the strong induction of M1 cytokines, including GM-CS and IL-6, and the lack of an IL-2 response in FEP suggests that a bacterial component could be the trigger [149] and that macrophages and DCs subsequently activate Th-1 cells followed by an immune-regulatory response involving Th-2 and Treg cells [149, 150].
13. Is IRS or CIRS the prevailing phenotype in schizophrenia?

Another relevant question is whether the distinct schizophrenia phenotypes are associated with an predominantly activated IRS or otherwise with a predominant CIRS immune phenotype. In the 1990ties, Maes et al. described that schizophrenia is accompanied by IRS activation with activated M1 (IL-6, sIL-1RA), Th-1 (sIL-2R) and Treg (IL-10) phenotypes [21, 22, 56, 146]. Table 2 summarizes the findings of the present review and shows the evidence that all schizophrenia phenotypes are characterized by signs of both IRS and CIRS activation. Table 2 shows that both systems appear to co-exist in all schizophrenia phenotypes and that the IRS may be the prevailing phenotype in chronic schizophrenia. However, it is worth noting that no studies have provided a direct proof as to whether IRS is the predominant phenotype as no previous reports have used the adequate statistical method described by Maes and Carvalho (2018) to compute the IRS / CIRS ratio. Using this novel method, Noto et al. [141] computed the IRS / CIRS ratio as the ratio of the sum of the z values of all IRS cytokines (IL-6, TNF-α, IL-17, GM-CSF, IFN-(, IL-12 and IL-2) on the sum of the z values of the CIRS cytokines (IL-4, IL-5, IL-13, IL-10, sIL-1RA, sIL-2R, sTNF-R1, sTNF-R2). Figure 2 shows that the IRS (p=0.0021) and CIRS (p=0.007) indices as well as the IRS / CIRS ratio (p=0.0031) were significantly greater in FEP patients than in controls. Moreover, the IRS and CIRS indices were significantly and positively correlated (r=0.639, p<0.001, n=53), indicating that FEP is characterized by a more generalized activation of the immune system with a co-activation of the IRS and CIRS and a more dominant IRS. Nevertheless, table 2 shows that also in chronic schizophrenia, TRS and deficit schizophrenia the IRS and CIRS are activated, indicating that there is a new equilibrium between both components.
Figure 2. Measurements of macrophagic M1, T helper (Th)-1, Th-17, Th-2, T regulatory (Treg) phenotypes in healthy controls (HC), patients with first episode psychosis before treatment (FEP_PRE) and after treatment with antipsychotics (FEP_POST). Also shown are key ratios including the Th-1 / Th-2 (Th1_Th2) and M1 + Th1 + Th17 / Th2 + Treg (M1Th1Th17_Th2Treg) ratios, as well as indices of overall IRS activity (allIRS) and overall CIRS activity (allCIRS) and their ratio (allIRS_allCIRS). All values are shown as z scores (141).

The same study also reported that CIRS components such as sIL-1RA, sIL-2R, sTNF-R1 and sTNF-R2 are not increased in FEP [141]. The stronger activation of M1 and Th-1 subsets in schizophrenia and the lack of a significant increase in those CIRS receptors may explain the
relatively stronger IRS response in FEP. All in all, these results show that while there is no significant imbalance between Th-1 and Th-2 cells and between M1 + Th-1 and Th-2 + Treg subsets in schizophrenia, this disorder may be accompanied by an overactive IRS that is not sufficiently counterbalanced by a less dominant CIRS.

Noto et al. [141] also reported that subchronic treatment with risperidone for some weeks may suppress M1, Th-1, Th-2 and Treg cytokines simultaneously (see Figure 2) and that the improvements in symptom profiles (negative symptoms, psychosis, excitation, and affective symptoms) from baseline to some weeks later are strongly predicted by increased plasma sTNF-R1s and IL-10 concentrations at baseline [141]. These findings suggest that the CIRS contributes to partial recovery from the acute phase of illness in FEP and that a deficit is the CIRS at baseline may negatively affect the clinical outcome.

14. Contributions of IRS as well as CIRS to pathophysiology

The current review shows that schizophrenia patients appear to be exposed to many adverse effects of M1 and Th-1 cytokines on neuronal circuity including oxidative and nitrosative damage to neurons, changes in neuroplasticity, neurogenesis, neuronal signaling and apoptosis, which are denoted as neuroprogression [110, 151, 152]. Systemic immune-inflammation can cross the blood-brain barrier, driving changes in central inflammatory processes, especially those of astrocytes and microglia [151, 152]. Activated microglia and their release of M1 and Th-1 cytokines have been proposed to contribute to the progressive loss of brain tissue in schizophrenia [153] as shown in longitudinal MRI studies [152, 154]. Th-17 cytokines including IL-17 exert additional neurotoxic properties in the brain [155, 156].

In addition, increased plasma levels of IL-6 downregulate the expression of AKT-1 and DROSHA genes thereby possibly affecting the microRNA machinery and many cellular
functions [108]. Also, IRS-related chemokines including CXCL-8 contribute to neuroprogressive processes by facilitating migration of leukocytes through the blood brain barrier and sustaining neuroinflammation in the brain thus leading to neurotoxicity [157, 158]. Activated Th-1 and M1 subsets stimulate IDO and kynurenine 3-monooxygenase [159] to produce more cytotoxic, excitotoxic, and neurotoxic TRYCATs including picolinic acid, xanthurenic acid and quinolinic acid [71], thereby causing cognitive impairments including in episodic and semantic memory [136].

Moreover, products of Th-2 cytokines including IL-4, which are frequently described as cytokines with immune-regulatory effects, in fact may present with pro-inflammatory effects. For example, IL-4 may elevate IFN-γ production and activate M1 macrophages [160], while IL-4 and IL-13 have neurotoxic effects through oxidative stress pathways [161]. CCL-11, a product of Th-2 cells may be one of the most important factors leading to neurocognitive deficits (including episodic and semantic memory and executive functions), formal thought disorders and symptom dimensions for example by directly affecting hippocampal neurogenesis [71]. Microglia also produces IL-5 which in turn plays a role in neuroinflammation by increasing the activation and proliferation of microglia cells [162].

All in all, it appears that FEP is characterized by a peripheral IRS (M1, Th-1 and Th-17, chemokines), which is possibly caused by infectious agents, and which may induce Th-2 and Treg responses and therefore an increased negative feedback on the activated immune-inflammatory pathways. Moreover, products of the CIRS (e.g. IL-4 and IL-13 and noxious TRYCATs) and other Th-2-related cytokines/chemokines (e.g. CCL-11 and IL-5) have profound adverse effects on brain neuronal functioning and thus neuroprogressive pathways thereby
causing different symptom dimensions and neurocognitive and memory deficits and the deficit phenotype [163].

Moreover, deficits in the CIRS as observed in schizophrenia may attenuate the regulatory feedback on the primary IRS, thereby priming the immune system to greater M1, Th1 and TH-2 responses following infections or other injuries. As reviewed here, attenuated CIRS functions comprise lowered plasma uteroglobin levels in schizophrenia [58], relatively lower levels of sIL-1RA, sIL-2R, sTNF-R1 and sTNF-R2 as compared with the increased levels of M1, Th-1 and Th-2 cytokines [141], and lowered levels of IgM-mediated autoimmune responses to TRYCATs [75].

15. Conclusions and outlook.

Figure 3 shows a summary of the findings of this study. Thus, an infection or other immune triggers could induce macrophagic M1 activation, which in turn activates T helper (Th)-1 subsets, which consequently activate the tryptophan catabolite (TRYCAT) pathway, Th-2 and T regulatory (Treg) subsets, acute phase protein (APP) production and thus the compensatory immune-regulatory reflex system (CIRS), which regulates the primary IRS response. Deficits in the CIRS (including lowered natural IgM-mediated immune regulation, lowered uteroglobulin, lowered IL-2 and TNF-α receptor levels) are accompanied by an exaggerated IRS response. Even after resolution of the acute episode, both the IRS and CIRS remain overactive, suggesting a new homeostatic setpoint between both components. The progression of schizophrenia, namely from the premorbid phase and first episode psychosis (FEP) through the debilitating stages of treatment resistant and chronic schizophrenia (TRS) and deficit schizophrenia, is accompanied by activation of both IRS and CIRS components. FEP is accompanied by an increased IRS /
CIRS ratio indicating a stronger immune-inflammatory process. The products of IRS and CIRS, including Th-1 (IL-1β, IL-6, TNF-α, GM-CSF, TRYCATs) and Th-2 (IL-4, IL-5, CCL-11) subsets as well as chemokines (CXCL-8) exert neurotoxic and neuroprogressive effects thereby inducing the symptom clusters of schizophrenia as well as cognitive deficits.

**The IRS - CIRS THEORY OF SCHIZOPHRENIA**

**Figure 3.** The immune-inflammatory responses system (IRS) and compensatory immune-regulatory reflex system (CIRS) theory of schizophrenia. Infections (and other injuries) may induce IRS activation via induction of macrophagic M1 and T helper (Th)-1 phenotypes, followed by activation of Th-17 and Th-2 and T regulatory (Treg) subsets. Deficits in the CIRS may increase the vulnerability to develop strong IRS responses following immune injuries. First episode psychosis (FEP), acute relapses, depressive symptoms dimensions, schronic schizophrenia (SCZ), treatment resistant schizophrenia and deficit schizophrenia are all accompanied by increments in IRS and CIRS. Even stable phase schizophrenia is accompanied by increased levels of IRS cytokines and CIRS products, including regulatory cytokines, acute phase proteins (APPs) and
tryptophan catabolites (TRYCATs). Products of M1, Th1, Th-17 and Th-2 cells may exert neurotoxic effects thereby causing neuroporgression with impairments in memory and frontal functions and the symptoms of schizophrenia as well.

Acknowledgements

This study was funded by Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University, grant number RA61/016 and Chulalongkorn University; Government Budget; and by the Asahi Glass Foundation, Chulalongkorn University Centenary Academic Development Project and Ratchadapiseksompotch Fund, Faculty of Medicine, Chulalongkorn University, grant number RA60/042.

Conflict of interest

The authors have no conflict of interest with any commercial or other association in connection with the submitted article.

Author’s contributions

All the contributing authors have participated in the manuscript. CR and MM designed the study. All authors contributed to interpretation of the data and writing of the manuscript. All authors approved the final version of the manuscript.
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