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The Complement System in Schizophrenia

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summary

Several lines of evidence suggest that immunological factors contribute to schizophrenia. Since 1989, the role of complement, a major effector of innate immunity and an adjuvant of adaptive immunity, has been explored in schizophrenia. Increased activity of C1, C3, C4 complement components in schizophrenia has been reported by two or more groups. Two studies on different subject cohorts showed increased MBL-MASP-2 activity in patients versus controls. More than one report indicated a significant high frequency of FB*F allotype and low prevalence of the FS phenotype of complement factor B in schizophrenia. From the data reported, it is likely that the disorder is accompanied by alterations of the complement classical and lectin pathways, which undergo dynamic changes, depending on the illness course and the state of neuro-immune crosstalk. Recent findings, implicating complement in neurogenesis, synapse remodeling and pruning during brain development, suggest a reexamination of the potential role of complement in neurodevelopmental processes contributing to schizophrenia susceptibility. It is plausible that the multicomponent complement system has more than one dimensional association with schizophrenia susceptibility, pathopsychology and illness course, understanding of which will bring a new perspective for possible immunomodulation and immunocorrection of the disease.

Schizophrenia is a severe mental disorder with a worldwide prevalence of 0.5–1.0%, which has enormous social and economic impact. The criteria of the Association of European Psychiatrists (ICD-10) and the American Psychiatric Association (DSM-IV) for the diagnosis of schizophrenia require that two or more characteristic symptoms be present—delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms (alogia or affective flattening)—and that other requirements, such as excluding affective disorders, and the presence of impaired function, be present. As a group, people with schizophrenia have functional impairments that begin in childhood, continue throughout adult life and make most patients unable to maintain normal employment or otherwise have normal social function.^{1,2} They also have a shortened lifespan compared to the general population,³ and suffer from an increased prevalence of a wide variety of other neuropsychiatric syndromes, including serious depression, substance abuse, obsessive–compulsive symptoms and abnormal involuntary movements prior to antipsychotic treatment.^{4,5} Schizophrenia is also associated with a wide range of cognitive impairments, the severity of which limits their function, even when psychotic symptoms are well controlled.^{6,7}

In spite of major research efforts of the global scientific community, the etiology and pathogenesis of this mental disorder are not yet clearly understood. Schizophrenia is apparently a polygenic disorder associated with developmental and other postnatal genetic risk factors.^{8–10} Several lines of evidence suggest that infectious and immunogenetic factors also contribute to the etiopathogenesis of schizophrenia.^{11–16} The complement cascade is a major component of the immune defense against infection, and the role of complement in schizophrenia is beginning to be more widely explored.

Overview of the complement system

The complement system is a major effector of innate immunity and an adjuvant of adaptive immunity. It consists of about 35 plasma (~4–5% of the total plasma protein) and cell-surface proteins, and has the function of recognizing foreign (microorganisms) or altered host materials (e.g., necrotic, apoptotic or infected cells), and lysing or opsonizing them (Table I). The mechanisms of action and activation of complement have been extensively reviewed^{21–24} In the complement system, large polymeric pattern recognition molecules including Clq, mannan-binding lectin (MBL) and the ficolins recognize microorganisms via their highly conserved surface features (or “pathogen-associated molecular patterns” [PAMPs]) such as lipopolysaccharides, lipoproteins, peptidoglycan, oligosaccharides and other surface structures.²⁵ Recognition of the targets is followed by opsonization (“preparation for eating”) with complement components marking targets for phagocytes expressing complement receptors. Further activation of the complement system builds up multiprotein complexes capable of lysing the lipid bilayer of target cells. Recent data extends the role of these complement pattern recognition molecules to the clearance of cellular debris and apoptotic cells.^{26,27} The innate and adaptive immune systems are often regarded as distinct arms of immunity; however, there is increasing data that innate and adaptive arms of immunity “crosstalk”, and that complement has an important role bridging between them (Table I).

Complement is activated by three pathways: the classical pathway, the alternative pathway and the more recently discovered lectin pathway (Fig. 1).²⁸ In the classical pathway, the recognition protein Clq binds to charge clusters on targets resulting in activation of the proteases Clr, then Cls. Activated Cls cleaves complement proteins C4 and C2, forming a complex protease C4b2a (C3 convertase), which activates C3 (cleaving to C3a and C3b). C3b either binds covalently to targets and opsonizes them, promoting clearance by phagocytosis,²¹ or binds covalently onto the C3 convertases to form C5 convertases (C4b2a3b [classical and lectin pathways] and C3bBb3b [alternative pathway]). At the final stage, C5 cleavage (to C5a and C5b) by C5 convertases initiates assembly of the membrane attack complex (MAC), made up of complement proteins C5b, C6, C7, C8 and C9. The MAC inserts into lipid bilayers and causes lysis of a target cell (Fig. 1 and Table I). The classical pathway initiator complex C1 (Clq+2 (Clr+Cls)) binds to and is activated by a wide range of targets, including damaged host cell products (such as nucleic acid, chromatin, cytoplasmic filaments, mitochondrial membranes), anionic phospholipids, apoptotic cells, some viruses, some Gram-negative and Gram-positive bacteria, amyloids and antibody-antigen complexes containing immunoglobulin IgG or IgM.^{29–31}

The lectin pathway initiators are complexes of pattern recognition molecules MBL or ficolins (L-, H- or M-ficolins) with MBL-associated serine proteases (MASPs) and MASP-2.^{32,33} The MASPs are homologues of Clr and Cls. MBL or any of the ficolins bind to structures presented by a wide range of pathogens and mediate complement activation via activation of MASP-2. MASP-2 cleaves and activates the complement proteins C2 and C4, thereby generating the C3 convertase, C4b2a.³⁴ Thereafter the lectin pathway cascade is the same as the classical pathway (Fig. 1). The lectin pathway, via MBL, has both antibody-dependent and antibody-independent modes of activation. It is activated through binding of the lectin domain of MBL to

carbohydrates on a number of microorganisms, and is considered as the immune first-line defense. It also interacts with the glycans of the common glycosylation variant of human IgG, named IgG-G0,³⁵ and with some IgA forms.³⁶ MBL can interact with a subpopulation of human IgM glycoforms, but the interaction does not activate the lectin pathway.³⁷ H- and L-ficolins have been shown to bind to a range of bacterial species,³⁸ possibly via acetyl groups (e.g., on *N*-acetylated sugars). M-ficolin is a cell-surface protein and is not widely explored yet.

The C3b deposited on a complement activator by the classical or lectin pathways can trigger alternative pathway activation by binding factor B (a homologue of the classical pathway C2) and forming a C3bFB complex. This is cleaved by the protease factor D to form an alternative pathway C3 convertase, C3bBb, which cleaves more C3 (Fig. 1). In this way, the alternative pathway acts as an amplifier for the other pathways, and increases the covalent deposition of C3b on the target. In addition, the alternative pathway can be activated directly by C3(H₂O), a spontaneously hydrolyzed form of C3. In this case, the factor B forms a complex with C3 (H₂O), becoming sensitive for cleavage by factor D. The new complex is a soluble C3 convertase C3(H₂O)Bb, which is homologous to the classical pathway C3 convertase, and converts more C3 into C3b, which is deposited randomly on nearby surfaces. This can be considered as a surveillance mechanism, as all surfaces in contact with blood receive frequent “hits” from randomly generated C3b molecules. If the bound C3b binds factor B, and forms C3bBb, the target surface will be opsonized and/or lysed. Once the alternative pathway has been activated, the C5 convertase (C3bBbC3b) of this pathway is formed by the binding of an activated C3b to the surface bound C3bBb on an activator (Fig. 1). Once C5 convertase is formed, the late stages of complement activation lead to the assembly of the MAC as described for the classical pathway. The alternative pathway is activated by IgG immune complexes and in the absence of antibody, by a wide range of bacteria, viruses, yeasts and protozoans.^{21,30}

If, however, the original deposited C3b molecule is deposited on a host cell, it is rapidly inactivated by cell-surface complement regulatory proteins such as complement receptor type 1 (CR1), decay-accelerating factor (DAF) and membrane cofactor protein (MCP), which are present on host cell membranes (Fig. 1). Other soluble regulatory proteins such as factor H, factor I and C4b binding protein also downregulate complement activation by preventing C3b from forming C3bBb.

Small bioactive peptides C3a, C4a, C5a (all about 10 kDa) called anaphylotoxins, released from activation of C3, C4 and C5, have vasoactive properties. C5a is also a chemotactic factor for neutrophils.

The role of complement in immunity is framed by its three main functions (Table I): i) it serves as first-line defense against foreign invaders such as microorganisms (bacteria, viruses, fungi, etc), ii) it bridges innate and adaptive immunity (reinforcing adaptive immune response), iii) it is involved in clearance of altered self (apoptotic or necrotic cells, protein aggregates like amyloids).

Excessive complement activation contributes to the pathology of a wide range of diseases, including rheumatoid arthritis, demyelinating diseases, and ischemia-reperfusion injury. On the other hand, inadequate complement activity is associated with the development of autoimmune disease (e.g., systemic lupus erythematosus) and susceptibility to infection.³⁹

Complement in the CNS

Complement proteins of the alternative and classical pathways are expressed by central nervous system (CNS) cells.^{40,41} MBL is detectable immunochemically in human brain tissue and cerebro-spinal fluid, and MBL mRNA is relatively abundant in mouse brain.^{42,43} The roles of complement within the brain have not been studied in detail, but are likely to be the same as

in other tissues, i.e., clearance of foreign and damaged host material. The expression of Clq in rat brain is massively induced in ischemia, consistent with a role in clearance of damaged cells.⁴⁴ Also as in other tissues, inappropriate or chronic complement activation is associated with host tissue damage. Complement-mediated damage is implicated in several neurodegenerative disorders.⁴⁵ Intracerebral levels of complement are increased in several chronic neurodegenerative disorders such as Alzheimer's disease,^{46,47} Huntington's disease,⁴⁸ Parkinson's disease⁴⁹ and Pick's disease.⁵⁰ The finding of increased complement deposition in these neurodegenerative diseases raises interesting questions about a novel role for complement in the pathophysiology of noninflammatory CNS disorders.

Recent observations implicate some complement components in basal and ischemia-induced neurogenesis (C3),⁵¹ and synapse remodeling and pruning (Clq and C3)^{52,53} in brain development.⁵⁴ Such findings provide a basis for further study of complement-mediated effects on neuroprotection and neurodevelopment^{41,55,56} and suggest a reexamination of the potential role of complement in neurodevelopmental disorders, such as schizophrenia and autism.

Complement in schizophrenia

The classical pathway

The role of the complement system in schizophrenia has not yet been widely explored. The multicomponent composition of complement makes it complex and expensive to examine the roles of individual components, and so more general assays that measure the overall activity of, for example, a whole pathway (total hemolytic activity), have been used. These are likely to be less informative than single component assays. Involvement of the immune system has been a relatively low priority for schizophrenia research, largely because evidence of classic inflammatory pathology has been consistently lacking, although several scientists since 1937 have pointed to the possible role of autoimmune and infectious processes in the etiology of schizophrenia.^{57–60}

Several studies have focused on the complement classical pathway activity in schizophrenia (Table II). Initial attention was focused on complement total hemolytic activity, to which classical pathway activity contributes about 85%. Spivak et al.⁶³ reported a decrease in complement total hemolytic activity in schizophrenic patients vs. controls, while a year later a Japanese group reported no difference.⁶⁴ More recent studies suggest that in schizophrenia there is a modest increase in complement total hemolytic activity (CH50), although neither study reached statistical significance.^{65–67} Significantly raised CH50 has been observed in a sample of schizophrenic patients, but only when they were in remission, a finding which is not consistent with the earlier studies.⁶⁸ Yet another recent investigation suggests raised classical pathway functional activity in a chronic schizophrenic patient cohort vs. healthy volunteers.⁶¹ Thus, while these results do not implicate a replicable finding, it is conceivable that differences in disease stage and course of the patient groups investigated may influence complement total hemolytic activity. Overall, the data concerning the hemolytic activities of individual components involved in the classical pathway of activation tend towards the conclusion that there is higher activity in schizophrenia (Table II). Only Hakobyan et al.⁶⁷ reported an almost 50% decrease in C2 hemolytic activity.

Data related to C3 and C4 serum or plasma concentrations are also inconsistent (Table II). There are reports of C3 concentration decreases in chronic⁷⁰ and increases in drug-free patients.⁷¹ However, the majority of the studies concluded nonsignificant or no alterations (Table II). Measurements of C3 and C4 concentration may be unsatisfactory in that they also measure C3 and C4 breakdown products, whereas activity assays measure only unactivated C3 or C4. Maes et al.⁷¹ showed high C4 concentration in plasma of nonmedicated schizophrenic patients that is not reflected in the results of other groups.^{62,63,72} In a recent correlation study on the

relationship between acute phase proteins and psychopathology in paranoid schizophrenia, serum levels of C3 and C4 were suggested as biological markers of acute negative symptoms of paranoid schizophrenia.⁷⁶ While no item of the positive scale of the PANSS (Positive and Negative Syndrome Scale) significantly correlated with the levels of the C3 and C4, three of the seven items of the negative scale show positive correlations with the levels of these proteins. These items were, for C3, poor rapport, social withdrawal/passive apathy, stereotyped thinking; and for C4, social withdrawal/passive apathy. Besides, two items of the general psychopathology scale also significantly correlated with C3 (active social avoidance) and C4 (deficient attention) serum levels.⁷⁶ However, the sample size in this study was small and the post hoc nature of the findings cannot be overlooked.

The alternative and lectin pathways in schizophrenia

The alternative pathway remains almost unexplored in schizophrenia. Our recent data showed that schizophrenic patients had the same functional activity of the alternative pathway as controls,⁶¹ although Yang et al.⁷⁴ reported an increased plasma level of factor B in schizophrenia.

The lectin pathway, however, has been more extensively explored. In the lectin pathway, MBL or ficolin molecules can form complexes with one of three different proteases, named MASP-1, MASP-2 and MASP-3. When MBL or ficolins bind to a target, the proteases are activated. MASP-2 activates complement, and MASP-1 may have some (minor) involvement in complement activation, but the role of MASP-3 is unknown. In our study of different pathways of the complement system in a sample of chronic patients, a significant increase was detected in the functional activity of the lectin (MBL) pathway in schizophrenic patients, which is a reflection of the activity of MBL–MASP-2 complexes.⁶¹ This finding is in agreement with previous results, showing higher MBL–MASP-2 complex activity in patients in remission, there were no significant differences in MBL serum concentration and the activity of MBL–MASP-1 complexes in comparison with controls.⁶⁸ A year later we investigated the same parameters in chronic schizophrenic patients in an acute symptomatic exacerbation.⁶⁹ A modest increase in MBL level and significantly higher activities of MBL–MASP-1 and MBL–MASP-2 complexes were detected. Exploration of L-ficolin–MASP complex activity showed that schizophrenic patients had more than 40% increase in serum L-ficolin level and 15% in L-ficolin–MASP-2 activity when compared with controls.⁶⁹

MBL–MASP complexes are heterogeneous,⁷⁷ in that MBL itself forms oligomers of different sizes, and each MBL oligomer may bind only one of MASP-1, -2 or -3. In individuals with high MBL concentration there may be excess free MBL not occupied by MASPs, particularly not by MASP-2.⁷⁸ The differently composed complexes have different functions.⁷⁹ The concentrations of these complexes show wide interindividual variation.⁷⁸ Thus, complement activation depends not only on MBL concentration and oligomeric state, but also on the quantity of MASP-2 and MASP-1 in serum, as after some certain threshold MASP-1 can compete out MASP-2 from binding to MBL.⁷⁸ Taking into account our recent findings on exploration of MBL–MASP and L-ficolin–MASP complexes in schizophrenia,^{61,68,69} it is likely that subtle interplay between MBL, ficolins and MASPs determines complex composition and modulation of the lectin pathway, which could be a very dynamic process depending on the current immune status of the organism and, particularly for schizophrenia, on the stage and course of illness, or on the presence of secondary factors such as coincidental infections, the impact of chronic smoking or effects of poor hygiene. To further explore the associations between raised lectin pathway activity and schizophrenia, we are undertaking multifactorial exploration of the whole lectin pathway, including measurement of H-ficolin and MASP-2 serum concentrations and genotype analyses of the components, as well as H-

ficolin–MASP-1 and H-ficolin–MASP-2 complex activities in the same sample cohort. However, data obtained from other (non-Armenian) populations are also required.

The influence of psychiatric medication

The influence of psychiatric medication on aspects of immunity and inflammation was considered by researchers well before studies on complement in schizophrenia.^{80,81} Spivak et al.⁶³ found that, in the group of schizophrenic patients who had never received psychotropic medication (n = 20), total hemolytic activity was significantly lower than in healthy controls (n=37). Nevertheless, no statistical differences were observed between haloperidol-treated (n = 34) versus drug-free (n=37) and haloperidol- and never-treated schizophrenic patient groups. The last is in accordance with the report of Sasaki et al.⁶⁴ showing no significant changes (slight increase) in CH50 after 8 weeks' neuroleptic administration in acute exacerbating schizophrenia. In our recent studies, neither correlation of neuroleptic treatment with CH50 and C4 hemolytic activities, nor comparative analysis of neuroleptic-free versus medicated schizophrenic patients (approximate gender and age-matched group) revealed an association between CH50, and C1, C2, C4 hemolytic activities, activities of MBL–MASP-1 and MBL–MASP-2 complexes and neuroleptic usage.^{67,68} Although Hakobyan et al.⁶⁷ found more than a 50% decrease in C3 hemolytic activity in drug-free patients in comparison with medicated ones, Maes et al.⁷¹ reported no difference in plasma C3 and C4 concentration in such patient groups. From the few and restricted data presented here, it appears that there is no significant effect of neuroleptic-medication on the total complement activity and on individual component levels and activities, although given the trends for increases seen in some studies, and the fact that differences between patients and controls on total complement activity also reached only trend levels in most studies, a role for neuroleptic medication cannot be excluded. Moreover, these data are confounded by several limitations: e.g., small sample sizes of the studies; differences in population stratification, diagnostic criteria and approaches, illness stage, course and treatment profile of patients, inappropriate statistics, etc. Thus, future comprehensive investigations are required for consideration of the influence of the psychotropic medication on the level and activity of the complement in schizophrenia.

Complement component polymorphisms in schizophrenia

Since the beginning of the 1980s, polymorphic variants of some complement components have been investigated for schizophrenia association. Most of the data obtained in this field are available on the "Schizophrenia Gene Database".⁸² So far, no association has been reported for C6 polymorphisms.^{83,84} Significant differences have been found in C3 polymorphism, with a decrease of C3*F allotype in schizophrenia,⁸⁴ contradictory to previous findings.⁸³ The most recent report was of no significant difference in C3 phenotype and allotype frequencies between schizophrenic patients and controls.⁸⁵ Since there is no consensus on C3*F prevalence in schizophrenic patients, this is still open to further investigation. C3 is a central protein of the complement system. Fragments of this versatile and flexible molecule interact with various proteins and fulfill diverse functions, i.e., complement activation, participation in phagocytosis and enhancement of antigen processing. All C3 allotypes appear to have the same hemolytic activity⁸⁶ and blood levels of the component,⁸⁷ but have been reported to have different capacity to bind to (unspecified) C3 receptors, e.g., the F type has higher affinity to the receptors compared to the S allotype.⁸⁸ Due to the importance of this interaction between C3 fragments and C3 receptors in multiple immunoregulatory processes, the investigation of C3 gene polymorphisms remains of interest in schizophrenia research.

In contrast to C3 components, there has been considerable investigation of components whose genes are located at the HLA class III region of the human genome (C2, factor B and C4). The main reason for this is that the HLA locus is the most important genetic region in the human genome in relation to infection and autoimmunity.⁸⁹ These complement components are

engaged at an early stage of all three pathways (Fig. 1), and any alteration in activity of these components could be crucial for the whole activation cascade. Nevertheless, the results are inconsistent and not compelling. Singer et al.⁹⁰ found a significant increase in frequency of the FB*F allele of factor B among paranoid schizophrenic patients (54% vs. 33% of controls), but Rudduck et al.⁹¹ provided contrary data supporting a decrease of this allele in familial schizophrenia. They also found a low frequency of FS phenotype of factor B in patients with positive family history of schizophrenia in comparison with controls, as well as with patients without such history.⁹¹ The observation on low prevalence of FS in schizophrenia was supported by Spanish⁸⁴ but not British researchers.⁸⁵ Wang et al.⁹² reported a significantly raised frequency of FB*S07 in schizophrenic patients. No evidence has been recorded for association of a C2 polymorphism.⁹²

Likewise, the results of a few studies on complement C4 in schizophrenia are inconsistent. Complement C4 is encoded by two separate polymorphic genes, producing the protein isotypes C4A and C4B, which have subtly different activities. Rudduck et al.⁹³ suggested a significant increase in homozygous C4B deficiency in schizophrenic patients, while Wang et al.⁹² and Schroers et al.⁹⁴ contradicted this. Our recent data on C4 protein isotypes in patients with a family history of the disease showed that serum C4B concentration was significantly decreased in schizophrenic patients vs. controls,⁷³ plausibly due to a C4B gene heterozygous deficiency in schizophrenia (Mayilyan, K.R. et al., unpublished data).⁹⁵

Since the beginning of the 21st century, success in the Human Genome and HapMap projects, as well as a breakthrough in molecular genetic methodology has transformed this area of research. However, first attempts to investigate an impact of the C4B (rs4600) and factor B (rs641153) single nucleotide polymorphisms (SNP) in schizophrenia susceptibility did not yield significant results.^{96,97} For future research, it would be critical to conduct a multi-approach screening of the entire “complement” region of the HLA region by using well-characterized subject groups and state-of-the-art molecular biology techniques. This will provide important information not only on the mechanism of a putative association of schizophrenia susceptibility with an individual polymorphic variant of any of these complement genes (i.e., factor B and C4), but also, about the possibility that certain “complotype” (extended HLA haplotype derived from C2, factor B, C4 polymorphic variants) in the HLA region plays a role in this disorder. A genetic epistasis between those loci should be considered as well, as these proteins are well-defined partners in the complement cascade and might functionally regulate expression of each other's gene. Finally, the multifactor estimation of individual genetic and/or haplotype variant(s) of these genes associated with schizophrenia course, clinical picture and treatment response may help elucidate the involvement of these proteins in the molecular pathophysiology of schizophrenia.

Conclusions

Increased hemolytic activity of the complement C1, C2, C4 components in schizophrenia has been reported by two or more groups (Table II). Two studies on different subject cohorts showed increased MBL MASP-2 activity in patients (Table II). Summarizing the data on activities of the complement pathway and individual components, it is possible that patients with schizophrenia as a group have alterations of the complement classical and lectin pathway proteins, which undergo dynamic changes, depending on the disease course, and particularly, the current condition of the neuroimmune crosstalk. However, it is unknown whether these findings, if valid, represent primary pathophysiologic features or are secondary to environmental epiphenomena that are associated with this illness.

More than one report indicates a significantly raised frequency of FB*F allotype,^{90,92} and low prevalence of factor B protein FS phenotype in schizophrenic patients.^{84,91} These results may

represent type 1 errors caused by incorrectly chosen comparison groups, small sample size, inappropriate diagnostic, laboratory and/or statistical methodology.

Supporting in part the data from Swedish research groups,⁹³ we have reported a decrease in C4B protein level in the serum of patients with schizophrenia,⁷³ which may be determined by a haplodeficiency of C4B genes (Mayilyan, K.R. et al., unpublished data). The genotyping data recently have been replicated in a family sample from the United States population by using simultaneously case-control and family-based association studies (FBAT).⁹⁵ FBAT analysis showed undertransmission of C4B alleles to patients with schizophrenia. A nonindependent case-control comparison showed a decrease in frequency of C4B in the patient group. Our results suggest that haplodeficiency of C4B is associated with an increased risk of schizophrenia.

Thus, it is likely that there are some alterations in the complement system involved in schizophrenia development and psychopathology. Because of the evidence for *in utero* developmental problems in schizophrenia, molecules involved in early brain development are reasonable candidates for investigations of the pathophysiology of the disorder. Inflammatory and immune reactions, in which complement has its unique and irreplaceable role, directly influence neuronal proliferation, differentiation, migration and apoptosis. Adverse events in the second trimester of intrauterine life, such as microbial infections (e.g., toxoplasma gondii, herpes simplex virus type 2)⁹⁸ could require complement activation to protect brain cells from microbial invasion and to clear damaged cells. Inappropriate activation of complement could damage developing neurons and glial cells, with subsequent abnormal neurodevelopment, which in turn would contribute to schizophrenia.

In recent years, longitudinal brain imaging studies of both early and adult onset schizophrenia indicate that progressive brain changes are more dynamic than previously thought,⁹⁹ with grey matter volume loss particularly striking in adolescence and appearing to be an exaggeration of the normal developmental pattern.¹⁰⁰ In this context, the complement system could have a dual role in schizophrenia: neuroprotective in etiology and neurodegenerative in pathogenesis. It will be worthwhile to study complement component expression in animal models of schizophrenia, for example, Koenig prenatal stress model, and in post-mortem schizophrenia brains versus controls, as was investigated in several other mental diseases such as Alzheimer's disease,^{47,42} Huntington's disease, etc.⁴⁸ However, it is important to note here that extensive studies of brain tissue of patients with schizophrenia show no evidence of neurodegeneration, raising questions about whether the progressive changes observed on magnetic resonance imaging are epiphenomena of treatment or of other associated factors, such as smoking, poor hygiene and diet. These concerns notwithstanding, a fuller understanding of the associations of changes in the complement system with schizophrenia may bring a new perspective for possible immunomodulation and immunocorrection of this mental illness.

For pursuing this aim, a multidimensional exploration of the complement system in schizophrenia would be necessary, including gene expression and protein level and activity investigations, in large, well-characterized clinical samples and with state-of-the-art molecular biology, protein and immune chemistry. Future work should focus on answering a number of questions: i) what complement alterations contribute to schizophrenia; ii) of them, which are triggered by infectious agents or related to the pathophysiology of the clinical condition, and which abnormalities inherited in the system represent risk factors contributing to the pathogenesis of schizophrenia; iii) what are the molecular mechanisms of the involvement of these genetic factors in the complement system, and what immunological functions are potentially affected, iv) how they influence neuro-immune crosstalk; and finally, v) how these aberrant processes are associated with the proposed neurodevelopmental abnormalities of schizophrenia. It would be interesting to determine in appropriate animal models whether the

maternal immune response to second trimester infection can change the levels of complement components during brain development, and whether such changes contribute to “schizophrenia-like” neurodevelopmental abnormalities in the fetal brain. In genetic association studies, genetic epistasis between multiple genes coding components of the complement system and different other immune loci of human genome (e.g., coding cytokines, chemokines, receptors, etc.) should be considered as well, as different proteins expressed by these genes are defined partners in certain immune and signal transduction processes and functionally regulate expression of each other. Finally, the multifactorial estimation of individual genetic and/or haplotype variant(s) of these genes associated with disease course, clinical picture and treatment response will elucidate the involvement of complement in the molecular pathophysiology of schizophrenia.

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References

1. Isohanni M, Jones P, Kempainen L, et al. Childhood and adolescent predictors of schizophrenia in the Northern Finland 1966 birth cohort--a descriptive life-span model. *Eur Arch Psychiatry Clin Neurosci* 2000;250(6):311–319. [PubMed: 11153966]
2. Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. *Dev Psychopathol* 2000;12(3):501–527. [PubMed: 11014750]
3. Harris EC, Barraclough B. Excess mortality of mental disorder. *Br J Psychiatry* 1998;173:11–53. [PubMed: 9850203]
4. Bermanzohn PC, Porto L, Arlow PB, Pollack S, Stronger R, Siris SG. Hierarchical diagnosis in chronic schizophrenia: A clinical study of co-occurring syndromes. *Schizophr Bull* 2000;26(3):517–525. [PubMed: 10993392]
5. Siris SG. Depression in schizophrenia: Perspective in the era of “Atypical” antipsychotic agents. *Am J Psychiatry* 2000;157(9):1379–1389. [PubMed: 10964850]
6. Kupferberg G, Heckers S. Schizophrenia and cognitive function. *Curr Opin Neurobiol* 2000;10(2):205–210. [PubMed: 10753790]
7. Green MF, Nuechterlein KH. Should schizophrenia be treated as a neurocognitive disorder? *Schizophr Bull* 1999;25(2):309–319. [PubMed: 10416733]
8. Gottesman II. Complications to the complex inheritance of schizophrenia. *Clin Genet* 1994;46(1 Spec No):116–123. [PubMed: 7988068]
9. Lewis DA, Lieberman JA. Catching up on schizophrenia: Natural history and neurobiology. *Neuron* 2000;28(2):325–334. [PubMed: 11144342]
10. Weinberger DR, Harrison PJ. Schizophrenia genes, gene expression, and neuropathology: On the matter of their convergence. *Mol Psychiatry* 2005;10(1):40–68. [PubMed: 15263907]
11. Gaughran F. Immunity and schizophrenia: Autoimmunity, cytokines, and immune responses. *Int Rev Neurobiol* 2002;52:275–302. [PubMed: 12498108]
12. Hinze-Selch D. Infection, treatment and immune response in patients with bipolar disorder versus patients with major depression, schizophrenia or healthy controls. *Bipolar Disord* 2002;4:81–83. [PubMed: 12479687]
13. Muller N. Immunological and infectious aspects of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2004;254(1):1–3. [PubMed: 14991371]
14. Jones AL, Mowry BJ, Pender MP, Greer JM. Immune dysregulation and self-reactivity in schizophrenia: Do some cases of schizophrenia have an autoimmune basis? *Immunol Cell Biol* 2005;83(1):9–17. [PubMed: 15661036]
15. Rothenmundt M, Arolt V, Bayer TA. Review of immunological and immunopathological findings in schizophrenia. *Brain Behav Immun* 2001;15(4):319–339. [PubMed: 11782102]

16. Rothermundt, M.; Arolt, V. Schizophrenia and Immunity. In: Ader, R., editor. Psychoneuro-immunology. Vol. 1. New York: Elsevier; 2007. p. 563-577.
17. Carroll MC. The complement system in regulation of adaptive immunity. *Nat Immunol* 2004;5(10): 981–986. [PubMed: 15454921]
18. Fang Y, Xu C, Fu YX, Holers VM, Molina H. Expression of complement receptors 1 and 2 on follicular dendritic cells is necessary for the generation of a strong antigen-specific IgG response. *J Immunol* 1998;160(11):5273–5279. [PubMed: 9605124]
19. Karp CL, Wysocka M, Wahl LM, et al. Mechanism of suppression of cell-mediated immunity by measles virus. *Science* 1996;273(5272):228–231. [PubMed: 8662504]
20. Kemper C, Chan AC, Green JM, Brett KA, Murphy KM, Atkinson JP. Activation of human CD4+ cells with CD3 and CD46 induces a T-regulatory cell 1 phenotype. *Nature* 2003;421(6921):388–392. [PubMed: 12540904]
21. Law, SKA.; Reid, KBM. Complement. Focus, D.; Male, editors. Oxford: IRL Press; 1995. p. 1-72.
22. Walport MJ. Complement. First of two parts. *N Engl J Med* 2001;344(14):1058–1066. [PubMed: 11287977]
23. Walport MJ. Complement. Second of two parts. *N Engl J Med* 2001;344(15):1140–1144. [PubMed: 11297706]
24. Sim RB, Tsiftoglou SA. Proteases of the complement system. *Biochem Soc Trans* 2004;173(1):367–375.
25. Janeway CA Jr, Medzhitov R. Innate immune recognition. *Annu Rev Immunol* 2002;20:197–216. [PubMed: 11861602]
26. Mevorach D, Mascarenhas JO, Gershov D, Elkon KB. Complement-dependent clearance of apoptotic cells by human macrophages. *J Exp Med* 1998;188(12):2313–2320. [PubMed: 9858517]
27. Nauta AJ, Daha MR, van Kooten C, Roos A. Recognition and clearance of apoptotic cells: a role for complement and pentraxins. *Trends Immunol* 2003;24(3):148–154. [PubMed: 12615211]
28. Mayilyan, KR.; Kang, YH.; Dodds, AW.; Sim, RB. The complement system in innate immunity. In: Heine, H., editor. *Innate Immunity of Plants, Animals and Humans*. Heidelberg: Springer; 2008. p. 219-236.
29. Korb LC, Ahearn JM. Clq binds directly and specifically to surface blebs of apoptotic human keratinocytes: Complement deficiency and systemic lupus erythematosus revisited. *J Immunol* 1997;158(10):4525–4528. [PubMed: 9144462]
30. Sim RB, Malhotra R. Interactions of carbohydrates and lectins with complement. *Biochem Soc Trans* 1994;22(1):106–111. [PubMed: 8206200]
31. Butko P, Nicholson-Weller A, Wessels MR. Role of complement component Clq in the IgG-independent opsonophagocytosis of group B streptococcus. *J Immunol* 1999;163(5):2761–2768. [PubMed: 10453019]
32. Petersen SV, Thiel S, Jensenius J-C. The mannan-binding lectin pathway of complement activation: Biology and disease association. *Mol Immunol* 2001;38(2–3):133–149. [PubMed: 11532276]
33. Endo Y, Takahashi M, Fujita T. Lectin complement system and pattern recognition. *Immunobiology* 2006;211(4):211–283. [PubMed: 16697915]
34. Vorup-Jensen T, Petersen SV, Hansen AG, et al. Distinct pathways of mannan-binding lectin (MBL)- and C1-complex autoactivation revealed by reconstitution of MBL with recombinant MBL-associated serine protease-2. *J Immunol* 2000;165(4):2093–2100. [PubMed: 10925294]
35. Malhotra R, Wornald MR, Rudd PM, Fischer PB, Dwek RA, Sim RB. Glycosylation changes of IgG associated with rheumatoid arthritis can activate complement via the mannose-binding protein. *Nat Med* 1995;1(3):237–243. [PubMed: 7585040]
36. Roos A, Bouwman LH, van Gijlswijk-Janssen DJ, Faber-Krol MC, Stahl GL, Daha MR. Human IgA activates the complement system via the mannan-binding lectin pathway. *J Immunol* 2001;167(5): 2861–2868. [PubMed: 11509633]
37. Arnold JN, Wormald MR, Suter DM, et al. Human serum IgM glycosylation: Identification of glycoforms that can bind to mannan-binding lectin. *J Biol Chem* 2005;280(32):29080–29087. [PubMed: 15955802]

38. Krarup A, Sorensen UB, Matsushita M, Jensenius J-C, Thiel S. Effect of capsulation of opportunistic pathogenic bacteria on binding of the pattern recognition molecules mannan-binding lectin, L-ficolin, and H-ficolin. *Infect Immun* 2005;73(2):1052–1060. [PubMed: 15664949]
39. Morgan BP, Harris CL. Complement therapeutics: History and current progress. *Mol Immunol* 2003;40(2–4):159–170. [PubMed: 12914822]
40. Gasque P, Dean YD, McGreal EP, VanBeek J, Morgan BP. Complement components of the innate immune system in health and disease in the CNS. *Immunopharmacology* 2000;49(1–2):171–186. [PubMed: 10904116]
41. Rus H, Cudrici C, David S, Niculescu F. The complement system in central nervous system diseases. *Autoimmunity* 2006;39(5):395–402. [PubMed: 16923539]
42. Lanzrein AS, Jobst KA, Thiel S, et al. Mannan-binding lectin in human serum, cerebrospinal fluid and brain tissue and its role in Alzheimer's disease. *Neuroreport* 1998;9(7):1491–1495. [PubMed: 9631454]
43. Wagner S, Lynch NJ, Walter W, Schwaible WJ, Loos M. Differential expression of the murine mannose-binding lectins A and C in lymphoid and non lymphoid organs and tissues. *J Immunol* 2003;170(3):1462–1465. [PubMed: 12538708]
44. Schäfer MK, Schwaible WJ, Post C, et al. Complement C1q is dramatically up-regulated in brain microglia in response to transient global cerebral ischemia. *J Immunol* 2000;164(10):5446–5452. [PubMed: 10799911]
45. Bonifati DM, Kishore U. Role of complement in neurodegeneration and neuroinflammation. *Mol Immunol* 2007;44(5):999–1010. [PubMed: 16698083]
46. McGeer PL, Akiyama H, Itagaki S, et al. Activation of the classical complement pathway in brain tissue of Alzheimer patients. *Neurosci Lett* 1989;107(1–2):341–346. [PubMed: 2559373]
47. Yasojima K, Schwab C, McGeer EG, et al. Up-regulated production and activation of the complement system in Alzheimer's disease brain. *Am J Pathol* 1999;154(3):927–936. [PubMed: 10079271]
48. Singhrao SK, Neal JW, Morgan BP, Gasque P. Increased complement biosynthesis by microglia and complement activation on neurons in Huntington's disease. *Exp Neurol* 1999;159(2):362–376. [PubMed: 10506508]
49. Yamada T, McGeer PL, McGeer EG. Lewy bodies in Parkinson's disease are recognized by antibodies to complement proteins. *Acta Neuropathol (Berl)* 1992;84(1):100–104. [PubMed: 1502878]
50. Singhrao SK, Neal JW, Gasque P, Morgan BP, Newman GR. Role of complement in the aetiology of Pick's disease? *J Neuropathol Exp Neurol* 1996;55(5):578–593. [PubMed: 8627348]
51. Rahpeymai Y, Hietala MA, Wilhelmsson U, et al. Complement: A novel factor in basal and ischemia-induced neurogenesis. *EMBO J* 2006;25(6):1364–1374. [PubMed: 16498410]
52. Stevens B, Allen NJ, Vazquez LE, et al. The classical complement cascade mediates CNS synapse elimination. *Cell* 2007;131(6):1164–1178. [PubMed: 18083105]
53. Fourgeaud L, Boulanger LM. Synapse remodeling compliments of the complement system. *Cell* 2007;131(6):1034–1036. [PubMed: 18083091]
54. Miller G. Neurobiology. Immune molecules prune synapses in developing brain. *Science* 2007;318(5857):1710–1711. [PubMed: 18079374]
55. O'Barr SA, Caguioa J, Gruol D, Perkins G, Ember JA, Hugli T, Cooper NR. Neuronal expression of a functional receptor for the C5a complement activation fragment. *J Immunol* 2001;166(6):4154–4162. [PubMed: 11238666]
56. van Beek J, Elward K, Gasque P. Activation of complement in the central nervous system: Roles in neurodegeneration and neuroprotection. *Ann N Y Acad Sci* 2003;992:56–71. [PubMed: 12794047]
57. Lehmann-Facius H. Über die Liquordiagnose der Schizophrenien. *Klin Wochenschr* 1937;16:1646–1648.
58. Ganguli R, Rabin BS, Kelly RH, Lyte M, Ragu U. Clinical and laboratory evidence of autoimmunity in acute schizophrenia. *Ann N Y Acad Sci* 1987;496:676–685. [PubMed: 3474998]
59. Knight J. Schizophrenia and influenza. *Lancet* 1991;338(8763):390. [PubMed: 1677734]
60. Kirch DG. Infection and autoimmunity as etiologic factors in schizophrenia A review and reappraisal. *Schizophr Bull* 1993;19(2):355–370. [PubMed: 8322038]

61. Mayilyan, KR.; Soghoyan, AF.; Sim, RB. Increased functional activities of the complement classical and MBL pathways in schizophrenia. 1st Joint Meet Eur Natl Soc Immunol 16th Eur Cong Immunol; Sept 6–9; Paris. 2006. Abst PA3001
62. Spivak B, Radwan M, Elimelech D, Baruch Y, Avidan G, Tyano S. A study of the complement system in psychiatric patients. *Biol Psychiatry* 1989;26(6):640–642. [PubMed: 2790102]
63. Spivak B, Radwan M, Brandon J, Baruch Y, Stawski M, Tyano S, Weizman A. Reduced total complement haemolytic activity in schizophrenic patients. *Psychol Med* 1993;23(2):315–318. [PubMed: 8332647]
64. Sasaki T, Nanko S, Fukuda R, Kawate T, Kunugi H, Kazamatsuri H. Changes of immunological functions after acute exacerbation in schizophrenia. *Biol Psychiatry* 1994;35(3):173–178. [PubMed: 7909694]
65. Shcherbakova IV, Neshkova EA, Dotsenko VL, et al. Activation of kallikrein-kinin system, degranulating activity of neutrophils and blood-brain barrier in schizophrenia. *Zh Nevrol Psikhiatr Im S S Korsakova* 1998;98(6):38–41. [PubMed: 9677697]
66. Shcherbakova I, Neshkova E, Dotsenko V, Platonova T, Shcherbakova E, Yarovaya G. The possible role of plasma kallikrein-kinin system and leukocyte elastase in pathogenesis of schizophrenia. *Immunopharmacology* 1999;43(2–3):273–279. [PubMed: 10596863]
67. Hakobyan S, Boyajyan A, Sim RB. Classical pathway complement activity in schizophrenia. *Neurosci Lett* 2005;374(1):35–37. [PubMed: 15631892]
68. Mayilyan KR, Arnold JN, Presanis JS, Soghoyan AF, Sim R. Increased complement classical and mannan-binding lectin pathway activities in schizophrenia. *Neurosci Lett* 2006;404(3):336–341. [PubMed: 16860475]
69. Mayilyan KR, Krarup A, Soghoyan AF, Hartung T, Sim RB. L-ficolin and MBL components of the complement activation lectin pathway in schizophrenia. *Mot Immunol* 2007;44(16):3940.
70. Wong CT, Tsoi WF, Saha N. Acute phase proteins in male Chinese schizophrenic patients in Singapore. *Schizophr Res* 1996;22(2):165–171. [PubMed: 8958601]
71. Maes M, Delange J, Ranjan R, Meltzer AY, Desnyder R, Cooremans W, Scharpé S. Acute phase proteins in schizophrenia mania and major depression: Modulation by psychotropic drugs. *Psychiatry Res* 1997;66(1):1–11. [PubMed: 9061799]
72. Cazzullo CL, Saresella M, Roda K, et al. Increased levels of CD8+ and CD4+ 45RA+ lymphocytes in schizophrenic patients. *Schizophr Res* 1998;31(1):49–55. [PubMed: 9633836]
73. Mayilyan KR, Dodds AW, Boyajyan AS, Soghoyan AF, Sim RB. Complement C4B protein in schizophrenia. *World J Biol Psychiatry*. 2007 Advance publication
74. Yang Y, Wan C, Li H, et al. Altered levels of acute phase proteins in the plasma of patients with schizophrenia. *Anal Chem* 2006;78(11):3571–3576. [PubMed: 16737209]
75. Glatt SJ, Everall IP, Kremer WS, et al. Comparative gene expression analysis of blood and brain provides concurrent validation of SELENBPI up-regulation in schizophrenia. *Proc Natl Acad Sci U S A* 2005;102(43):15533–15538. [PubMed: 16223876]
76. Movers AL, Henry M, García-Hernández A, Fernández-López L. Acute phase proteins as biological markers of negative psychopathology in paranoid schizophrenia. *Actas Esp Psiquiatr* 2007;35(4): 249–252. [PubMed: 17592787]
77. Mayilyan KR, Presanis JS, Arnold JN, Hajela K, Sim RB. Heterogeneity of MBL-MASP complexes. *Mot Immunol* 2006;43(8):1286–1292.
78. Mayilyan KR, Presanis JS, Arnold JN, Sim RB. Discrete MBL-MASP complexes show wide inter-individual variability in concentration: Data from UK vs. Armenian populations. *Int J Immunopathol Pharmacol* 2006;19(3):567–580. [PubMed: 17026842]
79. Sim RB, Clark H, Hajela K, Mayilyan KR. Collectins and host defence. *Novartis Found Symp* 2006;279:170–181. [PubMed: 17278394]
80. Zarrabi MH, Zucker S, Miller F, Derman RM, Romano GS, Hartnett JA, Varma AO. Immunologic and coagulation disorders in chlorpromazine-treated patients. *Ann Intern Med* 1979;91(2):194–199. [PubMed: 313732]
81. O’Riordan JW, Kelleher D, Williams Y, Bloomfield FJ. Effect of lithium therapy on inflammatory response. *Inflammation* 1986;10(1):49–57. [PubMed: 3957422]

82. Allen, NC.; Bagade, S.; Tanzi, R.; Bertram, L. The SchizophreniaGene Database. Schizophrenia Research Forum. <http://www.schizophreniaforum.org/res/sczgene/default.asp>
83. Rudduck C, Beckman L, Franzén G, Lindström L. C3 and C6 complement types in schizophrenia. *Hum Hered* 1985;35(4):255–258. [PubMed: 4029965]
84. Fañanás L, Moral P, Panadero MA, Bertranpetit J. Complement genetic markers in schizophrenia: C3, B F and C6 polymorphisms. *Hum Hered* 1992;42(3):162–167. [PubMed: 1511994]
85. Blackwood DH, Muir WJ, Stephenson A, et al. Reduced expression of HLA-B35 in schizophrenia. *Psychiatr Genet* 1996;6(2):51–59. [PubMed: 8840390]
86. Colten HR, Alper CA. Hemolytic efficiencies of genetic variants of human C3. *J Immunol* 1972;108(5):1184–1187. [PubMed: 5029137]
87. Agarwal DP, Benkmann HG, Goedde HW. Genetic polymorphism of the third component of complement (C3) and levels of I C- I A-globulin in sera of German and Spanish populations. *Hum Hered* 1972;22(4):356–361. [PubMed: 4119082]
88. Arvilommi H. Capacity of complement c3 phenotypes to bind on to mononuclear cells in man. *Nature* 1974;251(5477):740–741. [PubMed: 4427677]
89. Horton R, Wilming L, Rand V, et al. Gene map of the extended human MHC. *Nat Rev Genet* 2004;5(12):889–899. [PubMed: 15573121]
90. Singer L, Mayer S, Tongio MM, et al. Frequencies of HLA-A, C and Bf antigens in schizophrenic patients originated from Alsace. *Encephale* 1982;8(1):9–15. [PubMed: 6980113]
91. Rudduck C, Franzén G, Hansson A, Rorsman B. Properdin factor B (Bf) types in schizophrenia. *Hum Hered* 1984;34(5):331–333. [PubMed: 6566648]
92. Wang C, Jian BX, Jiang XD, Zhao XZ. Investigation of allotypes of HLA class III (C2, BF and C4) in patients with schizophrenia. *Chin Med J* 1992;105:316–318. [PubMed: 1618015]
93. Rudduck C, Beckman L, Franzén G, Jacobsson L, Lindström L. Complement factor C4 in schizophrenia. *Hum Hered* 1985;35(4):223–226. [PubMed: 3875548]
94. Schroers R, Nothen MM, Rietschel M, et al. Investigation of complement C4B deficiency in schizophrenia. *Hum Hered* 1997;47(5):279–282. [PubMed: 9358016]
95. Mayilyan, KR.; Weinberger, DR.; Wu, YL.; Kolachana, B.; McBride, K.; Yung, CY. Association of complement C4B gene deficiency with schizophrenia: Studies of European American families and controls. XV World Cong Psychiatr Genet; Oct 7–11; New York. 2007. Abst #306
96. Wei J, Hemmings GP. TNXB locus may be a candidate gene predisposing to schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2004;125(1):43–49. [PubMed: 14755442]
97. Tochigi M, Zhang X, Ohashi J, et al. Association study between the TNXB locus and schizophrenia in a Japanese population. *Am J Med Genet B Neuropsychiatr Genet* 2007;144(3):305–309. [PubMed: 17192952]
98. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry* 2001;58(11):1032–1037. [PubMed: 11695949]
99. Rapoport JL, Addington AM, Frangou S. The neurodevelopmental model of schizophrenia Update 2005. *Mol Psychiatry* 2005;10(5):434–449. [PubMed: 15700048]
100. Szulc A, Galinska B, Czernikiewicz A. Schizophrenia--neurodevelopmental and neurodegenerative theory revisited. *Psychiatr Pol* 2005;39(2):249–258. [PubMed: 15881620]

Fig 1.

The complement activation pathways. The sequence of classical pathway activation is shown at the bottom, with immunoglobulin (Ig) G antibodies bound to a bacterial surface as an example of a target. C1q binds to the surface (bottom left). C1 binding activates C1r then C1s, which then cleaves C4 and C2. The C4b2a complex (C3 convertase) forms on the bacterial surface and cleaves C3. One C3b binds to C4b2a, and forms a binding site for C5. C5 is cleaved, then the C5b6789 complex (the MAC, membrane attack complex) assembles and causes membrane damage. At the top of the figure, the lectin pathway is shown. MBL (mannan-binding lectin) or a ficolin binds directly to a bacterial surface, and MASP-2 (MBL-associated serine protease) is activated. This then cleaves C4 and C2, and the pathway follows the same sequence as the classical pathway. At the left, the alternative pathway is shown. C3b (derived from the classical or lectin pathway, or by activation by C3(H₂O)Bb, as discussed in the text, binds to the surface, then binds factor B (FB), which is activated by factor D (FD), forming the C3 convertase, C3bBb. More C3 is cleaved by C3bBb, then C5 activation and MAC assembly follows, as for the classical pathway. On the right, the host cell and its mechanisms for protection against complement attack are shown. CD59 binds the C5b678 complex and prevents binding of C9. CD35 (CR1), CD46 (MCP) and CD55 (DAF) all destabilize the C3 convertases or inhibit their formation. Soluble regulators like factor H (FH) may become transiently bound on the surface, and also regulate convertase formation.

TABLE I

The main immune functions of the complement system.

Role of Complement in Immunity		
First-Line Defense Against foreign Invaders	Bridging Innate and Adaptive Immunity	Housekeeping/Self-Waste Disposal
Opsonization and adjuvant activities: binding to microorganisms of any of C3b, iC3b, C3d, C4b, C1q, MBL, ficolins tag microorganisms for uptake by phagocytes or dendritic cells or retention by FDCs for recognition by cognate B lymphocytes.	Enhancement of antibody response: C4b, C3b, iC3b, C3d,g and C3d bind to CD21 and CD35 on B lymphocytes and enhance the signal via B-cell antigen receptors, thus, lowering the threshold of B-lymphocyte activation. ¹⁷ C4b, C3b, iC3b, C3d,g and C3d bind to CD21 and CD35 on FDCs resulting in secretion of chemoattractants for B lymphocytes, and are important in organizing GC in the follicles. ¹⁸ C3b and C4b promote clearance of immune (antibody-antigen) complexes (see housekeeping II).	Clearance of apoptotic and necrotic host cells: C1q, MBL, C3b and C4b, also L- and H-ficolins bind apoptotic and necrotic cells initiate complement activation, following chemoattraction of neutrophils, macrophages, etc., and/or formation of MACs.
Foreign cell lysis: complement activation via any pathway forms MACs on the cell membrane of microorganisms, which lyse the cell.	Improvement of adaptive immune memory: post-GC B lymphocytes continue to require complement (C4b, C3b, iC3b, C3d,g and C3d) in continued antigen selection, as maintenance of long-term memory in B cells is dependent on CD21 and CD35. C3b and C4b bound to immune complexes are source for required activation of FDC CD21 and CD35, essential for an effective recall of an immune response. ¹⁷	Clearance of immune complexes: via complement binding sites, C3b and C4b bind to immune complexes and attach them to the membrane of erythrocytes promoting their transportation within circulation and subsequent clearance in liver and spleen.
Activation of leukocytes/chemotaxis: MBL, L- and H-ficolins bound to microorganisms, activate leukocytes, promoting degranulation activity of neutrophils and modulating cytokine release by macrophages and/or monocytes. Soluble C5a serves as chemoattractant for leukocytes.	Regulation of T-cell immunity: C3a and C5a stimulate C3aR and C5aR of T lymphocytes and regulate their response. Products of complement activation also regulate T lymphocytes, directly, via CD46 on their membrane, ^{19,20} or indirectly, by modulating cytokine release, and activating APCs.	

The role of complement in immunity is defined by its three main functions: i) first-line defense against foreign invaders such as different types of microorganisms (bacteria, viruses, fungi, etc); ii) a bridge between innate and adaptive immunity (reinforcing adaptive immune response); iii) a janitor of self-waste disposal (maintenance and removing of altered self cells or cell remnants). MBL, manan-binding lectin; FDC, follicular dendritic cells; MAC, membrane attack complex; GC, germinal centers.

TABLE II
Complement component activity, concentration and expression data reported for schizophrenia (1989–2007).

Complement Component	Method	Report	p Value	#Sp vs. #C	Patients	Ethnicity	Ref.
Classical pathway activity							
Classical pathway functional activity	Wieslab ELISA	↑	<0.0001	103 vs.123	Chronic SP	Eu	61
Complement total hemolytic activity							
Complement total hemolytic activity	CH100	↓	NS	20 vs. 18	Chronic, drug-free SP	As/Af/Eu	62
	CH100	↓	<0.007	91 vs. 37	Chronic SP	As/Af/Eu	63
	CH50	↔	~1	14 vs. 20	Acute SP	As	64
	CH50	↑	NS	10 vs. 100	Male chronic SP (undifferentiated)	Eu	65, 66
	CH50	↑	NS	24 vs. 28	Acute SP	Eu	67
	CH50	↑	<0.02	45 vs. 29	SP in remission	Eu	68
C1, C3, C4 hemolytic activity		↑	<0.05	10 vs. 100	Male chronic SP	Eu	65, 66
		↑	<0.004	24 vs. 28	Acute SP	Eu	67
C4 hemolytic activity		↑	<0.02	45 vs. 29	SP in remission	Eu	68
C2 hemolytic activity		↑	<0.05	10 vs. 100	Male chronic SP	Eu	65, 66
		↓	<0.002	24 vs. 28	Acute SP	Eu	67
C5 hemolytic activity		↑	NS	10 vs.1 00	Male chronic SP	Eu	65, 66
Alternative pathway activity							
Alternative pathway functional activity	Wieslab ELISA	↔	~1	103 vs.123	Chronic SP	Eu	61
Lectin pathway activity							
Lectin pathway functional activity	Wieslab ELISA	↑	<0.001	103 vs.123	Chronic SP	Eu	61
MBL–MASP-2 activity	ELISA	↑	<0.01	45 vs. 62	SP in remission	Eu	68
	ELISA	↑	<0.035	103 vs.127	Chronic SP	Eu	69
MBL–MASP-1 activity	ELISA	↓	NS	45 vs. 62	SP in remission	Eu	68
	ELISA	↑	<0.019	103 vs.127	Chronic SP	Eu	69
L-Ficolin–MASP-2	ELISA	↑	<0.05	103 vs.127	Chronic SP	Eu	69
L-Ficolin–MASP-1	ELISA	undetectable for both SP & C groups		103 vs.127	Chronic SP	Eu	69
Concentration of components							

Complement Component	Method	Report	p Value	#Sp vs. #C	Patients	Ethnicity	Ref.
Serum/plasma C3 level	RID	↑	NS	20 vs. 18		As/Af/Eu	62
	RID	↔	~1	91 vs. 37	Chronic SP	As/Af/Eu	63
	RIE	↓	<0.01	39 vs. 41	Chronic SP	As	70
	RIE	↓	NS	44 vs. 41	SP in remission	As	70
	RIE	↓	NS	15 vs. 41	Acute SP	As	70
	RIE	↓	NS	50 vs. 50	Male SP	As	70
	LN	↑	<0.02	10 vs. 21	Drug-free SP	Eu	71
Serum/plasma C4 level	LN	↑	NS	17 vs. 18	Medicated SP	Eu	71
	LN	↑	NS	29 vs. 20	Drug-free SP	Eu	72
	RID	↔	~1	20 vs. 18		As/Af/Eu	62
	RID	↔	~1	91 vs. 37	Chronic SP	As/Af/Eu	63
	LN	↑	<0.03	10 vs. 21	Drug-free SP	Eu	71
	LN	↑	NS	17 vs. 18	Medicated SP	Eu	71
	LN	↔	NS	29 vs. 20	Drug-free SP	Eu	72
Serum C4B level	ELISA	↓	<0.01	45 vs. 51	SP in remission	Eu	73
Plasma factor B level	2D-GE	↑	<0.02	22 vs. 20	Male SP	As	74
Serum MBL level	ELISA	↑	NS	45 vs. 62	SP in remission	Eu	68
Serum L-ficolin level	ELISA	↑	<0.002	103 vs. 127	Chronic SP	Eu	69
Gene expression of components							
Blood cell ficolin-M	Microarray	↓	<0.0005	30 vs. 24		As	75

RID, radial immunodiffusion; LN, laser nephelometry; RIE, rocket immunoelectrophoresis; ELISA, enzyme-linked immunosorbent assay; 2D-GE, two-dimensional gel electrophoresis; NS, $p =$ not significant. SP, schizophrenic patients; Eu, European; As, Asian; Af, African.

↓decrease

↑increase

↔ ~ equal