Schizophrenia Bulletin vol. 40 no. 6 pp. 1412–1421, 2014
doi:10.1093/schbul/sbu049
Advance Access publication April 7, 2014

Th17 Pathway–Mediated Immunopathogenesis of Schizophrenia: Mechanisms and Implications

Monojit Debnath*[,1] and Michael Berk[2,3]

[1]Department of Human Genetics, National Institute of Mental Health & Neurosciences, Bangalore, Karnataka, India; [2]IMPACT Strategic Research Centre, School of Medicine, Deakin University, Geelong, Victoria, Australia; [3]Department of Psychiatry, Florey Institute of Neuroscience and Mental Health, Orygen Youth Health Research Centre, University of Melbourne, Parkville, Australia

*To whom correspondence should be addressed; Department of Human Genetics, National Institute of Mental Health & Neurosciences, Hosur Road, Bangalore 560029, Karnataka, India; tel: +91-80-26995121, fax: +91-80-26564830, e-mail: monozeet@gmail.com

Schizophrenia is a highly complex and severe neuropsychiatric disorder with an unknown etiopathology. Evidence for a dysregulated immune system in both the risk for and progression of schizophrenia has recently been overwhelming. Importantly, chronic low-grade inflammation both in the periphery and central nervous system has been shown to contribute predominantly to the pathogenesis of schizophrenia in a subset of individuals. Inflammation in the central nervous system is mediated by a range of proinflammatory cytokines, resident immune cells such as microglia, and brain infiltrating peripheral immunocompetent cells, such as T lymphocytes. Recently, Th17 cells, a subset of T helper cells have emerged as crucial players in mucosal defense against infections. It is linked to atopic, inflammatory, and autoimmune disorders. The risk factors/mechanisms leading to low-grade inflammation in schizophrenia are diverse and include infectious agents, stress, trauma, environmental toxins, genetic vulnerability, physical inactivity, obesity, poor diet, and sleep disruption. Herein, we propose that fetal programming of cellular immune components driven by intrauterine adversity can lead to the generation of long-lasting effector/memory Th17 cells. Th17 cells can disrupt the blood-brain barrier, infiltrate the central nervous system, and, along with other cytokines and microglia, lead to neuroprogression through neuroinflammation in schizophrenia.

Key words: Th17 cells/IL-17 cytokine/inflammation/neuroprogression/schizophrenia/pathogenesis/etiology/fetal

Introduction

Schizophrenia has long been considered as a disorder involving the immune system. The macrophage-T lymphocyte theory of schizophrenia, proposed in 1992[1] became one of the strong propositions supporting autoimmune and/or immunoinflammatory origin of schizophrenia. This was further supported by multiple lines of evidence showing altered functions of immune cells and components.[2–4] Importantly, altered T-cell number and function has consistently been demonstrated in schizophrenia.[5] In acute schizophrenia, higher CD3+ and CD4+ T-cell numbers were observed.[6] A recent study demonstrated an activated T-cell network in schizophrenia.[7] Altered distributions of T-cell subsets in cerebrospinal fluid (CSF)[8] and higher densities of T lymphocytes were also reported in the hippocampus of patients with schizophrenia,[9] providing indirect evidence of blood-brain barrier (BBB) impairment and T-cell infiltration. Animal studies have elucidated that peripheral T-cell disruption can lead to cognitive and behavioral impairment, further implying the relevance of T cells in brain and behavior.[10] Interestingly, reduced number and diminished functions of T cells in schizophrenia have also been reported by few studies. Acute paranoid schizophrenia was found to be accompanied by a reduced T-cell defenses.[11] In vitro studies have demonstrated significantly reduced proliferative responses of T cells to stimulation in schizophrenia.[12] Such responses were found to be functionally related to cell cycle machinery, intracellular signaling, oxidative stress, and metabolism of T cells.[12] In addition, recent pathway analyses of data from genome-wide association studies suggest that genes related to immune functions, involved in antigen processing and cell adhesion molecules relevant to T cells, are significantly associated with schizophrenia.[13] Furthermore, epigenetic studies also indicated that several genes involved in the activation of T cells were differentially methylated in schizophrenia.[14] Taken together, these data strongly suggest a significant role of T cells in the pathophysiology of schizophrenia.

The T cells are a crucial component of the adaptive immune response. Upon activation, naive CD4+ T cells

differentiate into a variety of effector Th subsets, each with its unique cytokine profile and functions. The Th subsets were initially classified as Th1 and Th2 cells based on their ability to produce different patterns of cytokines and perform different effector functions.[15,16] Recently, a new subset of Th cells, termed as Th17 cells have been identified, which play critical roles in infection, autoimmunity, and inflammation, particularly in mucosal surfaces of the lungs, skin, and gut.[17,18] Th17 cells secrete high amounts of IL-17A, IL-17F, IL-21, IL-22, and GM-CSF. Its master regulator is the rorc gene, which encodes the gene for Retinoic-acid Receptor-related Orphan Receptor gamma t, RORγt.[19] Th17 cells display a great deal of context-dependent plasticity, either in clearing specific pathogens or in inducing autoimmune tissue inflammations.[20] In addition to Th17 cells, CD4+CD25+FOXP3 regulatory T (Treg) cells have also been recently described as classical Treg cells, essential in maintaining peripheral tolerance, suppressing activation of the immune system, preventing autoimmune diseases, and limiting chronic inflammation.[21] Emerging findings suggest an interplay between IL-17 producing Th17 cells and CD4+CD25+FOXP3 regulatory T cells in controlling inflammatory and autoimmune disorders.[22] In this article, we propose that maternal immune activation (MIA) induced by intrauterine infection and other factors can be accompanied by the preferential generation of Th17 cells that subsequently might lead to priming the process of neuroprogression in schizophrenia through neuroinflammation.

Role of Th17 Cells in Neuro-immune cross talk

Emerging research indicates that Th17 cells can infiltrate the central nervous system (CNS) through the capillary and postcapillary venules of the BBB by disrupting tight junctions of BBB via the direct effects of IL-17A and IL-22 on endothelial cells.[23] In fact, Th17 cell and human brain endothelial cell interactions are becoming increasingly important aspects of transmigration and CNS inflammation.[24] Th17 cells may reach the CNS from blood to the CSF at the choroid plexus.[25] This is supported by studies that Th17 cells constitutively express the chemokine receptor CCR6, whose ligand, CCL20, is also constitutively expressed by epithelial cells of choroid plexus.[26] It is noteworthy that a cytokine, IL-23, is specially known for its ability to generate, expand, and stabilize autoreactive Th17 cells. A study has demonstrated that IL-23 drives encephalo-tropism of Th17 cells by promoting BBB disruption.[27] Such brain-homing capability of Th17 cells might contribute to the neuroinflammation, implicated in the pathogenesis of many neurological disorders.

In parallel, given that Th17 cells play a predominant role in mucosal cell integrity and defense, the hypothesis that altered gut permeability may play a role in schizophrenia takes on another dimension.[28] This may be putatively related to impairment of the gut's ability to block uptake of exogenous psychotomimetic compounds or, akin to what is described in depression, may be related to commensal bacterial translocation and the development of autoimmunity.[29] A surrogate marker of bacterial translocation, soluble CD14, was shown to be elevated in schizophrenia.[30] Although these hypotheses remain tentative, and require further investigation, emerging research suggests that immunomodulatory properties of gut microbiota extend to the brain. Some specific intestinal microbial species known to induce Th17 cells can initiate the inflammatory cascade in the CNS. Germ-free mice colonized with segmented filamentous bacteria were found to have increased Th17 cells in both the colon and small intestine, as well as within the spinal cord and developed experimental autoimmune encephalomyelitis (EAE).[31]

It is being increasingly recognized that Th17 cells play a pivotal role in the pathogenesis of autoimmune encephalomyelitis and they have emerged as a new player of neuroinflammation in multiple sclerosis.[32–34] Th17 cells are found in focal lesions in EAE and intimately interact with CNS resident cells, such as astrocytes, microglia, and neurons.[35] Th17 cells activate microglia in the CNS and lead to local production of IL-1β, tumor necrosis factor-α, and IL-6, which strongly implies its key role in neuroinflammation. This is accomplished by generating reactive oxygen species in mitochondria for antimicrobial purposes,[36] resulting in oxidative stress,[37] which is increasingly considered a potential biomarker in the etiopathophysiology and clinical course of schizophrenia.[38] Oligodendrocyte lineage cells are found to be sensitive to IL-17-mediated toxicity.[39] Interestingly, in animal model of Alzheimer's disease, Th17 cell-mediated neuroinflammation is found to be involved in neurodegeneration.[40] Taken together, it has now been established both in animal and human that Th17 cells can initiate CNS autoimmunity by supporting Th17-cell pathogenecity.[41] Roles of Th17 cells in physiological and pathophysiological conditions are summarized in figure 1.

Hypothesis

On the basis of various direct and indirect data, a significant role of Th17 cells in the pathogenesis of schizophrenia is proposed. Higher percentages of Th17 cells were reported in recent onset, first-episode and drug-naive schizophrenia subjects.[7,42] In addition, levels of IL-17, a signature cytokine of Th17 pathway, were elevated in a drug naive, first-episode schizophrenia cohort.[42] Importantly, the proportion of Th17 cells and plasma levels of IL-17 were positively correlated with the overall severity of clinical symptoms based on Positive and Negative Symptoms Scale (PANSS) scores.[42] Contrary to this, decreased levels of IL-17 are also reported in

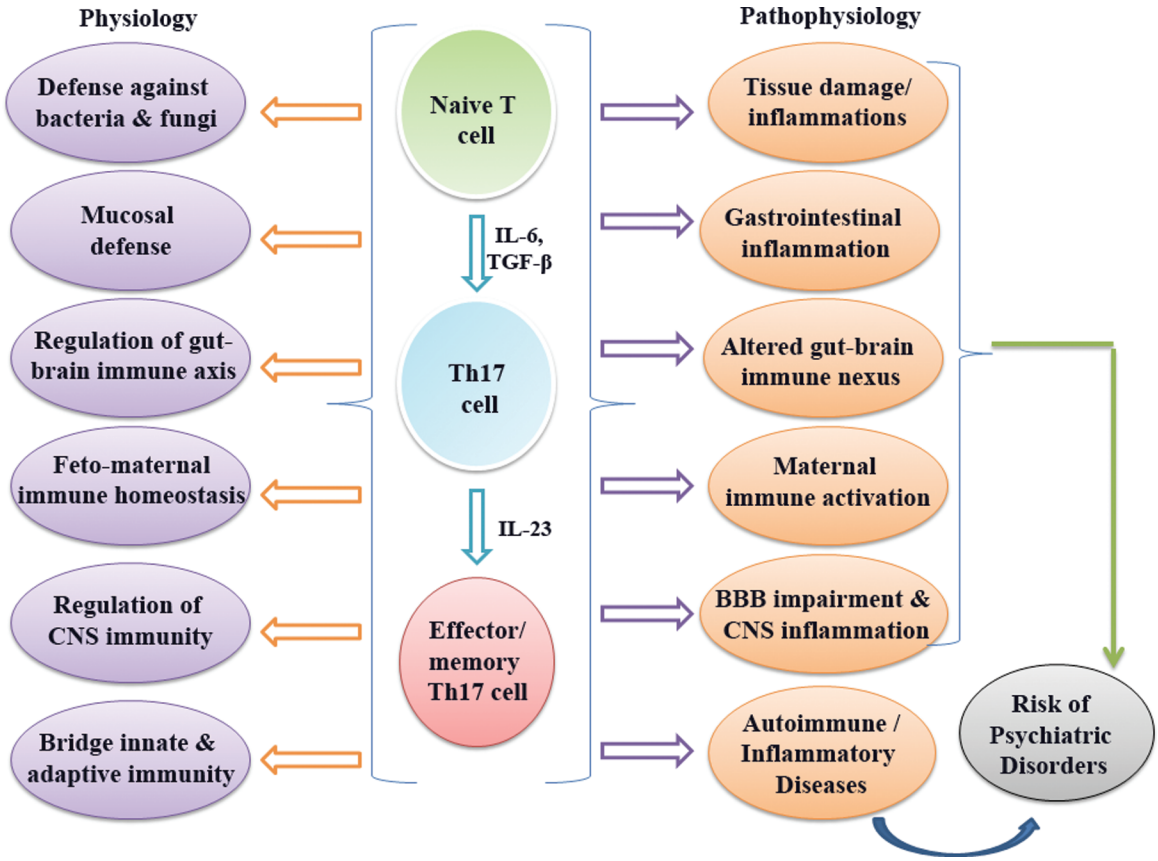

Fig. 1. Summary of functional roles of Th17 cells in physiology and pathophysiology.

schizophrenia.[43] Low levels of IL-17 were noted in first-episode and medication-free schizophrenia patients.[44] Decreased levels of IL-17 were also reported in chronic- and antipsychotic-medicated people with schizophrenia, where pathway analyses demonstrated that cytokines representing IL-17 pathway were positively correlated with PANSS scores,[45] indicating the potential role of IL-17 pathway in the etiology of schizophrenia.

The discrepancies in the above findings could be attributed to a number of parameters such as inadequate number of subjects studied, disease status (recent onset/chronic), types of cytokine evaluated, effects of age, sex, race, body mass index, smoking habits and psychotropic medications. Differentiation and maintenance of IL-17-producing Th17 cells are dependent on various transcription factors (RORγt, STAT3) and cytokines, such as IL-1, IL-1β, transforming growth factor-β (TGF-β), IL-23, and IL-6. Certain cytokines such as Interferon-γ (IFN-γ), IL-4, and IL-27 produced by Th1, Th2, and antigen-presenting cells, respectively, are known to suppress Th17 cells. Interestingly, in 1 study,[45] slightly lower levels of IL-1β, IL-6, and IL-17 were found, and in another study,[44] along with IL-6 and TGF-β, higher levels of Th17-suppressing cytokines such as IFN-γ, IL-4, and IL-27 were reported. Although TGF-β exerts both the immune-suppressive and proinflammatory functions, in inflammatory conditions, TGF-β promotes Th17 pathway. In addition to this, IL-23 is a potent initiator of Th17 pathway and IL-23/IL-17 axis acts as a critical mediator of autoimmune inflammatory diseases. A limitation of the above studies is that assessment of potential interactions between the Th17-activator (TGF-β/IL-1β/IL-6/IL-23), Th17-attenuator (IFN-γ/IL-2/ IL-4/ IL-27), and Th17-effector cytokines (IL-17A, IL-17F, IL-21, IL-22) in schizophrenia was not carried out. Therefore, the precise role of Th17 pathway in schizophrenia is yet to be empirically discerned.

Growing evidence suggests hyperactive TGF-β pathway in schizophrenia.[46–48] In addition, cytokines such as IL-1β and IL-6, initiators of the Th17 pathway, are consistently implicated in the pathogenesis of schizophrenia.[49,50] Moreover, in contrast to Th1 and Th2 immunity, Th17 cells demonstrate high-grade plasticity, and such plasticity allows Th17 cells a functional adaptation to various physiological situations during immune responses. Th17 cells display enhanced antitumor immunity and play important roles in transplant rejection. Th17 cells are more effective in host defense against microbes, especially bacteria and some fungi.[51] Th17 cells regulate innate immune responses and participate in bacterial clearance during CNS infection.[52] In addition, Th17 cells play an important role in gastrointestinal tract

function. Th17 cells bridge innate and adaptive immunity and mount robust antimicrobial inflammatory responses. Although the functional plasticity of Th17 cells provides protection against microbes, they also mediate pathological inflammation. In a recent study, Th17 plasticity in autoimmune arthritis was shown to be driven by the inflammatory environment.[53]

As infections strongly increase the risk for schizophrenia, a role of Th17 cells is predicted. Th17 pathway is linked to the pathogenesis of several autoimmune and inflammatory disorders.[54] Th17 cells are involved in the differential regulation of CNS autoimmunity. Inflammation in the brain parenchyma occurs only when Th17 cells outnumber Th1 cell.[55] Interestingly, a 30-year population-based register study has shown that a prior autoimmune disease and history of hospitalization with infection increased the risk schizophrenia by 29% and 60%, respectively.[56] The association of autoimmune diseases and schizophrenia is mediated by inflammation, brain-reactive antibodies, shared genetic factors, and common etiologic components like infections.[57] Increased prevalence of multiple autoantibodies including antibodies to neuronal surface antigens is found in schizophrenia.[58] Some of the antigens, such as *N*-methyl-d-aspartate receptor (NMDAR), a central component of synaptic plasticity, learning and memory act as a target of autoimmune reaction.[59] Antibodies to NMDAR has been identified in schizophrenia.[60,61] Antibodies that target proteins involved in synaptic function can cause limbic autoimmune encephalitis in some cases and this has also been linked to systemic autoimmune diseases.[62] Limbic encephalitis is known to be one of the best-appreciated causes of rapid behavioral dysfunction and is increasingly being implicated with schizophrenia.[63,64]

Mild encephalitis, characterized by low-level neuroinflammation is associated with a variety of psychopathological symptoms. Mild encephalitis hypothesis of schizophrenia has received wide appreciation in recent years.[65,66] The mild encephalitis hypothesis is thought to be triggered by infections, autoimmunity, toxicity, or trauma. Multiple epidemiological studies have demonstrated association of prenatal infection, prenatal stress, famine, environmental toxins, etc. with schizophrenia risk. All these factors are known to affect developmental immune system, crucial phases of neurodevelopment, and brain structures and functions.[67,68] There is a growing recognition that MIA during pregnancy also shapes the immunological phenotypes of offspring.[69] Offspring of immunostimulated pregnant mice were found to preferentially develop Th17 cells.[70,71] These and various other findings based on altered immune components lend further support toward the autoimmune/inflammatory hypothesis of schizophrenia.[72]

Emerging research indicates that the gut microbiota have the capacity to modulate brain immunity and functions.[73] However, an altered gut microbiome can lead to the development of autoimmune CNS disorders by fostering the production of brain-reactive autoantibodies[74] and behavioral and physiological abnormalities in neurodevelopmental disorders.[75] Th17 cells play important role in intestinal immune homeostasis; however, intestinal dysbiosis can lead to gastrointestinal inflammation through activation of Th17 cells.[18] Notably, gastrointestinal inflammation is found to be associated with immune activation and the pathogenesis of schizophrenia.[76] Considering the role of Th17 cells in gastrointestinal inflammation and the relevance of gastrointestinal inflammation in neurodevelopmental disorders, a significant role of Th17 pathway in schizophrenia seems imperative.

Schizophrenia has been proposed to be associated with neuroinflammation, as supported by multiple postmortem brain studies showing upregulated expression of inflammatory gene signatures.[50,77] Prenatal infection can lead to developmental neuroinflammation and might cause microglial activation with ensuing neuroinflammation in the adult CNS.[78,79] Given that microbial infections are an established risk factor for schizophrenia, and the role of the Th17 system particularly in mucosal defense, this is an intriguing nexus. Such findings provide evidence supporting an association of neuroinflammation with schizophrenia and establish an immune context for the mild encephalitis hypothesis of schizophrenia. Considering the importance of Th17 cells in the initiation of encephalitis and association of encephalitis with schizophrenia, an encephalitogenic function of Th17 cells can be envisaged in schizophrenia. In addition, Human endogenous retroviruses are shown to be associated with proinflammatory and neurotoxic cascades in schizophrenia.[80] Interestingly, human endogenous retrovirus triggers Th17 cytokine response in various immune-mediated disorders.[81] This further highlights the potential implications of Th17 cells in schizophrenia.

Other relevant findings implicating Th17 pathway in neuropsychiatric disorders has come from studies showing higher level of IL-17 in bipolar disorder and a correlation between increased serum level of IL-17A with the severity of autism.[82,83] Furthermore, increased Th17 cells are found to be associated with depression both in human and animals.[84,85] The shared inflammatory hypothesis of schizophrenia, bipolar disorder, autism, and immunoinflammation-induced priming of schizophrenia for increased expression of depression[86–88] provide further support toward Th17-mediated pathogenesis of schizophrenia.

Proposals

Prenatal infection and MIA strongly predisposes offspring to schizophrenia risk. It is hypothesized that prenatal infection might selectively lead to the development of Th17 cells. Prenatal infection affects fetal brain

development and enhances the risk of schizophrenia in offspring through the production IL-6.[89] Interestingly, IL-6 induces differentiation of Th17 cells from both naive and memory CD4+ T cells, and higher levels of IL-6 in schizophrenia is an established finding.[49] This may be linked to polymorphisms of the IL-6 rs1800795*C allele, which is associated with higher IL-6 blood levels in schizophrenia.[90] Prenatal infection activates toll-like receptor and amplifies the proinflammatory response by producing various inflammatory cytokines. This has been hypothesized to be one of the important mechanisms leading to inflammation and neuroprogressive changes in schizophrenia.[91] Activation of TLRs thus could potentiate Th17-cell differentiation, further implying a significant role of prenatal infection in Th17-cell homeostasis. Human Th17 cells remain in the body as a long-lived proliferating effector memory T cell with unique and functional genetic characteristic.[92,93] Activation of Th17 cells by a second hit (such as stress, infection, endocrine changes, etc.) and dysregulation of Th17 signaling may drive to chronic inflammation. The activated Th17 cells might infiltrate brain by disrupting the BBB and also lead to the activation of microglial cells. The release of Th17 effector cytokines and proinflammatory molecules from activated microglia can induce immunoinflammatory, oxidative, and nitrosative stress pathways that subsequently may enhance the risk of schizophrenia and neuroprogression. The effector cytokines of Th17 responses may provide a link between inflammation and neurodegeneration in schizophrenia.

Dopamine is known to interact directly with dopaminergic receptors on normal human T cells[94] and is involved in activation of T cells through upregulation of the expression of T-cell adhesion molecules. This helps T cells in trafficking and extravasation across blood vessels and tissue barriers including the CNS. Increased expression of dopamine receptors in T cells and a significantly higher expression of dopamine receptor 3 mRNA in T cells are reported in schizophrenia.[95,96] It has been recently demonstrated that stimulation of dopamine receptor D5 expressed on dendritic cells can potentiate Th17-mediated immunity.[97] In addition, antagonizing the dopamine D1-like receptor was found to inhibit Th17-cell differentiation.[98] Recently, dopamine was found to upregulate Th17 phenotype in individuals with generalized anxiety disorder.[99] The dopamine hypothesis is one of the most widely accepted constructs in schizophrenia. Considering the role of hyperdopaminergia in schizophrenia, it is proposed that Th17 responses could be significantly amplified in schizophrenia by dopamine. Similarly, the glutamate theory of schizophrenia is of relevance to Th17 immunity.[100,101] Knockout mice missing the metabotropic glutamate receptor-4 (mGluR4) showed increased sensitivity to experimental models of autoimmune encephalomyelitis mediated principally by increased IL-17-producing Th17 cells. Selective mGluR4 enhancers reduced sensitivity to autoimmune encephalomyelitis, which appears to be mediated by regulatory T (Treg) cells.[102] A summary of the proposed hypothesis has been depicted in figure 2.

Translational Implications and Evaluation of the Hypothesis

Pathogenetic paradigms invoking prenatal infection and maternal immune activation offer novel translational applications with potential to prevent this devastating disorder.[103] A growing body of evidence suggest IL-17 pathway as a major therapeutic target in autoimmune and inflammatory diseases.[104,105] A recent study has demonstrated that inhibition of STAT3 blocks Th17 development and inhibits experimental autoimmune uveitis.[106] Therapeutic targeting of STAT pathways is thus gaining importance in CNS diseases.[107] In addition to this, cytokines such as IL27p28/IL12p40 inhibit CNS diseases and/or CNS autoimmunity by antagonizing Th17 responses.[108,109]

The proposed hypothesis can be evaluated by examining the proportion of Th17 cells in human subjects with schizophrenia, well-characterized, first-episode, drug-naive, and ethnically homogeneous subsets of patients and controls matched for gender, age, parental socioeconomic conditions, and other confounding factors that potentially influence Th17-mediated immunity. In addition, determination of the peripheral and brain levels of various cytokines of Th17 pathway and their potential interactions with other Th1 and Th2 cytokines and other immune mediators including chemokines will lead to a better understanding of the significance of Th17 pathway in schizophrenia. The effects of Th17 activation and its derived cytokines on brain morphometry and cognitive functions in schizophrenia can also be tested by structural neuroimaging and neuropsychological testing. The temporal relationship between the symptom course of schizophrenia and changes in the blood Th17 products can be used as useful indicators for validating the hypothesis. Dopamine receptors expressed on immune cells modulate Th17-mediated inflammation.[110] This is supported by studies showing the attenuation of Th17-mediated immune response by a dopamine D1-like receptor antagonist.[111] Therefore, studies emphasizing the effects of antipsychotic drugs on Th17 pathway and the relationships between antipsychotic drugs modulating specific positive and negative symptoms with the changing proportion of Th17 cells will help to establish a mechanistic link between Th17 pathway and the etiopathogenesis of schizophrenia. Further, improved understanding of the influence of Th17 cells on the chronicity of schizophrenia patients especially with respect to negative symptoms and with underlying neurodegenerative changes might help us to determine the impact of Th17 cells on the fundamental aspects of this disorder.

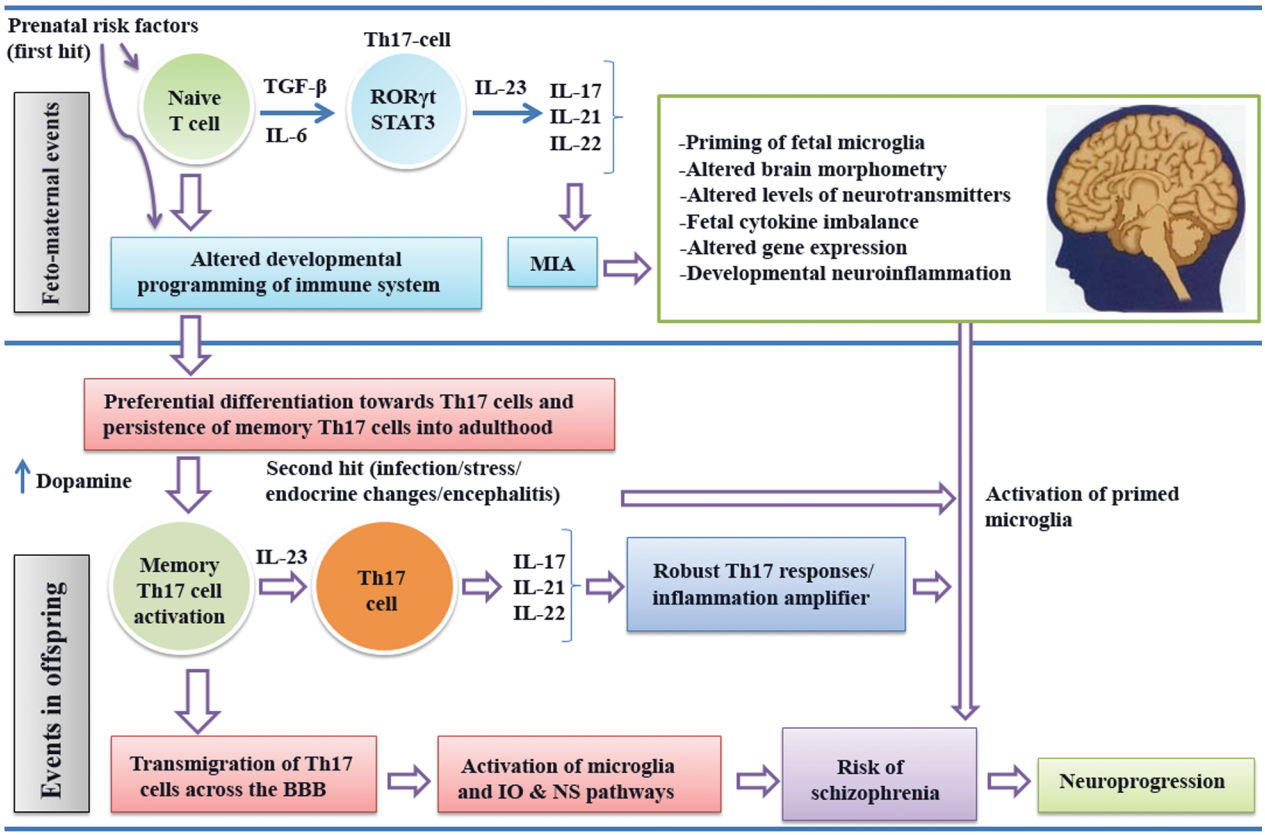

Fig. 2. Hypothetical model summarizing aspects of Th17 pathway–mediated immunopathogenesis of schizophrenia (IO&NS, Immuno-inflammatory, oxidative & nitrosative stress).

The proposed hypothesis can also be tested by developing a murine model. The impact of prenatal infection on the development of Th17 cells and subsequent inflammation could be tested by subjecting mice to bacterial lipopolysaccharide (LPS) and/or viral polyinosinic: polycytidylic acid (poly I:C) components, followed by estimation of different proinflammatory cytokines and oxidative/nitrosative stress markers. Further, the effects of Th17 effector cytokines on fetal brain development could be examined by applying various imaging procedures and by studying the expression profile of the markers involved in regulation of apoptotic and necrotic pathways in fetal brain tissues. The potential impact of dopamine on Th17 responses can be tested in vitro with the help of dopamine agonists and antagonists. The effect of prenatal inflammation on cognitive and behavioral attributes of the mice could be analyzed by testing their behavior using established paradigms for prepulse inhibition, latent inhibition, and other relevant social interaction measures.

The long-term effects of prenatal immune events on neurochemistry, neuromorphometry, and behavioral attributes could be monitored in the mice challenged with LPS/poly I:C. The attributes of long-lived Th17 cells on brain and behavior can be examined at different time intervals at postnatal life and may be correlated with changes of neurotransmitters, brain volume, and learning and memory. Furthermore, the detailed functional significance of Th17 pathway in brain can also be derived from knockout mice lacking important components of Th17 pathway.

Conclusion

Functional plasticity of Th17 cells in immunity and disease is quite well established. Recent understanding of the capacity of Th17 cells to infiltrate brain and induce neuroinflammation has generated renewed interest in delineating the immunopathogenesis of CNS disorders. Peripheral immune components and disruption of BBB are increasingly linked to psychosis. Although multiple lines of evidence link schizophrenia to chronic low-grade inflammation, the contribution of systemic immune changes to neuroinflammation is yet to be fully discerned. The proposed hypothesis could fill the gap and might establish a causal link between prenatal infection, a persistent systemic immune perturbations, and neuroinflammation in schizophrenia and offer novel treatment targets.

Funding

National Health and Medical Research Council Senior Principal Research Fellowship (1059660 to M.B.).

Acknowledgements

M.B. has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier and Woolworths, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck Merck and Servier. M.D. has no conflicts of interest in relation to the subject of this study

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