Microglial Activation and Psychotic Disorders: Evidence from Pre-clinical and Clinical Studies

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Abstract Clinical and pre-clinical studies have demonstrated an important role of neuroinflammation in the etiology of schizophrenia. While the underlying mechanisms remain poorly understood, there are some studies demonstrating an association between maternal immune activation and behavioral changes in adult offspring and identifying early life infection as a trigger for schizophrenia; in addition, inflammatory markers were found to be increased in the schizophrenic post-mortem brain. During maternal immune activation, pro-inflammatory mediators such as cytokines, chemokines, antibodies, and acute-phase proteins are released in the maternal bloodstream, thus increasing the permeability of the placental barrier and the fetal blood-brain barrier, allowing the inflammatory mediators to enter the fetal brain. In the central nervous system (CNS), these pro-inflammatory mediators are able to activate microglial cells that can release pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6. As a consequence, circulating immune cells may infiltrate the brain, increasing cytokine levels and releasing antibodies that aggravate the neuroinflammation. Neuroinflammation may affect processes that are pivotal for normal brain maturation such as myelination, synaptic pruning, and neuronal remodeling. Microglial cell activation and pro-inflammatory mediators have been extensively studied in schizophrenic post-mortem brain samples. Some results of these investigations demonstrated an increase in microglial activation markers, cytokines, and chemokines in post-mortem brain samples from individuals with schizophrenia. In contrast, there are studies that have demonstrated low levels of microglial activation makers in the schizophrenic post-mortem brain. Thus, based on the important role of neuroinflammation as a trigger in the development of schizophrenia, this chapter aims (1) to enumerate evidence of neuroinflammation and microglial activation from pre-clinical schizophrenia models, (2) to show links between schizophrenia and neuroinflammation in clinical studies, and (3) to identify mechanisms by which microglial activation may influence in the development of schizophrenia.

Keywords Microglia · Neuroinflammation · Psychosis · Schizophrenia · Schizophrenia-like behavior

Abbreviations

ATP	Adenosine 5-triphosphate
CCL3	Chemokine (C-C motif) ligand 3
CLR	C-type lectin receptors
CNS	Central nervous system
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
DAMPS	Damage-associated molecular patterns
DM	Damaged processes
DNA	Deoxyribonucleic acid
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte/monocyte colony-stimulating factor
HLA-DR	Human leukocyte antigen-antigen D related
HMGB-1	High mobility group box-1 protein
HSPs	Heat shock proteins
Iba1	Ionized calcium-binding adaptor molecule
IFITM	Interferon-induced transmembrane protein
IFN	Interferon
IkB	Inhibitors of NF-B
IL	Interleukin
IL-13RA1	IL-13 receptor alpha-1
IL-1RA	IL-1 receptor antagonist
iNOS	Inducible nitric oxide synthase
IRF	Interferon regulatory factor
KC	Keratinocyte chemoattractant
LIX	Lipopolysaccharide-induced CXC chemokine
Mal	MyD88 adapter-like
MAPKs	Mitogen-activate protein kinases
MCP-1	Monocyte chemoattractant protein-1
MD-2	Myeloid differentiation protein-2
MDA	Malondialdehyde
MHC	Major histocompatibility complex
MIP-1	Macrophage inflammatory protein-1
mRNA	Messenger ribonucleic acid
MYD88	Myeloid differentiation factor 88
NF-κB	Nuclear factor kappa B
NLR	NOD-like receptors
PAMPs	Pathogen-associated molecular patterns
pIRF3	Phosphorylated-IRF3
PK 11195	1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide
PND	Postnatal day
Poly I:C	Polyinosinic-polycytidylic acid

PRRs	Pattern-recognition receptors
RAGE	Receptors for advanced glycation end products
RANTES	Regulated upon activation normal T-cell expressed and secreted
RIG-1	Retinoic acid-inducible gene-1
RLR	RIG-1-like receptors
RM	Ramification
RNA	Ribonucleic acid
SERPINA-3	Serpin family A member-3
ssRNA	Double-stranded ribonucleic acid
STAT-1	Signal transducer and activator of transcription-1
TIR	Toll/IL-1 receptor
TIRAP	Domain-containing adaptor protein
TLR	Toll-like receptor
TNFR1	TNF receptor 1
TNF-α	Tumor necrosis factor alpha
TRAF	Tumor necrosis factor receptor-associated factor
TRIF	Toll/IL-1 receptor domain-containing adaptor-inducing interferon-β
TSPO	Translocator protein

1 Introduction

Clinical and pre-clinical studies have demonstrated an important role of neuro-inflammation in the etiology of schizophrenia. While the underlying mechanisms remain poorly understood, there are some studies showing evidence of microglial activation and increased levels of cytokines and chemokines in post-mortem schizophrenic brain samples, as well as in fetal and adult brains of offspring subjected to maternal immune activation during fetal life. In 1999, the first evidence of microglial and macrophage activation in the brains of patients with psychiatric disorders was reported. In the study, 3 of the 14 samples of post-mortem brains from patients with schizophrenia presented immunoreactivity to human leukocyte antigen-antigen D related (HLA-DR) protein in the frontal cortex and the hippocampus (Bayer et al. 1999). After that, a number of studies showed an increase in microglial markers in post-mortem schizophrenic brains, whereas few studies found no effect or a decrease in microglial markers. The studies that followed demonstrated an important role of maternal immune activation in releasing cytokines, chemokines, antibodies, and C-reactive protein (CRP) as an inductor of schizophrenia rather than the pathogen involved in maternal infection (Feigenson et al. 2014; Khandaker et al. 2014a, b). Pre-clinical studies have shown that during maternal immune activation, cytokines, chemokines, antibodies, and acute-phase proteins are released into the maternal bloodstream, thus increasing the permeability of the placental barrier and the fetal blood-brain barrier and allowing the inflammatory mediators to reach the fetal brain. In the central nervous system (CNS), these pro-inflammatory mediators are able to

activate microglia that can release pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6. In addition, circulating immune cells may infiltrate the brain, increasing the cytokine levels and releasing antibodies that aggravate the neuroinflammation (Garay et al. 2013; Feigenson et al. 2014; van den Eynde et al. 2014; Reus et al. 2017). Thus, based on the important role of neuroinflammation as a trigger for the development of schizophrenia, this chapter aims (1) to enumerate evidence of neuroinflammation and microglial activation in pre-clinical schizophrenia models, (2) to highlight links between schizophrenia and neuroinflammation in clinical studies, and (3) to identify mechanisms by which microglial activation may influence the development of schizophrenia.

2 Evidence of Neuroinflammation and Microglial Activation from Pre-clinical and Clinical Schizophrenia Studies

2.1 Microglia Overview

Microglia comprise approximately 10–15% of all glial cells and are tissue-resident macrophages that present important functions in the CNS, including in supporting newborn neurons, cell death and clearance, homeostasis, and regulation of neuronal and synaptic plasticity (Salter and Stevens 2017). Microglia are derived from primitive myeloid progenitors emanating from the embryonic yolk sac during development and then populate the CNS (embryonic day 8.5 in mice) prior to its blood vessel formation (Ginhoux et al. 2010). Resting microglia have a small cell body and possess long branching; after being activated, the cells replace their ramified branches with highly amoeboid, motile protrusions (Stence et al. 2001). A modern transcriptome profiling of microglia in mice showed that the response phenotypes fail to conform to M1 or M2 patterns, though the functional significance and ontogeny of microglia had not yet been characterized (Ransohoff 2016; Salter and Stevens 2017). Microglia present class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DP, HLA-DQ) major histocompatibility complex (MHC) molecules. The MHC class II is found only on antigen-presenting cells, such as microglia, dendritic cells, mononuclear phagocytes, and B cells, because these cells are essential in initiating an immune response. Microglia are an important component of the innate immune system, and during their resting states, they are active with extremely motile processes and protrusions; thus, this cell type is referred to as a "housekeeper" in the adult brain (Nimmerjahn et al. 2005) (see Fig. 1).

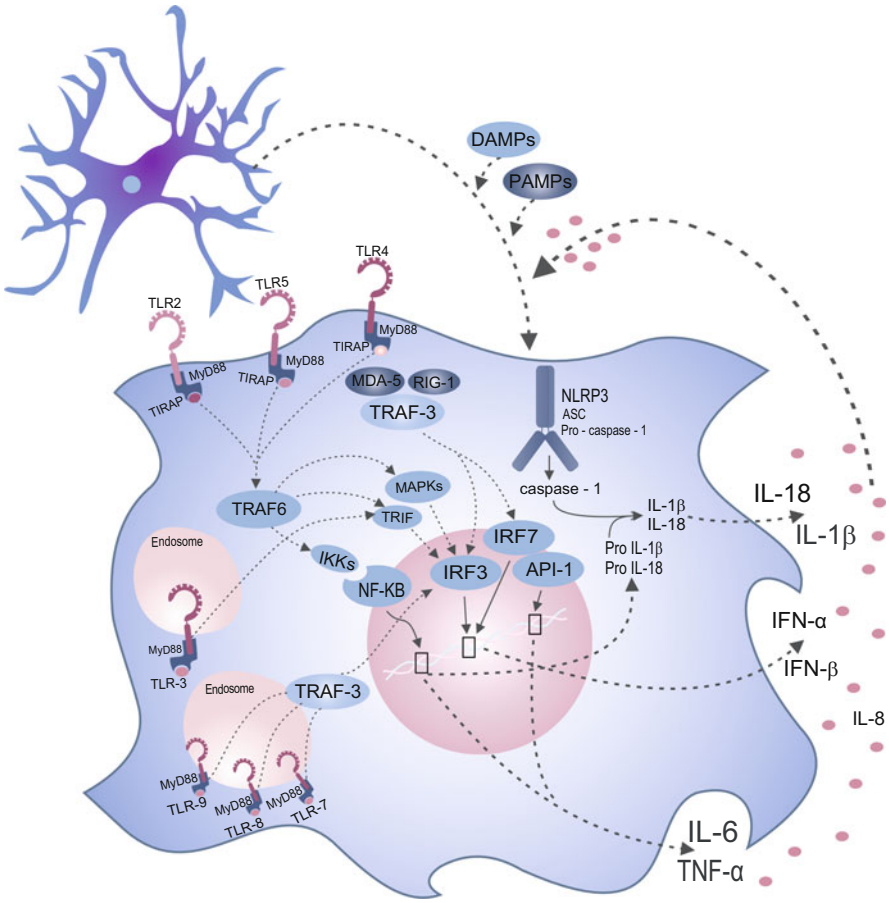

Fig. 1 Microglial activation. Resting microglial cell with ramified shape is activated by DAMPs, PAMPs, or pro-inflammatory mediators. After microglial activation, these cells present with highly amoeboid motile protrusions and release cytokines and chemokines. *API-1* apoptosis inhibitor gene-1; *ASC* caspase-recruitment domain; *DAMPS* damage-associated molecular patterns; *IFN-α, IFN-β* interferon-α, interferon-β; *IKKs* IκB kinase complex; *IL-1β, IL-6, IL-8, IL-18* interleukin-1β, interleukin-6, interleukin-8, and interleukin-18; *IRF-3, IRF-7* interferon regulatory factor-3, interferon regulatory factor-7; *MAPKs* mitogen-activated protein kinases; *MDA-5* melanoma differentiation-associated gene 5; *MyD88* myeloid differentiation factor 88; *NF-κB* nuclear factor kappa B; *NLRP-3* NLR family pyrin domain containing-3; *PAMPs* pathogen-associated molecular patterns; *RIG-1* retinoic acid-inducible gene-1; *TIRAP* domain-containing adaptor protein; *TLR* Toll-like receptor; *TNF-α* tumor necrosis factor alpha; *TRAF-3, TRAF-6* TNF receptor-associated factor-3, TNF receptor-associated factor-6; *TRIF* Toll/IL-1 receptor domain-containing adaptor-inducing interferon-β

2.2 *Evidence of Neuroinflammation and Microglial Activation in Pre-clinical Schizophrenia Models*

Several pre-clinical studies have demonstrated and supported evidence for the role of neuroinflammation in the development of schizophrenia. Among the different pre-clinical models that aim at recapitulating the development of schizophrenia, a subset of these is based on gestational exposure to maternal immune activation, a clinically relevant risk factor for schizophrenia. The experimental maternal immune activation induced by polyinosinic-polycytidylic acid (Poly I:C) mimics a viral infection because this chemical compound is a synthetic analogue of double-stranded ribonucleic acid (ssRNA). A multitude of studies that implement this model have observed long-lasting alterations of microglial markers, suggesting persistent microglial activation in adult animals exposed to gestational Poly I:C. For example, a study evaluated ionized calcium-binding adapter molecule-1 (Iba1), a microglia- and macrophage-specific calcium-binding protein that has actin-bundling activity and participates in membrane ruffling and phagocytosis in activated microglia. On gestation day 15, pregnant dams were given a single i.v. injection to the tail vein of Poly I:C or saline. The number of Iba1-positive cells was increased in the Poly I:C offspring's hippocampus and nucleus accumbens but was unchanged in the prefrontal cortex. In addition, MHC class II expression in microglia increased in the Poly I:C prefrontal cortex, but not in the hippocampus of adult male offspring at 18 weeks of life (Hadar et al. 2017). Similarly, Mattei et al. observed an increase in Iba1 immunoreactivity in the proximity of the hippocampal dentate gyrus of adult mice on PND 60 that were subjected to maternal immune activation by Poly I:C at embryonic day 15 compared with control offspring in adult life (Mattei et al. 2017). Further, using the same microglial marker, Iba1, the offspring of mice exposed to Poly I:C at embryonic day 9 were shown to have an elevated number of activated microglial cells in the hippocampus and striatum, but not in the frontal cortex, on PND 30 (Juckel et al. 2011). In another study, OX-42, an antibody designed to detect CD11b, was used as a marker of microglia in the brain. OX-42 immunoreactivity was detected on postnatal day (PND) 180 in adult Poly I:C offspring, showing an increase in the concentration of OX-42-positive staining and microglial density, and reduced microglia ramifications, indicating that the microglia were in the activated state in all brain regions. Additionally, there was a difference in the form of an overall significant increase in microglia score in the corpus callosum, hippocampus, and thalamus; however, this difference was not found in the pons, cortex, or striatum obtained from adult offspring of dams treated with Poly I:C on embryonic day 15 (Van den Eynde, Missault et al. 2014).

Activated microglial cells can increase the production and expression of pro-inflammatory cytokines, such as TNF-α and IL-1β, and neurotoxic substances, resulting in neuroinflammatory and neurodegenerative processes. Adult mice subjected to maternal immune activation by Poly I:C during the fetal stage presented high expression of proteins involved in the Toll-like receptor (TLR)-3 signaling pathway, such as signal transducer and activator of transcription-1 (STAT-1),

Toll/IL-1 receptor (TIR)-domain-containing adapter-inducing interferon-β (TRIF), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and phosphorylated-IRF3 (pIRF3), in the frontal cortex. Increased oxidative and nitrosative stress, as evidenced by increased malondialdehyde (MDA) and inducible nitric oxide synthase (iNOS), and increased levels of TNF-α, interferon (IFN)-α, and IFN-β in the frontal cortex were also observed (MacDowell et al. 2017a). In another study, mice were subjected to maternal immune activation on embryonic day 12.5. On PNDs 0, 7, 14, 30, and 60, the offspring brains were removed, and the frontal cortex, cingulate cortex, and hippocampus were used to evaluate the presence of cytokines and chemokines. On PND 0, the frontal cortex showed increased levels of IL-1β, IL-10, IL-12, and granulocyte/monocyte colony-stimulating factor (GM-CSF). On PND 7, the levels of granulocyte colony-stimulating factor (G-CSF) were increased, and on PND 60, the levels of IL-1α, IL-6, IL-9, and IL-10 were also increased. On PND 0, the cingulate cortex showed increased levels of IFN-γ, IL-12, and monocyte chemoattractant protein-1 (MCP-1). On PND 7, the levels of IL-17 increased, and on PND 60, the levels of IL-10 and IFN-γ increased. On PND 0, the hippocampus showed an increase in the level of IL-6. On PND 7, increased levels of IL-9, keratinocyte chemoattractant (KC), and macrophage inflammatory protein-1 alpha (MIP-1α) were observed, and on PND 14, increased levels of IL-1α and IL-6 were found (Garay et al. 2013).

Pratt et al. injected pregnant mice on embryonic day 12.5 with Poly I:C, and fetal brains were collected at embryonic day 16.5 to evaluate the inflammatory profile of microglial cells, which included cytokine and chemokine expression. Fetal microglia expressed high levels of cytokines and chemokines such as IL-1α, IL-4, IL-6, IL-9, GM-CSF, and M-CSF, which were regulated upon activation by normal T-cell expressed and secreted (RANTES), lipopolysaccharide-induced CXC chemokine (LIX), exotoxin, and MIP-1β (Pratt et al. 2013). Using another approach, Arad et al. injected dams with Poly I:C on day 4 after birth, and the offspring were breastfed. Two hours after Poly I:C injection, the milk of the dams presented elevated levels of IL-1β, IL-6, and corticosterone. At 6 and 24 h after the dams received the Poly I:C injection, the male offspring presented high levels of IL-6 and IFN-γ in the hippocampus. Twenty-four hours after the dams received the Poly I:C injection, both male and female offspring presented high levels of TNF-α in the hippocampus. In addition, lactational Poly I:C exposure triggered behavioral abnormalities in the adult offspring (PND 90 to 120), with male, but not female, offspring exhibiting attentional and executive function abnormalities (manifested in persistent latent inhibition and slow reversal) and female, but not male, offspring exhibiting despair and anhedonia (Arad et al. 2017).

A subset of studies aimed at characterizing the role of single cytokines. For example, Smith et al. demonstrated the important role of IL-6 in schizophrenia-like behavior. Specifically, an intraperitoneal injection of IL-6 on embryonic day 12.5 in pregnant mice triggered prepulse inhibition and latent inhibition deficits in the adult offspring, but IFN-γ maternal injection did not affect the schizophrenia-like behavior of adult offspring (Smith et al. 2007). The section above highlights several studies demonstrating that TLR-3 activation and pro-inflammatory cytokines could

influence the development of schizophrenia-like behavior in adult offspring. In contrast to other studies, on PND 90 to 104, adult offspring did not present any significant difference in the level of microglial activation compared to the control adult offspring (Missault et al. 2014). In this study, despite the confirmation of systemic inflammation in the pregnant mice, there was no difference in fetal microglial cell density or in the activation level on embryonic days 11.5–17.5 between the control and Poly I:C group (Smolders et al. 2015); see Table 1.

The Gunn rat is another animal model of schizophrenia (Gunn 1944). Gunn rats present behavioral abnormalities, deficits in prepulse inhibition, and neuropathological changes that are similar to the characteristics of schizophrenia-like behavior (Liaury et al. 2012). CD11b immunoreactivity is increased in microglial cells of the hippocampal dentate gyrus of Gunn rats (Liaury et al. 2012, 2014). Gunn rats showed a prepulse inhibition deficit compared to Wistar rats. The amount of CD11b microglial cell marker increased in the hippocampus of Gunn rats compared to the same brain structure of the Wistar rats (Limoa et al. 2016).

3 Evidence of Neuroinflammation from Schizophrenic Patients

3.1 Microglia Evaluation in Post-mortem Schizophrenic Brain

Brain samples from 3 of 14 patients with schizophrenia exhibited HLA-DR-positive tests in the frontal cortex and hippocampus (Bayer et al. 1999). HLA-DR is an MHC class II cell surface receptor that interacts with antigen-presenting cells such as microglia, mononuclear phagocytes, dendritic cells, and B cells. The microglial marker HLA-DR was increased in paranoid schizophrenic hippocampal samples compared with residual schizophrenic and matched control samples. In the same study, higher expression levels of CD3+ and CD20+ lymphocytes were found in the hippocampus of residual schizophrenics compared with paranoid schizophrenics and matched controls (Busse et al. 2012). The density of HLA-DR cells that were morphologically similar to microglia was increased in the dorsolateral prefrontal cortex of individuals with schizophrenia (Fillman et al. 2013). In a previous study, the frontal and temporal lobes of chronic schizophrenics presented greater microglial cell activation compared with control brains. However, the first layer of the cerebral cortex presented the same amounts of well-developed ramifications (RM), degenerative traits, and damaged processes (DM), and the number of DM cells in the remaining regions was higher than that of the RM cells (Wierzba-Bobrowicz et al. 2005). Another study evaluated 12 brains of female chronic schizophrenics. The schizophrenic frontal and temporal lobe samples presented ramified microglial cells with expression of MHC class II. Most cells presented with cytoplasm shrinkage, thinning, shortening and fragmentation of their processes, and apoptotic changes.

Table 1 Microglial cell and inflammatory markers in pre-clinical schizophrenia models

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
Poly I:C (5 mg/kg) on GD 9	Mutant hDISC1 and C57BL6/J mice	ED 9 at 6 h after Poly I:C	No	Whole brain	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, and TNF-α	IL-1β levels increased in the brains of C57BL6/J and mutant hDISC1 mice. IL-4 and IL-5 levels increased only in C57BL6/J mice	Abazyan et al. (2010)
Poly I:C (4 mg/kg)	Wistar rats	On PND 4 at 6 h and 24 h following lactation with saline or Poly I:C exposure	Female and male	Whole brain	IL-6, IFN-γ, and TNF-α	IL-6 and IFN-γ were elevated at both time points only in male Poly I:C offspring compared to their controls [IL-6: main effect of sex, $F(1.55) = 5.74$, $p < 0.05$; main effect of immune activation, $F(1.55) = 4.63$, $p < 0.05$; immune activation vs. sex interaction, $F(1.55) = 7.76$, $p < 0.01$, and a significant difference in post hoc comparisons, $p < 0.01$; IFN-γ: sex vs. treatment interaction, $F(1.56) = 4.43$, $p < 0.05$, and a significant difference in post hoc comparisons, $p < 0.01$]. Both male and female	Arad et al. (2017)

						Poly I:C offspring had a lower hippocampal level of TNF-α at 24 h, but not at 6 h, following exposure to Poly I:C compared to the saline offspring [treatment x time interaction, $F(1.56) = 6.78$, $p < 0.05$, and significant differences in post hoc comparisons, $p < 0.005$]	
Poly I:C (20 mg/kg) on GD 12.5	C57BL/6 J mice	PND 0, PND 7, PND 14, PND 30, and PND 60	No	Frontal cortex, cingulate cortex, and hippocampus	Iba1, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, eotaxin, G-CSF, GM-CSF, IFN-γ, KC, MCP-1, MIP-1α, MIP-1β, RANTES, and TNF-α	IL-1β levels in the hippocampus and cingulate cortex were similar with age but quite different in the frontal cortex where they were highest on PND 0 and PND 7 and then dramatically decreased at PND 14. Levels of IL-9 were steadily high with age in the cingulate cortex and hippocampus and were also relatively high in the frontal cortex during the period of rapid synaptogenesis (PND 0–PND 14) but decreased in the frontal cortex with maturity. Conversely,	Garay et al. (2013)

(continued)

Table 1 (continued)

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
						IL-6 decreased at PND 60 in the hippocampus and cingulate cortex but not in the frontal cortex, where it remains high in adulthood. A second point of interest is that some cytokines, including IL-4, IL-2, and IL-17, are higher in mid-postnatal life but lower at birth and in the adult. Third, several cytokines dip in concentration specifically at PND 14, a period of intense synaptogenesis; these include IL-3, IL-13, IL-12 (p40), eotaxin, MIP-1α, and KC in addition to IL-2 and IL-5 specifically in the cingulate cortex and hippocampus. Fourth, another set of cytokines increased in concentration with age, including IL-6, IL-10, IFN-γ, GM-CSF, IL-12 (p70), IL-17, and MIP-1β	

Poly I:C (4 mg/kg) on GD 15	Wistar rats	PND 33–34	Female and male	Hippocampus, nucleus accumbens, and medial prefrontal cortex	IL-1β, TNF-α, IL-6, Iba1, and MHC II	Pro-inflammatory cytokine mRNA levels were unchanged in all brain areas. The density of Iba1-positive cells (microglia) was increased in the Poly I:C hippocampus and nucleus accumbens but unchanged in the medial prefrontal cortex. Using FACS, detected an increase in MHC II expression in microglia derived from the Poly I:C medial prefrontal cortex, but not the hippocampus	Hadar et al. (2017)
Poly I:C (20 mg/kg) on GD 9	BALB/c mice	PND 30	Females and males	Hippocampus, frontal cortex, striatum, and as a control region the occipital cortex	CD11b/Iba1	Poly I:C treatment caused a significant increase of microglial markers in the hippocampus ($p = 0.028$) and a significant increase in the striatum ($p = 0.028$). Poly I:C offspring from LPS mothers exhibited significantly less branches and processes in microglial cells compared to the control mice ($p = 0.002$), showing a	Juckel et al. (2011)

(continued)

Table 1 (continued)

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
						reduced surface of processes in Poly I:C mice, suggesting that Poly I:C treatment of mothers caused a higher activation status in the offspring generation	
Gunn rats	Gunn and Wistar rats (8 weeks old)	0 h	Male	Hippocampal dentate gyrus	CD11b	There was no significant difference between cell numbers in the Gunn rats and controls. However, there was a significant increase in CD11b expression in the hippocampal dentate gyrus in GUNN rats	Liaury et al. (2012)
Gunn rats Minocycline hydrochloride (40 mg/kg)	Gunn and Wistar rats (6 weeks old)	14 days	Male	Whole brain	CD11b	Immunohistochemistry analysis revealed that microglial cells in the minocycline-treated Gunn rat group showed less expression of CD11b compared to vehicle-treated Gunn and Wistar groups	Liaury et al. (2014)
Poly I:C (5 mg/kg) on GD 9.5	C57BL/6 J mice	PND 60	Female and male	Frontal cortical areas	IL-1β, IL-6, IL-10, IFN-α, IFN-β,	MIA by Poly I:C induced an increase in the main	MacDowell et al. (2017a)

					CX3CL1, STAT1, TGF-β, and TNF-α	pro-inflammatory cytokines TNF-α and IL-6 mRNA levels, but no changes were seen in the IL-1β mRNA levels	
Poly I:C (4.0 mg/kg) on GD 15	Wistar rats	PND 128 (Poly I:C/minocycline; Poly I:C/H_2O; NaCl/minocycline; NaCl/H_2O)	Male	Ventral striatum, cingulate gyrus, medial prefrontal cortex, nucleus accumbens core, dentate gyrus of the hippocampus, and cerebellum	Iba1, IL-1β and TNF-α	In the dentate gyrus, a significant decrease in microglia Iba1 reactivity in the Poly I:C/H_2O group compared to control NaCl/H_2O was detected. In the hippocampus a significant increase of IL-1β mRNA in the Poly I:C/H_2O compared to NaCl/H_2O was found. In addition, they detected a significant effect of minocycline on IL-1β mRNA levels in the Poly I:C/minocycline group compared to Poly I:C/H_2O in the hippocampus. The increase in TNF-α mRNA in Poly I:C/H_2O in the hippocampus did not reach significance compared to NaCl/H_2O but was significantly higher compared to NaCl/minocycline	Mattei et al. (2014)

(continued)

Table 1 (continued)

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
Poly I:C (2, 4, or 8 mg/kg) on GD 9 and GD 15	Wistar-Hannover rats	PND 90 until PND 104	No	Maternal serum and fetal brains	IL-1β, IL-6, IL-10, and TNF-α	Surprisingly, not the highest dose tested, but the 4 mg/kg dose induced the largest increase in IL-1β mRNA in maternal blood, which was significant at GD 15 ($p < 0.05$). The highest increase in TNF-α mRNA expression in the blood of GD 15 mothers was also observed at the 4 mg/kg dose, while at GD 9 the strongest expression was observed using 8 mg/kg Poly I:C, an effect which was statistically significant ($p < 0.05$). The brains of fetuses exhibited a moderate increase in the IL-1β and TNF-α levels compared to controls. The largest increase in pro-inflammatory cytokines was observed in offspring belonging to the 4 mg/kg group.	Missault et al. (2014)

						While at GD 9 this rise in pro-inflammatory cytokines was balanced by a rise in anti-inflammatory IL-10, this was not the case at GD 15	
LPS (500 or 10 μg/kg) on GD 17	Mice	1.5 h after injected to LPS	Female and male	Maternal serum, amniotic fluid, fetal liver, and fetal brain	TNF-α	TNF-α increased in maternal serum and amniotic fluid in response to LPS. Although maternally administered LPS also increased the level of TNF-α protein in the fetal liver and brain, no significant difference in TNF-α mRNA level in fetal liver and brain was found. When the pregnant mice were pretreated with 10 μg/kg at 4, 12, 24, or 48 h before LPS 500 μg/kg, TNF-α in maternal serum and amniotic fluid was inhibited. Low doses of LPS pretreatment attenuated LPS-induced increases in TNF-α protein in the fetal liver and fetal brain.	Ning et al. (2008)

(continued)

Table 1 (continued)

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
						Perinatal exposure to low doses of LPS induced a reduced sensitivity to subsequent LPS challenge	
Poly I:C (20 mg/kg) On GD 12.5	C57BL/6 J mice	ED 16.5	Females and males	Fetal brains	IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, G-CSF, GM-CSF, IFN-γ, LIF, LIX, KC, MCP-1, MIP-1α, MIP-1β, MIP-2, M-CSF, VEGF, and RANTES	Although the mRNA for IL-6 had increased, the IL-6 protein levels failed to reach statistical significance in the Luminex assay, although the trend was upward. Of the classic pro-inflammatory cytokines, IL-1α was significantly elevated. Other cytokines showing significant elevations include G-CSF, GM-CSF, M-CSF, IL-4, and IL-9. Unexpectedly, a number of chemokines also showed statistically significant increases, including eotaxin, MIP-1β, LIX-CXC chemokine, and RANTES. $CD11b^{+}$ fractions, the $CD11b^{-}$ fractions also produced significant	Pratt et al. (2013)

						quantities of cytokines following maternal inflammation, often in larger quantities than the $CD11b^+$ fractions. These included IL-1β, IL-9, IL-10, and IL-13	
LPS (50 μg/kg) on PND 3 and ketamine (5, 15, and 25 mg/kg) for 7 days during adulthood	Wistar rats	PND 60	Male	Prefrontal cortex hippocampus and striatum	IL-1β, IL-6, IL-10, and TNF-α	In the prefrontal cortex, hippocampus, and striatum, two-way ANOVA revealed an interaction for ketamine versus LPS in the levels of IL-1β. A decrease in the IL-1β levels in the prefrontal cortex for LPS plus ketamine 5 mg/kg ($p = 0.019$), a decrease in the hippocampus ($p = 0.008$) and striatum ($p = 0.018$) for LPS plus ketamine 15 mg/kg was shown. The two-way ANOVA demonstrated LPS effects on IL-1 in the prefrontal cortex ($p < 0.001$), in the striatum ($p < 0.001$). In the hippocampus no effects were found for LPS ($p = 0.056$). The levels of IL-1β were not	Reus et al. (2017)

(continued)

Table 1 (continued)

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
						altered in the ketamine group in the prefrontal cortex ($p = 0.306$), in the hippocampus ($p = 0.060$), and striatum ($p = 0.093$)	
Poly I:C (20 mg/kg) on GD 11.5, 12.5, 15.5, and 17.5	Transgenic CX3CR1-eGFP knock-in mice	3 and 5 h after injection	Female and male	Cortex and hippocampus	IL-1β and iNOS	Despite the presence of a systemic inflammation in the pregnant mice, there was no significant difference in fetal microglial cell density or immunohistochemically determined activation level between the control and inflammation group	Smolders et al. (2015)
LPS (0.5 or 2.5 mg/kg) at GD 16	Sprague-Dawley rats	2 or 8 h after injected to LPS	Female and male	Amniotic fluid, fetal brain, and placental	IL-1β, IL-6, and TNF-α	The low dose (0.5 mg/kg) of LPS increased the levels of cytokines in the placenta with significant increases of IL-1β ($p < 0.0001$), IL-6 ($p < 0.0001$), and TNF-α ($p = 0.0001$) over the 2 and 8 h time course. In the amniotic fluid, there was an increase of IL-6 levels ($p = 0.0006$). Two	Urakubo et al. (2001)

						hours after maternal administration of a high dose (2.5 mg/kg) of LPS, there were significant elevations of cytokines in placenta IL-6 ($p < 0.0001$), TNF-α ($p < 0.0001$), a significant increase of TNF-α in amniotic fluid ($p = 0.008$), and a small but significant decrease in TNF-α ($p = 0.035$) in the fetal brain	
Poly I:C (4 mg/kg) on GD 15	Sprague-Dawley rat	PND180	Female and male	Corpus callosum, hippocampus, thalamus, pons, cortex, and striatum	CD11b/OX-42 and CD68/ED-1	Significant differences over the different brain regions were observed ($p \leq 0.001$), with an overall significant increase being indicated in microglia scores in the corpus callosum ($p \leq 0.05$), hippocampus ($p \leq 0.05$), and thalamus ($p \leq 0.01$) but not in the pons, cortex, and striatum ($p = 0.1$, $p = 0.5$, and $p = 0.1$, respectively). In the corpus callosum, both microglia intensity ($p \leq 0.001$) and density	van den Eynde et al. (2014)

(continued)

Table 1 (continued)

Pre-clinical model	Species	Animal age	Sex	Anatomical area	Biomarkers evaluated	Results	Reference
						($p \leq 0.05$) significantly contributed to the overall significant increase in OX-42. The ED-1 staining on the other hand revealed very few reactive microglia. No difference in ED-1 immunoreactivity was found between Poly I:C and control offspring	

ANOVA analysis of variance, *CX3CL1* fractalkine, *CD11b* microglial marker, *ED* embryonic day, *FACS* fluorescence-activated cell sorting, *G-CSF* granulocyte colony-stimulating factor, *GD* gestation day, *GM-CSF* granulocyte/monocyte colony-stimulating factor, H_2O water, *Iba1* ionized calcium-binding adaptor molecule, *IL* interleukin, *IFN* interferon, *iNOS* inducible nitric oxide synthase, *KC* keratinocyte chemoattractant, *LIF* leukemia inhibitory factor, *LIX* lipopolysaccharide-induced CXC chemokine, *LPS* lipopolysaccharide, *MCP* monocyte chemoattractant protein, *M-CSF* monocyte colony-stimulating factor, *MIA* maternal immune activation, *MIP* macrophage inflammatory protein, *NaCl* sodium chloride, *OX-42* general macrophage-associated marker, *PND* postnatal day, *Poly I:C* polyinosinic-polycytidylic acid, *RANTES* regulated upon activation normal T-cell expressed and secreted, *STAT1* signal transducer and activator of transcription 1, *TGF-β* transforming growth factor-β, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor

Several microglial cells presented phagosomes and/or degenerated mitochondria (Wierzba-Bobrowicz et al. 2004). The dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus, and mediodorsal thalamus were evaluated in 16 schizophrenic brain samples. HLA-DR-positive cell expression was not different between the schizophrenia and control groups. The post-mortem interval correlated with the ramified cell numbers in the anterior cingulate cortex and the dorsolateral prefrontal cortex and with the amoeboid cell density in the hippocampus. Two schizophrenic patients who had committed suicide during acute psychosis presented highly elevated microglial cell numbers in the anterior cingulate cortex and the mediodorsal thalamus (Steiner et al. 2006). In another study from the same research group, microglial HLA-DR expression was evaluated in the dorsolateral prefrontal cortex, anterior cingulate cortex, mediodorsal thalamus, and hippocampus of 16 schizophrenic patients. Microglial HLA-DR expression did not presently affect the diagnosis of microglial density in the dorsolateral prefrontal cortex, anterior cingulate cortex, mediodorsal thalamus, and hippocampus. However, the study found microgliosis in the dorsolateral prefrontal cortex, cingulate cortex, and mediodorsal thalamus of the schizophrenic suicide patients (Steiner et al. 2008). In a study by Sinkus et al., the mRNA levels for the MHC class I antigen HLA-B was increased in schizophrenic nonsmokers, while the levels for smokers were indistinguishable from those of controls. HLA-A was expressed in a pattern where inflammatory illness was associated with increased expression in controls but not in subjects with schizophrenia (Sinkus et al. 2013). Radewicz et al. found an increase of HLA-DR expression in the dorsolateral prefrontal cortex in eight schizophrenics compared with ten controls. Regarding the superior temporal gyrus, there was an increase in microglia in seven schizophrenics compared with ten controls. In the anterior cingulate gyrus, the results did not reach significance (Radewicz et al. 2000). Calprotectin is a calcium-binding protein of the S100 family and is a nonspecific inflammatory marker. Samples of post-mortem brain tissue from Brodmann area 9 were obtained from the prefrontal cortices of subjects with schizophrenia and of controls. Calprotectin presented higher levels in the schizophrenic brains (Brodmann area 9 from prefrontal cortex) compared to the controls, and this protein was found to localize in microglial cells (Foster et al. 2006).

Through investigation of the microglial activation using Iba1 antibody marker, which is expressed in macrophages and microglia and is upregulated during the activation of these cells, the brain samples presented unaltered immunoreactivity in the cingulate white matter (Connor et al. 2009) and the dorsolateral prefrontal cortex in the post-mortem schizophrenic brain (Hercher et al. 2014). Moreover, in another study, the regional differences in the ependymal and subventricular zone cytoarchitecture were unchanged in schizophrenic brain samples (Comte et al. 2012). CD68 was evaluated for resting and active microglia in the caudate nucleus and the mediodorsal nucleus of the thalamus in a post-mortem study of 11 elderly people with schizophrenia. No differences were found between the schizophrenic and control subjects (Falke et al. 2000). HLA-DRA did not present any differences in the dorsolateral prefrontal cortex or the parietal cortex samples between the schizophrenic and control groups (Nakatani et al. 2006). Messenger RNA expression of

HLA-A did not present any differences in the frontal cortex of schizophrenic subjects compared to control subjects (Saetre et al. 2007). The temporal cortex of the schizophrenic brain samples did not present differences in HLA-DRB3 and HLA-DPA1 expression compared with control brain samples (Schmitt et al. 2011). Another study evaluated the MHC class I and complement protein C3 expression in two frontal cortical regions of post-mortem brains of schizophrenic patients. MHC class I protein expression was decreased in the dorsolateral prefrontal cortex, but the protein expression did not present any change in the orbitofrontal cortex of nonsmoking schizophrenic patients, and this study did not find any association between schizophrenia and changes in C3 mRNA expression (Kano et al. 2011). A subsequent study presented a reduction in microglial immunoreactivity for the endogenous NMDA receptor agonist, quinolinic acid, in the hippocampus of schizophrenic patients and presented no difference in HLA-DR expression between schizophrenic and the control group brain samples (Gos et al. 2014). The MHC class II receptors HLA-DR and HLA-DRBA were downregulated in the temporal lobe of schizophrenic post-mortem brain samples (Durrenberger et al. 2015). No differences were found in the CD40 and HLA-DP/DQ/DR markers in four brain samples of schizophrenic patients (Togo et al. 2000). CD68 for resting and active microglia was evaluated in the entorhinal cortex, the subiculum and CA1 of the hippocampus, midfrontal cortex, orbitofrontal cortex, and calcarine cortex in schizophrenic brain samples. There were no differences between the schizophrenic and the control brain samples in the densities of any of the markers (Arnold et al. 1998). Kurumaji et al. evaluated [3H] PK 11195 as a ligand for the translocator protein (TSPO) receptor in the cerebral cortex, thalamus, and extrapyramidal system of the post-mortem brains of 13 chronic schizophrenics and 10 control subjects. The [^{3}H] PK 11195-specific binding was decreased in the superior parietal cortex, primary visual area, and putamen of schizophrenics, although there were no changes in this binding in the other brain areas (Kurumaji et al. 1997); see Table 2.

3.2 Cytokine and Chemokine Evaluation in Post-mortem Schizophrenic Brain Samples

In a clinical study, the mRNA expression of IL-6, IL-8, and SERPINA-3 presented higher levels in the dorsolateral prefrontal cortex of individuals with schizophrenia compared with their controls (Fillman et al. 2013). IL-6, IL-1β, IL-8, and SERPINA-3 mRNA levels were quantified in the contralateral fresh frozen orbitofrontal cortex. The volumes of the cortical gray matter and the superior frontal gyrus had a significant negative correlation with IL-1β, IL-6, and SERPINA-3 mRNA levels in the schizophrenic group. Thus, cortical gray matter volume reduction in schizophrenic patients was associated with neuroinflammation, and the researchers also found that the expression of inflammatory mRNA in the orbitofrontal cortex was correlated with those found by Fillman et al. (2013), in the dorsolateral prefrontal

Table 2 Microglial and neuroinflammatory markers in schizophrenic post-mortem brain samples

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 23$) and control ($n = 14$)	Ventromedial temporal and frontal lobe and the calcarine	CD68	No statistically significant differences were found between the patients with schizophrenia and the control patients without neuropsychiatric disease for the densities of any of the markers	Arnold et al. (1998)
Schizophrenia (residual $n = 9$ and paranoid $n = 9$) and control ($n = 22$)	Dorsal raphe nucleus	HLA-DR and AgNOR	There was no change in the density of HLA-DR-positive microglial reaction in schizophrenic patients (residual and paranoid) compared to controls. Thus, a positive correlation existed between microglial densities evaluated by the AgNOR silver staining parameter in a residual subgroup of schizophrenic patients, which revealed a significant increase in this subgroup	Brisch et al. (2017)
Schizophrenia ($n = 15$) and control ($n = 15$)	Zona subventricular	MHC II	There were no differences between schizophrenic patient groups and controls in the width of the hypocellular gap or in the density of cells in the hypocellular gap. Because ventricular enlargement in schizophrenia may disrupt ependymal cells, we quantified them but observed no difference between diagnostic groups and controls	Comte et al. (2012)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 22$) and control ($n = 45$)	Cingulate cortex	Iba1	No significant difference in Iba1 immunoreactivity between groups. It was not associated with NeuN+ density in white matter	Connor et al. (2009)
Schizophrenia ($n = 10$) and control ($n = 10$)	Temporal lobe	IL-13RA1, MHC II, HLA-DRA, and HLA-DPA1	The MHC II receptors, HLA-DRA, and HLA-DPA1 were significantly upregulated in neurodegenerative disorders and downregulated in schizophrenia. IL-13RA1 was significantly downregulated in schizophrenia	Durrenberger et al. (2015)
Schizophrenia ($n = 12$) and control ($n = 11$)	Caudate nucleus and mediodorsal nucleus	CD68	No statistically significant differences were found between schizophrenic and control subjects for the densities of any markers. There was no evidence that abnormal neurodegeneration occurs in these two important subcortical structures	Falke et al. (2000)
Schizophrenia ($n = 37$) and control ($n = 37$)	Dorsolateral prefrontal cortex	IL-1β, IL-6, IL-6ST, IL-8, and SERPINA-3	The individuals presented increased levels of IL-1β, IL-6, IL-8, and SERPINA-3 mRNA expression ($p < 0.001$). Other characteristics of this group included high mRNA expression of IL-6ST ($p < 0.033$)	Fillman et al. (2013)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 35$) and control ($n = 35$)	Dorsolateral prefrontal cortex	IL-1β, IL-1RL1, IL-6, IL-8, IL-6ST, PTGS2, IL-18, SERPINA-3, and TNF	The SERPINA-3 mRNA was specifically increased in schizophrenic brain samples ($p < 0.05$) compared with both controls; IL-8 mRNA showed a significant diagnostic effect ($p < 0.05$), but surprisingly, with a decreased expression in individuals with schizophrenia compared with controls. IL-1β, IL-18, TNF, and PTGS2 mRNAs showed no significant diagnostic effects overall and no consistent pattern of expression according to diagnosis. IL-1RL1 and IL-6 mRNAs were not significantly changed	Fillman et al. (2014)
Schizophrenia ($n = 15$) and control ($n = 15$)	Dorsolateral prefrontal cortex	Calprotectin	Calprotectin was detectable in all samples, and mean levels were noted to be highest in schizophrenic brains ($p < 0.05$) and lowest in controls	Foster et al. (2006)
Schizophrenia ($n = 30$) and control ($n = 30$)	Prefrontal cortex	TLR-4, MyD88, mRNA, NF-κB, p65, κBα, RNA, IL-1β, IL-6, iNOS, COX-2, MDA, and NO_2	TLR-4, MyD88, and NF-κB expression increased in the prefrontal cortex of patients with schizophrenia. These alterations seem to depend on the presence/absence of antipsychotic treatment at death	Garcia-Bueno et al. (2016)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 13$) and control ($n = 12$)	CA1, CA2/CA3, and dentate gyrus hippocampal	HLA-DR	Fewer quinolinic acid-immunoreactive microglial cells were observed in the CA1 hippocampal subregion of schizophrenic patients compared to controls (left $p = 0.028$, right $p = 0.018$). No significant diagnosis-dependent changes were observed in the CA2/CA3 and dentate gyrus regions	Gos et al. (2014)
Schizophrenia ($n = 35$) and control ($n = 33$)	Frontal cortex	IFN-γ	IFN-γ demonstrated high levels significantly different between schizophrenia and control samples ($p = 0.043$)	Harris et al. (2012)
Schizophrenia ($n = 20$) and control ($n = 20$)	Dorsolateral prefrontal cortex	Iba1	The density of Iba1-stained microglia did not differ among the groups; however, a qualitative assessment of microglial morphology found numerous activated microglial cells in three schizophrenic samples, but not in the controls	Hercher et al. (2014)
Schizophrenia ($n = 35$) and control ($n = 35$)	Dorsolateral prefrontal cortex	MHC I	The MHC I protein expression was reduced in the dorsolateral prefrontal cortex but not in the orbitofrontal cortex of schizophrenic patients	Kano et al. (2011)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 13$) and control ($n = 10$)	Cerebral cortex, thalamus, and extrapyramidal system	[3H] PK 11195	The specific [3H] PK 11195 binding was significantly decreased in three brain areas (superior parietal cortex, primary visual area, and putamen) of schizophrenics, although there were no changes in the binding in the other brain areas	Kurumaji et al. (1997)
Schizophrenia ($n = 16$) and control ($n = 14$)	Prefrontal cortex and cerebellum	TLR-4, MyD88, κBα, iNOS, MDA, NF-κB, and COX-2	In the prefrontal cortex, TLR-4, MyD88, and IκBα protein levels were lower in schizophrenic patients, while NF-κB activity, COX-2 expression, and the MDA appeared to be increased. In the cerebellum it occurred opposite, except for COX-2 expression that remained augmented and MDA levels unaltered	MacDowell et al. (2017b)
Schizophrenia ($n = 7$) and control ($n = 7$)	Dorsolateral prefrontal cortex	HLA-DRA, HLA-DRB4, and CCL3	The expression of CCL3 was downregulated in schizophrenia. The expression of the HLA-DRA and HLA-DRB4 genes was not altered in schizophrenia	Nakatani et al. (2006)
Schizophrenia ($n = 8$) and control ($n = 10$)	Dorsolateral prefrontal cortex, the superior temporal gyrus, and the anterior cingulate gyrus	GFAP and HLA-DR	There was an increase of HLA-DR expression in the dorsolateral prefrontal cortex in eight schizophrenics	Radewicz et al. (2000)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
			compared with ten controls. For the superior temporal gyrus, there was an increase in microglia in seven schizophrenics compared with ten controls. In the anterior cingulate gyrus, the results did not find significance	
Schizophrenia ($n = 55$) and control ($n = 55$)	Frontal cortex	IFITM-2, IFITM-3, SERPINA-3, GBP1, SCD, MAG, and TF	IFITM-2, IFITM-3, SERPINA-3, and GBP1 showed increased mRNA levels in schizophrenic brain samples ($p \leq 0.01$)	Saetre et al. (2007)
Schizophrenia ($n = 10$) and control ($n = 10$)	Temporal cortex	IL-1α, IL-1β, IL8, IL-1RAP, CCL2, HLA-DPA1, and HLA-DRB3	A microarray analysis, followed by qPCR validation, found a decrease in IL-8 and IL-1α mRNA expression in the temporal cortex of schizophrenic patients compared with healthy control patients. However, increases detected in the microarray were not reproduced by qPCR for cytokines and chemokines such as IL-1β and CCL2	Schmitt et al. (2011)
Schizophrenic smokers ($n = 28$), schizophrenic non-smokers ($n = 14$), control smokers ($n = 23$), and	Hippocampus	HLA-A and HLA-B	Messenger RNA levels for the class I major histocompatibility complex antigen HLA-B were increased in schizophrenic non-smokers, while levels for smokers	Sinkus et al. (2013)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
control non-smokers ($n = 24$)			were indistinguishable from those of controls. β2-macroglobulin, HLA-A, and Notch4 were all expressed in a pattern where inflammatory illness was associated with increased expression in controls but not in subjects with schizophrenia	
Schizophrenia ($n = 17$) and control ($n = 11$)	Hippocampus	CD3, CD20, and HLA-DR	Higher densities of CD3 and CD20 lymphocytes were observed in residual versus paranoid schizophrenia. In contrast, HLA-DR microglia was increased in paranoid schizophrenia versus residual schizophrenia	Steiner et al. (2006)
Schizophrenia ($n = 16$) and control ($n = 16$)	Dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus and mediodorsal thalamus	HLA-DR	Immunostaining was found in all brain regions and was not restricted to macrophage-like amoeboid cells but also appeared in ramified cells. Region-specific HLA-DR-positive cell density was not significantly different between cases with schizophrenia and controls. However, amoeboid microglial cells were lateralized toward the right hemisphere in healthy subjects but not in the schizophrenia group	Steiner et al. (2006)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
			($p = 0.01$). Post-mortem interval correlated with ramified cell numbers in the anterior cingulate cortex ($p = 0.01$), the dorsolateral prefrontal cortex ($p = 0.04$), and amoeboid cell density in hippocampus ($p = 0.03$)	
Schizophrenia ($n = 9$) and control ($n = 6$)	Frontal lobes and gyrus temporal inferior	HLA-DP, DQ, and DR	Frontal and temporal lobes of chronic schizophrenic patients presented higher microglial cell activation compared with control brains. However, the first layer of the cerebral cortex presented the same amounts of well-developed ramification and degenerative traits and damaged processes; the number of DM cells in the remaining regions was higher than that of RM cells	Steiner et al. (2008)
Schizophrenia ($n = 16$) and control ($n = 10$)	Dorsolateral prefrontal cortex, anterior cingulate cortex, hippocampus and mediodorsal thalamus	HLA-DR	The results revealed no effect of diagnosis on microglial density (dorsolateral prefrontal cortex ($p = 0.469$), anterior cingulate cortex ($p = 0.349$), mediodorsal thalamus ($p = 0.569$), and hippocampus ($p = 0.497$)). However, significant microgliosis was observed in the	Steiner et al. (2008)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
			dorsolateral prefrontal cortex ($p = 0.004$), anterior cingulate cortex ($p = 0.012$), and mediodorsal thalamus ($p = 0.004$) of suicide patients. A similar trend was seen in the hippocampus ($p = 0.057$)	
Schizophrenia ($n = 4$)	Hippocampus and temporal exocortex	CD40	Vascular expression of CD40 was enhanced in the lesions of schizophrenia disease	Togo et al. (2000)
Schizophrenia ($n = 22$) and control ($n = 14$)	Prefrontal cortex	IL-1β and IL-1RA	Both protein and mRNA levels of IL-1RA were specifically decreased in the prefrontal cortex of schizophrenic patients, whereas IL-1β levels were not significantly altered in all the regions examined. The IL-1RA decrease was not correlated with the dose of antipsychotics given to patients. There was no influence of this illness on protein levels for IL-1β receptor type 1 in the prefrontal cortex	Toyooka et al. (2003)
Schizophrenia ($n = 62$) and control ($n = 62$)	Frontal cortex	IL-1β, IL-6, IL-8, IFN-β, NF-κB, and Schnurri-2	Schizophrenic subjects had markedly higher mRNA levels for IL-1β, IL-6, and IFN-β, which induce IFITM expression; lower mRNA levels	Volk et al. (2015)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
			for Schnurri-2, a transcriptional inhibitor that lowers IFITM expression; and higher mRNA levels for NF-κB. IL-8 did not quite reach statistical significance	
Schizophrenia ($n = 14$) and control ($n = 13$)	Frontal cortex and hippocampus	HLA-DR	Schizophrenic patients revealed subjects with abundant microglial immunostaining in both gray and white matter. This finding provides evidence for distinct neuropathological changes in brains of patients with schizophrenia	Wierzba-Bobrowicz et al. (2004)
Schizophrenia ($n = 12$)	Frontal and temporal cortex	MHC II	Most cells showed degenerative traits (cytoplasm shrinkage, thinning, shortening, and fragmentation of their processes) up to apoptotic changes. Perivascular microglia displayed the lowest intensity of degenerative changes. Ultrastructurally, some damaged microglial cells contained phagosomes and/or degenerated mitochondria. Most abnormal microglia showed morphological signs of the former normal function of immunocompetent and phagocytosing cells	Wierzba-Bobrowicz et al. (2004)

(continued)

Table 2 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 47$) and control ($n = 45$)	Orbitofrontal cortex	IL-1β, IL-6, IL-8, and SERPINA-3	The volumes of cortical gray matter and superior frontal gyrus were significantly negatively correlated with IL-1β, IL-6, and SERPINA-3 mRNAs levels in the schizophrenia group. Thus, cortical gray matter volume reduction in schizophrenic patients was associated with neuroinflammation. The expression of inflammatory mRNAs in the orbitofrontal cortex was significantly correlated with those found in studies in the dorsolateral prefrontal cortex	Zhang et al. (2016)

[3H] PK 11195 1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide, *AgNOR* argyrophilic nucleolar organizing region, *CCL2* chemokine (C-C motif) ligand 2, *CCL3* chemokine (C-C motif) ligand 3, *CD11b* microglial marker, *COX-2* cyclooxygenase-2, *GBP1* guanylate-binding protein 1, *GFAP* glial fibrillary acidic protein, *GM-CSF* granulocyte/monocyte colony-stimulating factor, *HLA* human leukocyte antigen class I (A, B, C), *HLA* human leukocyte antigen class II (DR [A, alpha; B, beta], DQ, DM, and DP), *Iba1* ionized calcium-binding adaptor molecule, *IFITM* interferon-induced transmembrane, *IFN* interferon, *IL* interleukin, *IL-13RA1* interleukin 13 receptor alpha 1, *IL-1RA* interleukin 1 receptor accessory, *IL-1RAP* interleukin 1 receptor accessory protein, *IL-1RL1* interleukin 1 receptor-like 1, *IL-2R* interleukin-2 receptor, *IL-6ST* interleukin 6 signal transducer, *iNOS* inducible nitric oxide synthase, *κBα* inhibitory protein, *MAG* myelin-associated glycoprotein, *MDA* malondialdehyde, *MHC I and II* major histocompatibility complex class I and II, *mRNA* relative messenger RNA, *MyD88* myeloid differentiation factor 88, *NeuN* neuron-specific nuclear protein, *NF-κB* nuclear factor kappa B, NO_2 nitrite levels, *PTGS2* prostaglandin-endoperoxide synthase 2, *qPCR* quantitative polymerase chain reaction, *RNA* ribonucleic acid, *SCD* stearoyl-CoA desaturase, *Schnurri-2* inhibits NF-κB function, *TF* transferrin, *TGF-β* transforming growth factor-β, *TLR-4* Toll-like receptors 4, *TNF* tumor necrosis factor

cortex, except for IL-8 (Zhang et al. 2016). SERPINA-3 mRNA was also present at high levels in the dorsolateral prefrontal cortex of individuals with schizophrenia (Fillman et al. 2014). IFN-γ, as evaluated by the ELISA technique, was elevated in

the BA10 brain region of schizophrenic patients (Harris et al. 2012). Schizophrenic subjects presented markedly higher mRNA levels of IL-6, IFN-β, and NF-κB transcription factor in the prefrontal cortex compared with the control group (Volk et al. 2015). TNF receptor 1 (TNFR1) mRNA was significantly increased in both Brodmann areas 24 (BA24) and 46 (BA46) in patients with schizophrenia (Dean et al. 2013). In contrast, IL-1β mRNA levels were not changed in post-mortem brain tissues of the prefrontal or parietal cortices, putamen, or the hypothalamus. In addition, endogenous IL-1 receptor antagonist (IL-1RA) decreased in the prefrontal cortex of schizophrenic patients (Toyooka et al. 2003). IL-13 receptor alpha-1 (IL-13RA1) was downregulated in the temporal lobe of schizophrenic patients (Durrenberger et al. 2015). Chemokine (C-C motif) ligand 3 (CCL3) gene expression was also downregulated in the dorsolateral prefrontal cortex and parietal cortex (Nakatani et al. 2006), and in the temporal cortex, the expression of IL-1α and IL-8 was downregulated in schizophrenic brain samples (Schmitt et al. 2011); see Table 2.

4 Mechanisms by Which Neuroinflammation Could Influence the Development of Schizophrenia

During pregnancy or early life infection, replication of microorganisms and the release of their immunogenic compounds can occur. These immunogenic compounds derived from microorganisms are denominated as pathogen-associated molecular patterns (PAMPs), and they are recognized by the immune system through equipped receptors denominated as pattern-recognition receptors (PRRs) (Barichello et al. 2015; Morris et al. 2018). These receptors, such as Toll-like receptors (TLR), nucleotide-binding oligomerization domain (NOD)-like receptors (NLR), C-type lectin receptors (CLR), retinoic acid-inducible gene-1 (RIG-1)-like receptors (RLR), receptors for advanced glycation end products (RAGE), and intracytosolic deoxyribonucleic acid (DNA) sensors, are crucial components in the activation of the innate immune system (Keestra-Gounder and Tsolis 2017; Zhou et al. 2017). The PRRs can also recognize a broader array of endogenous danger signals such as adenosine 5-triphosphate (ATP), heat shock proteins (HSPs), and high mobility group box-1 proteins (HMGB-1) that are denominated as damage-associated molecular patterns (DAMPs) (Nakahira et al. 2015; Wilkins et al. 2017); see Figs. 1 and 2.

TLR receptors are divided into two groups, of which one is expressed on the cell membrane for ligand recognition (TLR-1, TLR-2, TLR-4, TLR-5, TLR-6, and TLR-10) and the other is localized in the intracellular endosomal space for the recognition of pathogen nucleic acids: TLR-3, TLR-7, TLR-8, and TLR-9 (Kigerl et al. 2014). TLR-3 can signal through a TRIF-dependent pathway that recruits the TNF receptor-associated factor-3 (TRAF-3), thus resulting in the activation of interferon regulatory factor-3 (IRF-3) and IRF-7. This pathway triggers the

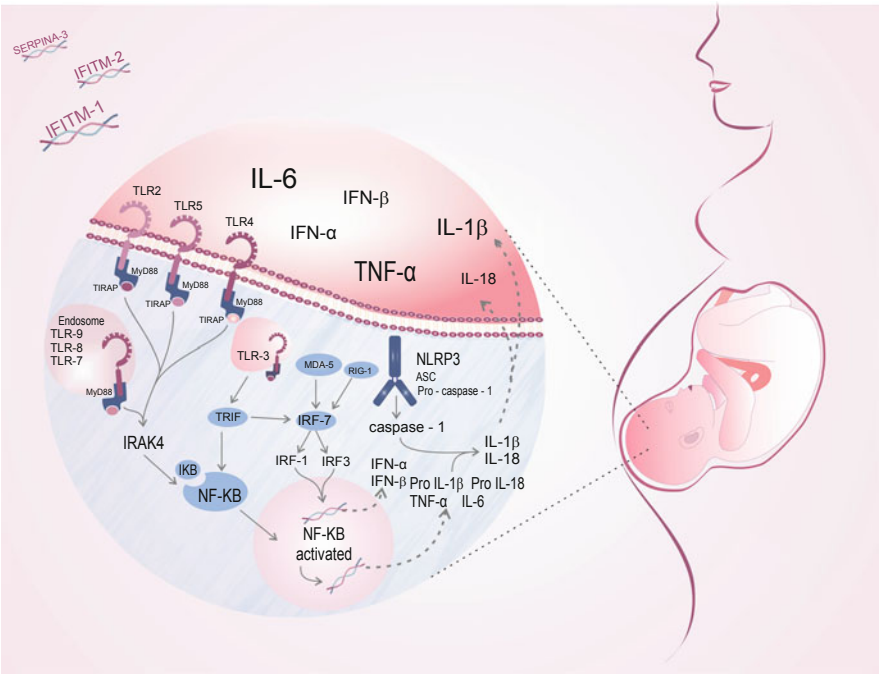

Fig. 2 Maternal immune activation and a possible mechanism in which neuroinflammation could influence the development of schizophrenia. TLRs, MDA-5, and RIG-1 are innate immune sensors involved in the detection of microorganisms. TLR-3, RIG-1, and MDA-5 promote the expression of type I and type III IFNs and the NF-kappa B-dependent expression of pro-inflammatory cytokines. Maternal immune activation increases the levels of cytokines such as IL-6, TNF-α, and IL-1β in the serum, as well as in the amniotic fluid, placenta, and fetal brain. *ASC* caspase-recruitment domain; *IFITM-1, IFITM-2* interferon-induced transmembrane protein-1, interferon-induced transmembrane protein-2; *IFN-α, IFN-β* interferon-α, interferon-β; *IκB* inhibitors of NF-κB; *IL-1β, IL-6, IL-18* interleukin-1β, interleukin-6, interleukin-18; *IRAK-4* interleukin receptor-associated kinase-4; *IRF-1, IRF-3, IRF-7* interferon regulatory factor-1, interferon regulatory factor-3, interferon regulatory factor-7; *MDA-5* melanoma differentiation-associated gene 5; *MyD88* myeloid differentiation factor 88; *NF-κB* nuclear factor kappa B; *NLRP-3* NLR family pyrin domain containing-3; *RIG-1* retinoic acid-inducible gene-1; *SERPINA-3* serpin family A member-3; *TIRAP* domain-containing adaptor protein; *TLR* Toll-like receptor; *TNF-α* tumor necrosis factor alpha; *TRAF-3, TRAF-6* TNF receptor-associated factor-3, TNF receptor-associated factor-6; *TRIF* Toll/IL-1 receptor domain-containing adaptor-inducing interferon-β

production of type I interferons, such as IFN-α or IFN-β. In another pathway, TLR-3 activates TRIF, AP1, and NF-κB, inducing the expression of pro-inflammatory cytokine genes. TLR-3 serves as a sensor of dsRNA produced during the replication of single-stranded RNA (ssRNA) and is also activated by a synthetic chemical compound analogue of dsRNA, Poly I:C (Verma and Bharti 2017). TLR-3 is an essential sensor of the host's immune responses to protect it against viral infections. A pre-clinical model of schizophrenia demonstrated high expression of TLR-3 signaling, IFN-α, and IFN-β in the frontal cortex of adult offspring subjected to

maternal immune activation by Poly I:C during fetal life (MacDowell et al. 2017a). In addition, TLR-3 activation inhibited embryonic neuronal stem cell replication and population of the superficial layers of the neocortex by neurons (de Miranda et al. 2010).

TLR-4, CD14, and myeloid differentiation protein-2 (MD-2) form a complex heteromer that, after activation, recruits the MyD88 adapter-like (Mal) and the TIR domain-containing adaptor protein (TIRAP). Mal/TIRAP recruits myeloid differentiation primary response gene 88 (MYD88) adaptor. The MyD88 adaptor molecule connects with the serine/threonine kinase IL-1 receptor-associated protein leading to phosphorylation of IRAK-1 and IRAK-2 and the recruitment of TNF receptor-associated factor-6 (TRAF-6) adaptor. TRAF-6 activates inhibitory IκB kinases (IkBα and IkBβ) and mitogen-activated protein kinases (MAPKs), resulting in NF-κB and activator protein-1 (AP-1) transcription factor activation and production of cytokines. In parallel, the TLR4 complex also recruits TRIF-related adaptor molecules that interact with TRIF adaptor and activate the interferon regulatory factor-3 (IRF-3) transcription factor. The post-mortem cerebellum of human schizophrenic subjects presented an increase in protein expression of TLR-4, MyD88, and IκBα. In contrast, NF-κB activity was reduced, iNOS expression was not changed, while cyclooxygenase-2 (COX-2) protein levels were increased and there were no changes in lipid peroxidation (MDA). In the post-mortem schizophrenic prefrontal cortex, TLR-4, MyD88, and IκBα protein levels were lower in schizophrenic patients, while nuclear transcription NF-κB activity, COX-2 expression, and malondialdehyde (MDA) were increased (MacDowell et al. 2017b). Another study found evidence of alterations in the expression of the TLR-4 signaling and MyD88 and NF-κB in the prefrontal cortex of patients with schizophrenia. However, there were no changes in the IκBα protein levels, IL-1β, and IL-6 mRNA levels in the prefrontal cortex. An additional study evaluated the effect of antipsychotic treatment on schizophrenic post-mortem brain samples. The antipsychotic treatment schizophrenic group presented higher levels of TLR-4, MyD88 protein, and MyD88 mRNA compared to control samples. An MDA decrease was observed in the antipsychotic-free group compared to the control and antipsychotic treatment groups, but the antipsychotic-free group presented high levels of NF-κB protein compared with controls. This study demonstrated that it is necessary to pay special attention to the potentially confounding factor of antipsychotic treatment, because these alterations seem to depend on the presence or absence of antipsychotic treatment at death (Garcia-Bueno et al. 2016).

A number of studies have shown an increase in expression of SERPINA-3 and its gene in schizophrenic brain samples (Arion et al. 2007; Fillman et al. 2013, 2014; Zhang et al. 2016). The transcriptome signature of altered genes related to immune function may be a consequence of high levels of pro-inflammatory cytokines such as IL-6, TNF-α, IL-1β, or IFNs, during the stages of prenatal development or during early life. These pro-inflammatory mediators could not only alter brain development but also be responsible for these immune-/inflammation-related genes such as SERPINA-3, interferon-induced transmembrane protein (IFITM)-1, IFITM-2, and IFITM-3 that are found in the schizophrenic adult brain (Arion et al. 2007; Saetre et al. 2007; Hwang et al. 2013; Volk et al. 2015); see Tables 2 and 3.

Table 3 Neuroinflammatory markers in the CSF of schizophrenic patients

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 16$) and control ($n = 10$)	CSF	IL-lβ, IL-2, IL-2R, IL-6, and TNF-α	No significant differences were found in levels of TNF-α and IL-2 or IL-6 in CSF fluid. IL-1β and IL-2R were significantly decreased in patients' CSF compared to controls	Barak et al. (1995)
Schizophrenia ($n = 14$) and control ($n = 16$)	CSF	IL-1β, IFN-γ, IL-10, IL-6, and TNF-α	Schizophrenia patients showed a significant increase in IL-6 in CSF ($p = 0.02$). IL-1β, IFN-γ, IL-10, and TNF-α were often below the levels of detection of this assay	Coughlin et al. (2016)
Schizophrenia ($n = 16$) and control ($n = 11$)	CSF	IL-lα and IL-2	IL-1α levels were found below the detection limits of the assay in both controls and the schizophrenic groups, and there were no statistically significant differences of IL-1α and IL-2 between the schizophrenic and control groups	el-Mallakh et al. (1993)
Schizophrenia ($n = 31$) and control ($n = 14$)	CSF	IL-6	In the CSF, IL-6 was found to be significantly higher in the subtypes of schizophrenics "delayed responder" than the "poor responders" ($p = 0.017$) and the controls ($p = 0.013$)	Garver et al. (2003)
Schizophrenia ($n = 14$) and control ($n = 9$)	CSF	IL-1β and IL-6	IL-1β and IL-6 CSF levels did not present a significant difference between medicated schizophrenic patients and controls	Katila et al. (1994)
Schizophrenia ($n = 10$) and control ($n = 10$)	CSF	IL-1α and IL-2	IL-2 levels in the CSF were found higher in neuroleptic-free schizophrenic patients compared to control group. The levels of IL-1α did not present significant difference	Licinio et al. (1993)
Schizophrenia ($n = 60$) and control ($n = 21$)	CSF	IL-1α and IL-2	There were no differences between schizophrenic patients and normal volunteers in measures of CSF IL-lα and IL-2	Rapaport et al. (1997)

(continued)

Table 3 (continued)

Number of patients and controls	Sample	Biomarkers evaluated	Results	Reference
Schizophrenia ($n = 32$) and control ($n = 35$)	CSF	IL-6	Patients with schizophrenia had significantly higher CSF IL-6 levels compared to the controls ($p = 0.0027$)	Sasayama et al. (2013)
Schizophrenia ($n = 23$) and control ($n = 37$)	CSF	IL-1β, IL-2, IL-4, IL-6, IL-8, 1L-10, IL-18, TNF-α, IFN-α-2a, and IFN-γ	Patients with schizophrenia had increased CSF levels of IL-6 compared with healthy volunteers	Schwieler et al. (2015)
Schizophrenia ($n = 26$) and control ($n = 30$)	CSF	IL-1β, IL-6, IL-8, IL-2, IL-4, IL-5, IL-10, GM-CSF, IFN-γ, and TNF-α	IL-1β, IL-6, and IL-8 were reliably detectable in CSF of both patients and controls. IL-2, IL-4, IL-5, IL-10, GM-CSF, IFN-γ, and TNF-α were found in low concentrations or were undetectable in both patients and controls. In patients, IL-1β concentrations were markedly elevated compared with controls	Soderlund et al. (2009)
Schizophrenia ($n = 85$) and control ($n = 51$)	CSF	TGF-β1 and TGF-β2	TGF-β1 and TGF-β2 did not present any differences in the CSF of chronic schizophrenic patients and the control group	Vawter et al. (1997)

CSF cerebrospinal fluid, *GM-CSF* granulocyte/monocyte colony-stimulating factor, *IFN* interferon, *IL* interleukin, *IL-2R* interleukin-2 receptor, *TGF-β* transforming growth factor-β, *TNF* tumor necrosis factor

5 Conclusion

There are a significant number of studies showing an increase in microglial markers and pro-inflammatory gene expression in the post-mortem brains of schizophrenic patients compared with controls. The transcriptome signature of altered genes related to immune function may be a consequence of high levels of pro-inflammatory cytokines during the stages of prenatal development or during early life. These pro-inflammatory mediators could not only alter brain development but also be responsible for these immune/inflammation-related genes found in the schizophrenic adult brain.

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