Chapter

Role of Immunity in Pathogenesis of Psychosis

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Abstract

The involvement of immunity in the pathogenesis of schizophrenia and related psychoses was suspected a century ago but was shadowed by the dopaminergic hypothesis after the discovery of antipsychotics. We currently know that this latter theory has many limits and cannot account for the wide variety of psychotic conditions. The immune-inflammatory theory is now one of the most promising axes of research in terms of pathogenesis of several mental health conditions. Immunity and inflammation play a role at least in a subgroup of patients with psychosis. The immune system is complex with a variety of components and mediators that can all have effects on the brain and thus mediate psychiatric symptoms. In this chapter we will explore the scientific evidence of the role of immune system in pathophysiology of psychosis. The sections of this chapter will discuss the role of innate system components (cytokines, microglia, inflammation.), the role of adaptive system (lymphocytes and antibodies) with a section focusing on auto-immunity and particularly antineuronal antibodies. Finally we will discuss how this research can impact patients management and elaborate recommendations for future research.

Keywords: schizophrenia, psychosis, inflammation, auto-immunity, antineuronal antibodies, pathophysiology

1. Introduction

The role of the immune system in mental disorders was suspected since the last century [1]. Then, the discovery of efficient antipsychotic drugs led researches to focus on the dopaminergic theory undermining the first immunological findings. Nonetheless, this theory has many limits and cannot account for the wide diversity of clinical presentations in patients with psychosis. In the last decades, there was a breakthrough in technical investigations that led to significant improvement of our understanding of the immune system functioning and the immune theory became a promising axis of research.

The immune system has a complex organization with an innate system (mediated by macrophages, neutrophils and cytokines) and an adaptive system which is antigen specific (mediated by T and B lymphocytes and antibodies secreted by B lymphocytes).

Many researchers have found immunological abnormalities in patients with psychosis involving both the innate and the adaptive system [2]. All immune

system components can have effects on the brain cells and thus they can produce psychiatric symptoms [2]. Increase in inflammation markers was detected in schizophrenia [3]. Early life and prenatal exposition to infections predicted adult schizophrenia [4, 5]. High rates of auto-antibodies were reported in psychiatric conditions especially antineuronal antibodies [6–8]. There are genetic findings that also consolidate these theories [9]. All these findings allow to conclude that immunity plays a role in pathophysiology of psychosis at least in a subgroup of patients. There are already trials using treatments targeting the immune system with encouraging results [10]. This axis of research can have an impact on the understanding and treatment of schizophrenia and related psychoses and allow a new era of immuno-psychiatry.

2. Evidence of involvement of immune system in pathogenesis of psychosis

2.1 Role of inflammation and innate immune system

Inflammation and innate system are the first line response, nonspecific to an antigen, when an infection occurs. It involves neutrophils, macrophages, microglia and secretion of acute-phase proteins like inflammatory cytokines. There is evidence for inflammation dysfunction in psychosis. Interleukins and C Reactive Protein (CRP) increase in patients with psychosis [11, 12]. An increase in the production of proinflammatory cytokines such as Interleukin 6 (IL-6) was detected in patients with schizophrenia [13] and patients at high risk for psychosis [14] and predicted development of adult schizophrenia when detected in children [4]. This increase in IL-6 was also found in the cerebrospinal fluid [15] in schizophrenia patients. A meta-analysis showed that pro-inflammatory cytokines increased in acute psychosis phase either during a first episode or during a relapse, and normalized after antipsychotic treatment [16].Thus, these markers could be used to detect acute psychosis and predict relapses. Peripheral inflammation can also affect the brain [17]. In fact, inflammation can activate endothelial cells in brain vessels and increase their permeability to immunological cells [18]. Moreover, inflammation that begins in periphery can reach the brain, probably through vagus nerve signals [17] and can activate microglia. Microglia is an essential component of central nervous system and has a hemopoietic origin [19]. Inflammation can activate microglia which in turn can release cytokines in the brain. Microglia also interacts with lymphocytes and can play a role of antigen presenting cell. This is consistent with the "microglia activation hypothesis" [20] that emphasizes the role of cytokines and free radicals produced by the activated microglia in pathophysiology of psychosis. Those substances can cause white matter and neurogenesis abnormalities and neuronal alterations associated with psychosis. Cytokines can also amplify the oxidative stress via toxic nitric oxide, which in turn, activates the hypothalamic–pituitary–adrenal axis [17]. This leads to the activation of the corticosteroid system that releases stress hormones such as cortisol [17, 21]. All these inflammatory processes could result in mood and cognition disturbances in humans [18, 22] through direct effect on the brain and through the cortisol secretion alterations. Corticosteroid levels alterations are known to induce affective and behavioral disturbances.
The activation of corticosteroid system by cytokines following an inflammatory immune response has already been demonstrated in major depressive disorder and could also be part of the pathophysiology of psychosis [17, 18, 22].

Schizophrenia has been associated with prenatal infections [5] and with childhood central nervous system infections [4]. These findings suggest a common

underlying pathway between schizophrenia and infectious conditions involving mainly inflammatory immune response [21].

2.2 Role of lymphocytes and adaptive system

The adaptive system represents the second line antigen-specific immune response. It involves lymphocytes B and T and antibodies secreted by lymphocytes B. It also allows to keep a memory of past infections.

Findings from experimental studies found abnormalities in lymphocytes function and number in patients with schizophrenia, particularly T-cells [12, 22]. Interleukin 2 (Il-2) is involved in immune response regulation. T cells of schizophrenia patients produce reduced amounts of Il-2 in vitro [23], and schizophrenia was associated with more activated lymphocytes, expressing CD56, compared to controls [24], especially in acute relapses, with changes in the ratio CD8/CD4 cells [22]. Baseline lymphopenia can be associated with severe psychosis and predict poor outcome and poor treatment response [25]. These findings are consistent with The "macrophage-T-lymphocyte theory" postulating that cytokines produced by activated lymphocytes T and macrophages play a main role in pathophysiology of schizophrenia [26]. In fact, CD4 T-lymphocytes secrete cytokines such as IFN-γ and IL-12 which can activate CD56-lymphocytes that secrete TNF-α and IFN-γ. Pro-inflammatory cytokines are associated with schizophrenia as was shown in the previous section [16]. A decrease in CD19 B-lymphocytes count was demonstrated in patients treated with adjunctive celecoxib [27] and this was associated with negative symptoms improvement. Post-mortem studies reported evidence of microglia activation [28, 29] and increased number of lymphocytes [30] in schizophrenia. Most studies focused on blood cells count [22], while there can also be changes in cerebrospinal fluid as demonstrated by many authors [24, 31, 32].

2.3 Role of auto-immunity and antineuronal antibodies

The involvement of autoimmunity in psychosis was suspected about a century ago [1, 33]. There is evidence for the role of auto-immune antibodies, in the pathogenesis of psychiatric disorders in general and in psychosis in particular [7, 33]. Psychotic and auto-immune conditions share many clinical and biological features like a young age onset [1, 34, 35], stress-triggered [6, 36], they have chronic course with relapses and possible residual symptoms [6, 34]. Besides, psychosis is often associated with auto-immune conditions [35] and high levels of auto-immune antibodies were found in patients with psychosis (e.g. antibodies anti-gliadin and anti-casein) [7, 37] and particularly antineuronal antibodies [2, 8, 38]. Antineuronal antibodies can target cell surface components, such as the N-Methyl D Aspartate (NMDA) receptor, or they can target intra-cellular nuclear or cytoplasmic antigens.

The most studied antineuronal antibodies in the literature are cell surface antibodies anti-NMDA [38]. Patients with anti-NMDA antibodies often present with predominant psychotic symptoms and subsequently develop other neurological symptoms [39]. This is called NMDA encephalitis and can be treated using immunotherapy and removal of auto-antibodies [40]. Some patients have anti-NMDA and mild psychotic symptoms but have no neurological symptoms of encephalitis. Authors have suggested the concept of " auto-immune psychosis " [41, 42] to describe this entity.

There are many arguments for NMDA receptor hypofunction in schizophrenia [2, 38]. The administration of ketamine and phencyclidine, which are NMDA receptor blockers, is known to cause clinical [43, 44] and physiological symptoms [45] similar to schizophrenia. Glutamate and glycine are necessary for NMDA

receptor activation and they have decreased levels in schizophrenia [38, 46, 47]. Psychosis is also associated with abnormal D-amino acids levels (including D-serine and D-alanine) [48, 49] which are modulators of neuronal activity [50] and act as co-agonists of NMDA receptor at the Glycine Modulatory Site [38, 46]. There is also an increase in antagonist agents of NMDA receptor in schizophrenia [51]. These findings were used in developing treatment trials for psychosis by augmenting NMDA receptor function [38, 41].

Antineuronal antibodies can also target intracellular antigens such as Antineuronal Nuclear Autoantibodies (ANNA) (called anti-Hu and anti-Ri) and Anti cytoplasm of Purkinje cells Antibodies (PCA) (called anti-Yo). Those antibodies have been classically associated with paraneoplastic syndromes [52, 53] but they were also found in persons with neurological or psychiatric conditions with no associated tumor [8]. For example, these antibodies were found in association with neurological diseases [54], with auto-immune diseases [55], with neuropsychiatry symptoms of neurolupus [56], with autism [57, 58] and with obsessive compulsive disorder [59, 60]. A study found ANNA antibodies were significantly higher in schizophrenia and bipolar disorder patients compared to healthy controls [8] with no tumor detected after 5 years follow up. In this study, PCA antibodies were associated with the presence of affective symptoms. Most authors are now focusing on anti-NMDA antibodies but future studies should address these antinuclear and cytoplasmic antibodies.

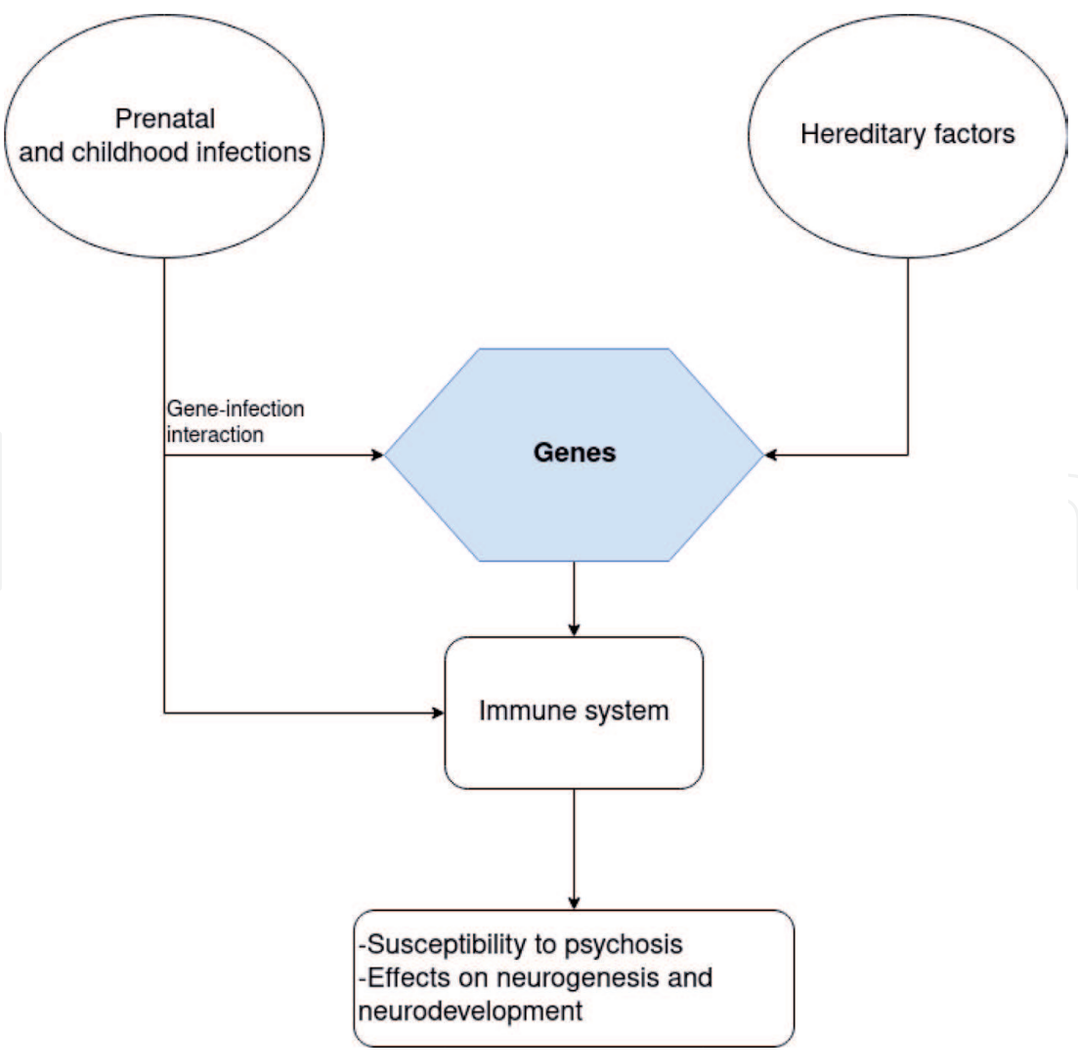

Figure 1.
Early life interactions resulting in susceptibility to psychosis.

2.4 Genetic findings

Genome Wide Association Studies (GWAS) found an association between schizophrenia and genes that are related to immune system cells [61]. Another GWAS showed that a single nucleotide polymorphism in major histocompatibility complex on chromosome 6 was associated with schizophrenia [62]. This region of chromosome 6 includes genes expressing proteins involved in pro-inflammatory cytokines. A genetic association was also found between schizophrenia and multiple sclerosis, an immune mediated disease [63].

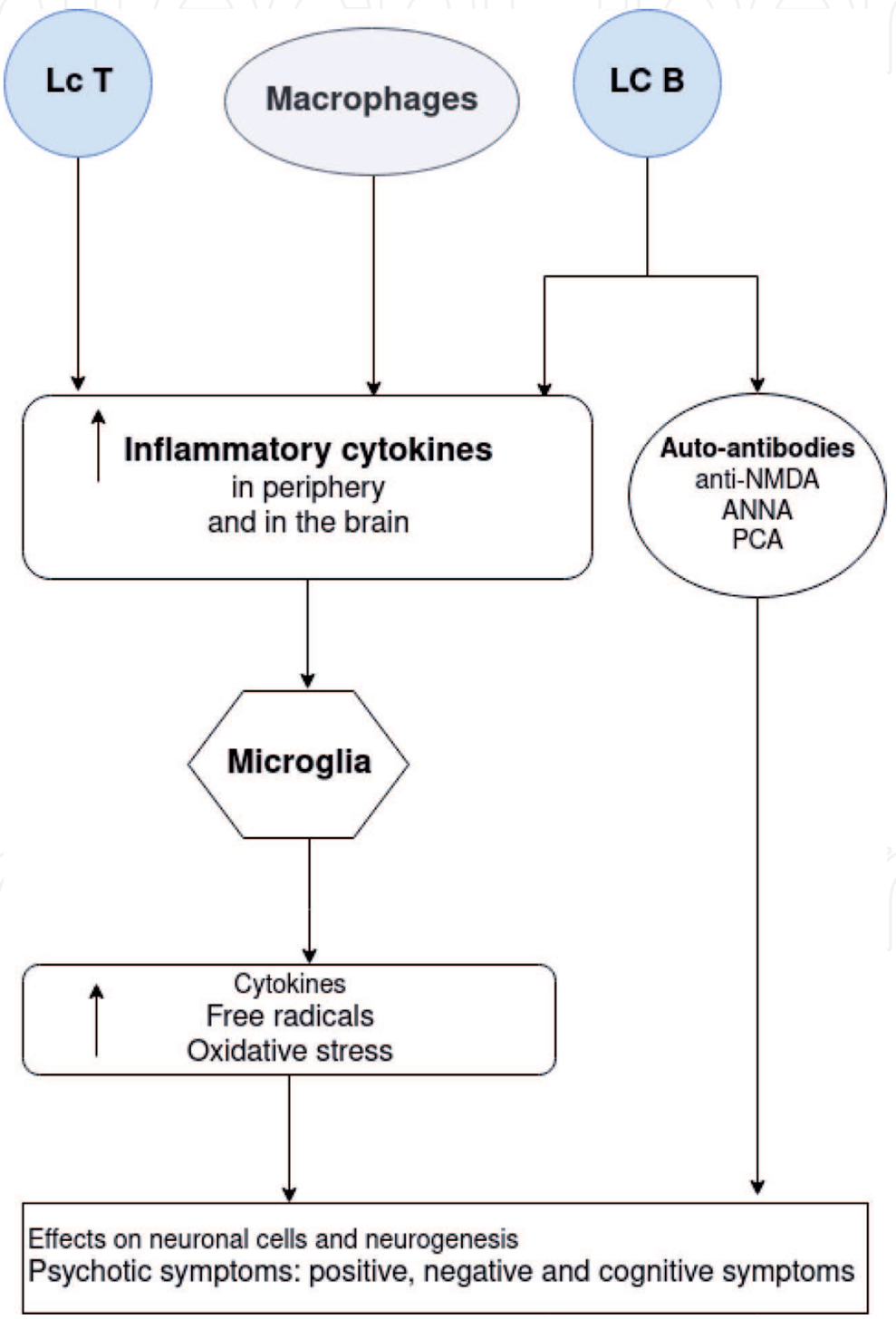

Figure 2.
Simplified diagram of possible immune interactions resulting in psychotic symptoms. Lc, lymphocyte; NMDA, N-methyl D-aspartate receptor; ANNA, antinuclear neuronal antibodies; PCA, anti Purkinje cell cytoplasm antibodies.

As we previously discussed, NMDA-receptor downregulation is associated with schizophrenia. A meta-analysis showed that there is hypoexpression of the mRNA of a subunit of NMDA receptor called GluN1 [64] in schizophrenia. Besides, the expression and activity of DAAO, an enzyme that catabolizes D-amino acids which act like agonists of NMDA receptor, are increased and DAAO gene is considered as risk gene for schizophrenia [65].

During the early life and prenatal development, the association between genetic susceptibility and early infections can affect immunological pathways illustrating the gene-infection interaction (**Figure 1**).

2.5 Summary of immune systems interactions leading to psychotic symptoms

In the previous sections, we presented evidence for the implication of innate and adaptive system in psychosis pathogenesis. This separation between innate and adaptive systems is schematic and is usually used for its clarity. In reality, all these components interact with each other in order to perform an adequate immunological response to infection (**Figure 2**). How do all these systems interact and lead to psychosis symptoms? In a classic immune response to an infection, innate system is the first actor through macrophages activation and cytokines secretion. Then, T and B-lymphocytes are activated and also produce inflammatory cytokines. On the one hand, inflammation activates microglia in the brain which in turn secretes inflammatory cytokines. This environment of inflammation and oxidative stress could lead to hypothalamic activation and then corticosteroid system activation with release of stress hormones. Oxidative stress within the brain and stress hormones are known to account for mood and behavioral disturbances. On the other hand, B-lymphocytes can secrete auto-antibodies that react with neuronal brain cells. These antineuronal antibodies can target cell surface (such as anti-NMDA) or target intracellular antigens (such as ANNA and PCA). All these auto-antibodies were associated in the literature with psychiatric conditions.

3. Treatment implications

Antipsychotics, either first or second generation, were the only treatments used in patients with psychosis for decades. Nonetheless, they have many limitations. They are quite effective on positive symptoms but they failed at treating negative and cognitive dimensions or global functioning [66]. Moreover, there is a significant rate of treatment resistance of nearly 30% [67]. Besides, they can induce severe neurological, metabolic or hematologic side effects [68]. The rationale of these treatments is based on the dopaminergic theory which cannot account for all aspects and symptoms of psychosis. Thus, researchers are looking for treatment alternatives.

Given the substancial evidence of immune dysfunction in psychosis, scientists have tried medications acting on the immune system. There have been many trials with anti-inflammatory medications combined with antipsychotics [10] using aspirin [69, 70], celecoxib [27, 71, 72] and N-acetyl-Cystein [73, 74] with encouraging results (**Table 1**). Celecoxib [27] and N-acetylcysteine [73, 74] were associated with negative symptoms improvement. Meta-analyses about adjunctive minocycline, a tetracycline antibiotic with anti-inflammatory properties, found global improvement in PANSS total score [76] and cognitive function [77, 80]. Two meta-analyses assessed trials using other molecules with anti-inflammatory and neuroprotective properties such as eicosapentaenoic acid, pregnonolone, estrogens, Selective Estrogen Receptor Modulators [77] and statins [79]. Only eicosapentaenoic acid

Adjunctive therapy	Main trials results
N-Acetyl-Cystein	PANSS improv [73]; Neg symp improv [74];
Aspirin	PANSS improv [69, 70]
Celecoxib	PANSS improv [71, 75]; Neg symp improv [27]; No signif improv [72]
Minocycline	PANSS improv [76]
Pregnenolone	PANSS improv, Cognitive improv (5 trials) [77]
Estrogen	PANSS improv (8 trials) [77]
Erythropoietin	Cognitive improv [78]
Eicosapentaenoic acid	No sig improv (20 trials) [77]
Statins	PANSS improv [79] with negative symp improv on simvastatine
Tocilizimab	Negative symptoms improv [80]; no signif improv [81]
NMDA modulators	No cog improv [82, 83]; negative symptoms improv in UHR [84]

improv, improvement; no signif, no significant; PANSS improv, PANSS total score improvement; UHR, Ultra High Risk for psychosis.

Table 1.
Main results of trials using adjunctive immunotherapy combined with antipsychotics.

was not associated with significant clinical improvement. Results reported global improvement in total PANNSS scores on all other agents and cognitive function improvement on pregnonolone and negative symptoms improvement on simvastatine. A pilot trial demonstrated improvement of cognitive function on recombinant human erythropoietin [78]. Despite limitations, like study sample size, and despite the presence of some negative results [70, 72], authors reported promising results. There was an overall good tolerance.

Some biological agents can act as inflammatory response modulators, such as monoclonal antibodies and mesenchymal stem cells, and were studied in recent trials in neurological and psychiatric disorders like autism and schizophrenia [85]. Trials using adjunctive monoclonal antibodies, like tocilizumab and canakinumab, in psychosis reported improvement in negative [80] or positive symptoms [86] or no significant improvement [81].

There is another axis of research based on NMDA receptor augmenting strategies based on the increase of agonists of this receptor or decrease of antagonists. There were tens of placebo controlled trials using agonists of Glycerine Modulatory Site in NMDA receptor [38] such as glycine or D-amino acids. The results were mixed [38, 82]. Methodological bias and differences in the used molecules can account for the variability of the results. A meta-analysis did not find improvement in cognitive function using glutamate positive modulators in schizophrenia [83]. However a pilot study showed an improvement in negative symptoms using D-serine, which is an agonist of NMDA receptor, in teenagers with high risk of psychosis [84]. Thus, it could be useful to use NMDA augmenting in prevention for early psychosis stages (**Table 1**).

Clinical trials are now focusing on anti-inflammatory strategies and NMDA augmenting. It would be useful to widen our perspective and consider other therapeutic options. For example, we could consider treatments inspired from well-established auto-immune conditions like removal of antibodies or immunosuppression. Many of the trials mentioned above still suffer from lack of data. There are limitations to the generalization and clinical application of these therapies. There are confounding factors like the type of antipsychotic drug used in combination, patients compliance, inclusion criteria, illness stage, medical history and other factors that

modulate immune response such as body mass, smoking status, or associated stress. All these factors need to be addressed and controlled in larger studies. However, despite these limitations, we can notice that there is accumulative evidence of the potential of anti-inflammatory and immunotherapy strategies in treating patients with psychosis. We need a better definition of patients subgroups and specific symptoms that could benefit from these therapies. A stratification of patients could be made using the immunological status and/or clinical dimensions.

4. Recommendations for future research

It is now clear that we should not limit our research and treatment strategies to antipsychotics. Immunological alterations seem to account for psychotic symptoms in a subgroup of patients. These patients can benefit from immunotherapy. The challenge is to better characterize this subgroup and define the features that predict a good response to immunotherapy. A stratification should be made using biological markers, clinical symptoms, response to antipsychotic treatments, disease stage etc. We could define an immune phenotype that predicts treatment response. It was used successfully in a trial about depression [87]. In this trial, patients who had baseline high levels of inflammatory mediators had significant improvement of depressive symptoms on infliximab which is an anti-inflammatory agent. This approach should be explored in psychosis.

Some clinical symptoms do not respond well to antipsychotics like the negative and cognitive dimensions [66]. These symptoms could benefit from other therapeutic strategies. As mentioned above, many immunotherapy trials reported improvement in negative or cognitive domains [27, 74, 76, 78, 79]. There are arguments that corroborate this theory: inflammation was associated with impairments in memory and learning [88] and in spatial memory [89]. There is still no established physiopathology accounting for immune therapies effects on negative and cognitive symptoms but hypothetical mechanisms can be proposed. Inflammation and cytokines are associated with cognitive impairments [88, 89]. Inflammation is also incriminated in the genesis of negative symptoms and motivational deficits through the action of cytokines on basal ganglia and through decrease of neuronal activity in reward system [90]. Thus, anti-inflammatory drugs could improve cognitive symptoms by reducing inflammation.

All these clinical and biological features (i.e. negative and cognitive symptoms, inflammatory phenotype etc.) should be considered as endophenotypes related to psychosis and used to categorize and stratify patients in future trials. A subgroup of patients with schizophrenia could have immune alterations accounting for psychotic symptoms and would be more prone to respond to immune therapy. This subgroup could have some characteristics: prominent negative symptoms and cognitive dysfunction, poor response to conventional treatments, a specific immune phenotype characterized for example by elevated baseline inflammatory markers or increased lymphocytes number. The immune phenotype predicting therapeutic response has to be better specified in future studies (which markers? What are the specific sub-types of lymphocytes? Etc). The duration of illness can influence clinical presentation and treatment response. Some immunotherapies proved more effective when administered at an early stage of psychosis [84]. A staging of psychotic conditions should be considered, as for staging used in cancers, in some immune diseases, and bipolar disorder [91].

Antipsychotic treatment resistance is a challenge for scientists and causes disability and high personal and social burden. Those patients could benefit from new generation treatments like immunotherapy. Some immunological markers can predict severe

psychosis and poor treatment response on antipsychotics [14, 22, 25]. In the future, we could define precise immunological markers that may predict antipsychotic resistance and good response to immunotherapy.

The inflammatory status can differ between acute exacerbation phases and residual phases [16, 30]. Thus, inflammation markers could be used to predict and diagnose psychotic relapses or first episode psychoses in addition to clinical examination.

Multicenter large trials are needed with study of lymphocytes numbers and subtypes, cytokines types and with control of confounding factors. Dosage of anti-inflammatory treatments and interactions with antipsychotics should also be addressed. New strategies based on auto-immune model can broaden the therapeutic arsenal.

A novel axis of research based on the "gut-brain theory" should be considered in future research. In this theory, the intestinal microbiota composition could play a role in many central nervous system diseases through a bidirectional pathway between gut and brain [92]. Mechanisms of this interplay probably involves neurohumoral communication, vagus nerve signals and tryptophan metabolism [75].

5. Conclusions

The role of immunity in the pathogenesis of psychosis is now established, at least in a subgroup of patients. The challenge is to determine solid criteria to recognize this subgroup with possible benefit from immunotherapy. Another challenge is to develop efficient therapies based on immune system interactions with acceptable tolerance.

Conflict of interest

Authors have no conflicts of interest.

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