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Deciphering microbiome and neuroactive immune gene interactions in schizophrenia

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Abstract

The body's microbiome represents an actively regulated network of novel mechanisms that potentially underlie the etiology and pathophysiology of a wide range of diseases. For complex brain disorders such as schizophrenia, understanding the cellular and molecular pathways that intersect the bidirectional gut-brain axis is anticipated to lead to new methods of treatment. The means by which the microbiome might differ across neuropsychiatric and neurological disorders are not known. Brain disorders as diverse as schizophrenia, major depression, Parkinson's disease and multiple sclerosis appear to share a common pathology of an imbalanced community of commensal microbiota, often measured in terms of a leaky gut phenotype accompanied by low level systemic inflammation. While environmental factors associated with these disease states might contribute to intestinal pathologies, products from a perturbed microbiome may also directly promote specific signs, symptoms and etiologies of individual disorders. We hypothesize that in schizophrenia, it is the putatively unique susceptibility related to genes that modulate the immune system and the gut-brain pleiotropy of these genes which leads to a particularly neuropathological response when challenged by a microbiome in dysbiosis. Consequences from exposure to this dysbiosis may occur during pre- or post-natal time periods and thus may interfere with normal neurodevelopment in those who are genetically predisposed. Here, we review the evidence from the literature which supports the idea that the intersection of the microbiome and immune gene susceptibility in schizophrenia is relevant etiologically and for disease progression. Figuring prominently at both ends of the gut-brain axis and at points in between are proteins encoded by genes found in the major histocompatibility complex (MHC), including select MHC as well as non-MHC complement pathway genes.

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Keywords

gut-brain axis; neurodevelopment; synapses; immune system; enteric nervous system; complement C4; gene-environmental interactions

Introduction

Schizophrenia is a severe psychiatric disorder that is characterized by a series of complex and debilitating symptoms, such as delusions, hallucinations, anhedonia, social withdrawal and disorganized thought processes (APA, 2013). The neurobiological mechanisms orchestrating the causes and pathophysiology of this disorder are not known. There are many implicated pathways and causality is likely multifactorial. Schizophrenia has a very evident familial component, but twin studies demonstrate that this heritability is not fully penetrant (Cannon et al., 2000; Kato et al., 2005; Tsujita et al., 1998). Current hypotheses regarding etiology focus on genetic and environmental factors that may interact during sensitive neurodevelopmental time points (Demjaha et al., 2012; European Network of National Networks studying Gene-Environment Interactions in et al., 2014; Kavanagh et al., 2015; Modinos et al., 2013; Nimgaonkar et al., 2017; Schizophrenia Working Group of the Psychiatric Genomics, 2014; Tsuang, 2000; Ursini et al., 2018). Toward this end, the immune system has become a highly-interrogated candidate for studies of schizophrenia susceptibility. This immune focus derives from evidence of environmental immune challenges as risk factors for the disease and on associations of the disorder with the immune gene-rich 6p21–6p22 chromosomal regions (International Schizophrenia et al., 2009; Jones et al., 2005; Kirch, 1993; Knuesel et al., 2014; Meyer, 2013; Muller, 2014; Rothermundt et al., 2001; Shi et al., 2009; Stefansson et al., 2009; Torrey and Peterson, 1976; Yolken and Torrey, 2008). Supporting an immune dysfunction hypothesis for schizophrenia are findings that immune proteins encoded in the 6p21–6p22 region also work in various central nervous system (CNS) capacities including the formation and maintenance of properly functioning synapses (Boulanger, 2009).

An important regulator of immune system homeostasis is the gastrointestinal (GI) mucosa and the large population of resident microbes that help to establish and coordinate the body’s immune tolerance and defense. This process may unfold insufficiently if there is a predisposing polymorphism or mutation in a gene that modifies immunological functions (i.e. an immune gene) and/or if exposures to environmental factors such as diet, infection, stress, toxins, and medications disrupt the normal functioning and balance of the gut microbiome (Abegunde et al., 2016; Sandhya et al., 2016; Wu et al., 2011). At risk is the ability of the host to launch an appropriate immune response against pathogens and the ability to accurately recognize self vs non-self cellular and molecular entities (Chistiakov et al., 2014; Dinan and Cryan, 2015; Sandhya et al., 2016; Wekerle, 2017). The timing of the environmental trigger is a particularly important consideration given the dynamism of gene activities during neurodevelopment. An environmental exposure during pregnancy or adolescence in a genetically susceptible individual could result in an inadequately seeded microbiome that has lifelong health effects.

Experimental findings from mechanistic studies in rodent models demonstrate that direct CNS effects are tangible consequences of a gut microbiome that is perturbed during early neurodevelopment or in adulthood (Codagnone et al., 2018; Dinan et al., 2014) (Collins et al., 2012; Diaz Heijtz et al., 2011; Erny et al., 2015; Foster and McVey Neufeld, 2013; Hsiao et al., 2013; Luczynski et al., 2016; Sampson and Mazmanian, 2015; Stilling et al., 2014). Translational support from clinical populations is more difficult to obtain, especially data that might reflect endophenotypes characteristic of schizophrenia and that are not the product of medication. In this paper, we examine the evidence that a gut microbiome in dysbiosis and the dysregulation of immune genes known to be associated with schizophrenia are integrally linked. We review the neurobiology of select immune genes implicated from genetic susceptibility studies of schizophrenia and evaluate gene duplicity of function peripherally and in the CNS in the context of a gut-immune-brain interactome. To the extent possible in this still burgeoning field, we address microbial interactions with these gene products at both the gut and CNS sites.

Overview of immune gene dysregulation in schizophrenia

In individuals with schizophrenia, genome-wide association studies (GWAS) revealed a significant disease connection driven by a structurally complex region of chromosome 6 (Corvin and Morris, 2014; International Schizophrenia et al., 2009; Kodavali et al., 2014; Sekar et al., 2016; Shi et al., 2009; Stefansson et al., 2009). This large stretch contains over 400 genes that encompass the major histocompatibility complex (MHC), the proteins of which are encoded by the human leukocyte antigen (HLA) genes (Horton et al., 2004). Complement C4 loci, the most recent genes demonstrating strong biological and functional associations with schizophrenia, are also located in this region (Sekar et al., 2016). Among brain pathologies evident in schizophrenia are deficient densities of dendritic spines in the prefrontal cortex and hippocampus, and this neuropathology is thought to be a product of aberrantly accelerated synaptic pruning during adolescence (Bennett et al., 2013; Clarke et al., 2018). Although the functions of MHC and complement pathway proteins are most well understood in the peripheral immune system, both actively participate in homologous processes in the brain including synapse formation, tagging, and removal (Boulanger, 2009; Fourgeaud and Boulanger, 2007; Glynn et al., 2011; Goddard et al., 2007; Huh et al., 2000; McAllister, 2014; Presumey et al., 2017; Shatz, 2009; Stephan et al., 2013; Stevens et al., 2007).

The Major Histocompatibility Complex in schizophrenia and in the gut

The MHC proteins are found on cell surfaces where they bind and deliver self and non-self antigens to appropriate T-cells. Class I MHC molecules are recognized by cytotoxic CD8(+) T-cells, and class II MHC are recognized by CD4(+) helper T-cells. Class III MHC encode cytokines, heat shock proteins and several complement components including C4 (Murphy et al., 2012). While the primarily described function of MHCI class proteins, in particular, has been to process and present antigens in systemic circulation in support of establishing and effecting immunity, rodent studies show that these proteins are also involved in such CNS activities as neurogenesis, neuronal migration and synaptic pruning and plasticity (Glynn et al., 2011; Goddard et al., 2007; Huh et al., 2000; McAllister, 2014; Shatz, 2009).

As indicated earlier, these neurobiological processes are highly relevant to schizophrenia and its neurodevelopmental origins (Balu and Coyle, 2011; Mei and Xiong, 2008; Stephan et al., 2006). In rodents, MHCI expression in the CNS is dynamic with elevated levels early during development and which generally taper off upon adulthood (Chacon and Boulanger, 2013; Needleman et al., 2010). During aging, expression levels increase again, apparently as a function of glial cell expression, whereas expression earlier in the lifespan appears to be predominantly neuronal. MHCI may also be expressed by astrocytes when the brain's immune system is activated (Mokhtari and Lachman, 2016; Sobue et al., 2018).

If antigens are mislabeled when immunity is being primed, the host may become susceptible to infectious disease, cancer and autoimmunity. Susceptibility to these conditions may be driven or otherwise compounded by a genetic predisposition encoded by the HLA genes. A number of common infections – *Toxoplasma gondii*, cytomegalovirus, Herpes Simplex Virus Type I - are thought to persist in schizophrenia as evident from persistent elevations of antibody levels in individuals with the disorder compared to controls (Hornig, 2013; Yolken and Torrey, 2008). Studies that incorporate HLA typing found that certain of these polymorphisms were significantly associated with specific neurotropic infections and that this HLA-based susceptibility was altered in schizophrenia (Avramopoulos et al., 2015; Parks et al., 2018). These results support and extend findings from earlier studies that also detected associations between HLA polymorphisms and exposure to neurotropic viruses in schizophrenia (Bamne et al., 2012; Kim et al., 2007; McAllister, 2014; Shirts et al., 2008). As such, the extent to which a pathogenic agent or other condition can activate the immune response, including an imbalanced commensal microbial composition, may be governed by HLA susceptibilities.

A study in mice which evaluated possible mechanisms by which MHC genes might influence the gut microbiome found that specific genotypes modulated antibody responses against gut commensals, thus providing protection against or rendering susceptibility to enteric infection (Kubinak et al., 2015). Furthermore, it is this immune response directed toward gut bacteria that is thought to perpetrate inflammatory bowel diseases, in part, through altered MHCII activation of CD4(+) T cells (Thelemann et al., 2014). In humans, HLA haplotypes are definitively associated with the autoimmune intestinal disorder, celiac disease (Cukrowska et al., 2017; Karhus et al., 2018; Leonard et al., 2017), and with some cases of inflammatory bowel diseases such as Crohn's disease and ulcerative colitis (Gomes et al., 2018; Jung et al., 2016; Lee et al., 2018; Palmieri et al., 2017; Saito et al., 2018). Interestingly, these bowel disorders in turn are overrepresented in individuals with schizophrenia (Fadgyas-Stanculete et al., 2014; Filipovic and Filipovic, 2014; Gupta et al., 1997; Vaknin et al., 2004; Vu et al., 2014).

The complement system in schizophrenia and in the gut

The complement system is composed of three pathways (classical, lectin and alternative) that function to amplify and direct the innate immune response in order to protect the host from potentially dangerous antigens such as infectious pathogens, antigenic foods and cellular debris. Complement components also work with the adaptive immune system to respond to foreign proteins and form immune complexes with antibody-bound antigens. The

complement system antigen clearing process culminates with the activation and recruitment of phagocytes to aid removal of antigenic culprits by the membrane attack complex (Murphy et al., 2012).

As observed for MHCI proteins, components of the classical complement pathway including C1q, C3, C4, are involved with synapse activities during neurodevelopment and to a less well characterized extent during adulthood. This brain complement system encodes components that participate in an immune signaling cascade and results in the formation and directed pruning of synapses during development, in early neurodegenerative diseases and in response to inflammation and exposure to brain pathogens in adults. (Hong et al., 2016; Lui et al., 2016; Vasek et al., 2016) (Bialas and Stevens, 2013; Boulanger, 2009; Fourgeaud and Boulanger, 2007; Nimgaonkar et al., 2017; Presumey et al., 2017; Ransohoff and Stevens, 2011; Schafer et al., 2012; Stephan et al., 2013; Stevens et al., 2007). In experimental models of neurodevelopment, C1q and C3 are highly expressed in rodent cortex at postnatal day 5 with a reduction to baseline amounts at postnatal day 30 (Stevens et al., 2007). While C1q and C3 are generally not detectable in the normal adult mouse brain, there is evidence for CNS expression of complement components following injury, immune challenge and aging (Bellander et al., 2001; Mocco et al., 2006; Stephan et al., 2013; Xiao et al., 2016).

Research of the complement pathways in schizophrenia received a significant boost by the findings of Sekar et al (2016), who showed that the number of copies of complement C4 genes dictated the amount of protein that was produced, with greater levels associated with a greater risk of schizophrenia (Sekar et al., 2016). In a clinical study that incorporated brain imaging, C4 copy number was positively correlated with neuropil contraction, an indicator of increased pruning, or decreased formation of synapses, in a number of different brain regions including the prefrontal cortex (Prasad et al., 2018). Similarly, predicted C4 RNA expression based on copy number was associated with reduced cortical activation and memory deficits in psychosis patients compared to healthy controls (Donohoe et al., 2018). Other preliminary clinical findings suggest that the expression of complement genes C5 and SERPING1 was associated with cortical thickness, another indicator of possible overpruning in schizophrenia (Allswede et al., 2018). The role of the complement system in schizophrenia and its relationship to infection-based hypotheses is further reviewed in more detail elsewhere (Nimgaonkar et al., 2017; Presumey et al., 2017).

People with inflammatory bowel diseases often have psychiatric comorbidities (Bernstein et al., 2018). The complement pathway is involved in inflammatory bowel disease pathogenesis; thus, there is precedence that complement activation peripherally and perhaps in response to gut dysbiosis and inflammation could trigger gut-brain axis pathways. In pediatric inflammatory bowel disease, C4 copy number was positively correlated with inflammatory indices and decreased microbial diversity (Nissila et al., 2017). In another study of pediatric inflammatory bowel disease, the combination of both HLA and complement C4 copy number typing identified a haplotype that was strongly linked to disease and not to controls (Kolho et al., 2016). C4 copy number was further implicated as a susceptibility target for Crohn’s disease, indicating copy number elevations may amplify the response to infections and the development of autoimmune diseases in general (Cleynen et al., 2016). In individuals with Crohn’s disease, C3 mRNA was expressed in epithelial cells

located at crypts of diseased tissue, whereas C4 was expressed throughout the intestinal epithelium in both normal and diseased tissue (Laufer et al., 2000). Thus, the role of complement is complex with some studies reporting both protective and pathogenic effects (Elvington et al., 2015; Schepp-Berglind et al., 2012). In a comparison of mice lacking the C1q/mannose binding lectin genes to those deficient in the C3 gene, the induction of colitis by dextran sulfate sodium was only successful in the C1q/MBL double deficient mice, although ultimately all complement deficient mice died. Interestingly, antibiotic treatment prevented this lethal effect suggesting a role for the gut microbiome in complement regulation (Schepp-Berglind et al., 2012). Yadav et al (2017) recently demonstrated in an animal model expressing a specific multiple sclerosis-associated HLA and T-cell receptor haplotype that gut dysbiosis triggered experimental autoimmune encephalomyelitis in adolescence and young adulthood but not afterwards. This dysbiosis induced the expression of complement C3 locally in the GI tract as well as systemically (Yadav et al., 2017). Finally, in gastric biopsies of children with autism, Crohn's disease, *Helicobacter pylori* infection and normal controls, distinct gastritis typified each disease state compared to controls. In autism, however, 20/25 children were also uniquely distinguished by a CD8-dominated gastritis and colocalization of IgG and C1q on the subepithelial basement membrane (Torrente et al., 2004). This study is particularly intriguing given suggestions that autism and schizophrenia may be linked on a spectrum of shared genes and/or environmental interactions (Cattane et al., 2018). Determination of the disease phenotype as autism or schizophrenia may simply be variation of the presence and timing of environmental modifications on a similar genetic template.

At the crossroads of intestinal pathologies, immune genes and schizophrenia

Chronic low-grade inflammation is increasingly observed in schizophrenia and it may typify a phenotype that is associated with especially poor outcome over the course of the disorder (Bechter, 2013; Bulzacka et al., 2016; Fond et al., 2018a; Fond et al., 2018b). As described above, immune proteins that are genetically associated with schizophrenia are operative in inflammatory processes that occur systemically as well as in the gut. Demonstrating an interactive and definitive connection between GI inflammation and immune gene susceptibility specifically in schizophrenia, however, is difficult and to date can only be inferred from associative data. Reports of significant gastrointestinal inflammation associated with the disease state, and not the result of a medication effect, support a GI phenotype for schizophrenia (Severance et al., 2012a; Severance et al., 2015). The microbiome and its dysbiosis is specifically implicated in schizophrenia based on case-control analyses of markers of microbial translocation and changes in microbial taxa associated with the disorder (Castro-Nallar et al., 2015; He et al., 2018; Lv et al., 2017; Schwarz et al., 2018; Severance et al., 2016a; Severance et al., 2013; Shen et al., 2018; Yolken et al., 2015; Yuan et al., 2018). One study extends this association to the complement system where increased rates of circulating immune complexes containing complement C1q bound to food antigen antibodies, a source of GI inflammation, were found in individuals with schizophrenia compared to controls (Severance et al., 2012b).

The pertinent question, therefore, is could activation of peripheral MHC and complement pathways by an imbalanced microbiome result in homologous immune molecule activation in the brain and specifically disrupt synapse function and neural circuitry? There are hypothetical scenarios by which a microbiome-gut-brain mechanism might unfold to trigger activation of brain MHC and complement. A promising candidate mechanism, as depicted in Figure 1, involves HLA-driven disease-associated endothelial barrier defects present in a cascade involving gut dysbiosis, inflammation, and the translocation of microbes and their products (metabolites, toxins, neurotransmitters) into systemic circulation where microbes or microbial products may access the brain (Pollak et al., 2018; Severance et al., 2016b). This scenario has been studied using as an opportune model, the neurotropic parasite *Toxoplasma gondii,* to explore how enteric infection leads to CNS infection via defects in blood-gut and blood-brain barrier integrity (Kannan et al., 2017). Coinciding with this experimental infectious process was the expression of multiple complement components systemically and in the CNS where deposition of complement C1q in the vicinity of nearby synapses was observed (Xiao et al., 2016). The translational application of these findings is supported by numerous epidemiology investigations that implicate *Toxoplasma gondii* infection as a risk factor for the development of schizophrenia (Torrey et al., 2012). One study showed that individuals who were seropositive for this parasite not only had higher rates of blood-gut and blood-brain barrier permeabilities, but also exhibited elevated levels of antibodies reactive against NMDA receptors (Kannan et al., 2017). Epidemiological accounts of autoimmune comorbidities in schizophrenia are extensive, can be related to complement dysfunction and microbial dysbiosis, and are reviewed in this context elsewhere (Severance et al., 2018).

Perinatal exposure to microbial dysbiosis

As indicated, the precise timing of the gut microbiome perturbation is a critical issue for neurodevelopmental brain disorders, with evidence that inflammation during sensitive time periods in early life can lead to such disorders as autism, cerebral palsy, epilepsy and schizophrenia (Jiang et al., 2018). Epidemiological studies have long implicated maternal immune activation, such as exposure to the infectious disease process, as a risk factor for the development of schizophrenia (Allswede et al., 2016; Blomstrom et al., 2012; Brown et al., 2004a; Brown et al., 2000; Brown et al., 2004b; Buka et al., 2008; Ellman et al., 2009; Karlsson et al., 2012; Mortensen et al., 2010; Pedersen et al., 2011; Severance et al., 2014; Xiao et al., 2009). A long literature of preclinical work directly supports brain behavioral and biochemical deficits in offspring exposed prenatally to immune activation (Brown and Derkits, 2010; Estes and McAllister, 2016; Labouesse et al., 2015; Meyer, 2014). Recent reports indicate that this exposure to prenatal immune activation results in the upregulation of complement components C1q and C4 in cortical regions of the brains of offspring (Duchatel et al., 2018; Han et al., 2017). In a study of clinical samples, maternal C1q was also elevated peripherally at time of birth in mothers whose children went on to develop serious psychoses as adults compared to mothers whose children were mentally healthy as adults (Severance et al., 2014). This inappropriate activation of complement during development has obvious detrimental implications regarding impaired construction of

properly sculpted neuronal networks. In individuals with elevated C4 copy numbers, the associated increased expression could subject the brain to overpruning (Sekar et al., 2016).

The maternal microbiome is predominantly vertically transferred to offspring and as such is well-staged to severely impact offspring immune gene expression if the microbiome tips toward an inflammatory state. Such microbiome shifting sources might include exposures to stress, pathogens, altered diet, and medications (Codagnone et al., 2018; Jasarevic et al., 2018). In mice reared in a germfree environment, microglial function was particularly associated with significantly altered transcriptomics and structural densities in male embryos and in female adults; an accompanying transcriptomic survey of human fetal microglia was consistent with the mouse results (Thion et al., 2018). The sex specificity of the microglial functional response has been demonstrated previously (Desbonnet et al., 2014; Erny et al., 2015), and has interesting implications for schizophrenia which is often thought to materialize differently in males vs females (Mendrek and Mancini-Marie, 2016; Shimamoto and Rappeneau, 2017). Microglia perform immune surveillance in the CNS and when activated, release toxic or protective agents in an effort to phagocytose tissue debris and pathogens. Microglia are themselves modulators of synapse form and function including mediation of complement expression. Thus, any alterations or depletions of these brain immune cells likely influences the ensuing presence of active complement, as indicated from studies of the retinogeniculate model, which show that the removal of synapses by microglia was dependent on the complement cascade (Schafer et al., 2012).

Conclusions

Remaining issues relating to the interconnections between immune genes, the microbiome and schizophrenia include ones of causality. Important questions are those regarding whether or not immune associations in schizophrenia are truly representative of disease pathophysiology or if rather they reflect stress, medication effects, lifestyle factors and exposures common in less than ideal environments. Other brain disorders in addition to schizophrenia which exhibit significant associations with a disrupted microbiome include autism, multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis and Huntington’s disease (Tremlett et al., 2017). Consistent findings across these brain disorders is the presence of dysbiosis, inferred based on biomarkers of a leaky gut or case-control differences in the compositions of taxa of bacteria, viruses and other microbes. Changes in the gut microbiome have also been associated with obesity, diabetes, autoimmune disease and asthma (Tremlett et al., 2017), which are all risk factors for and/or are common comorbidities found in schizophrenia and other psychiatric disorders (Annamalai et al., 2017; Benros et al., 2011; Eaton et al., 2006; Henderson et al., 2015; Wu et al., 2018). Thus, a prevailing question is which came first, the disorder or the dysbiosis? Stress is a major mediator of gut dysfunction and permeability; as such, dysbiotic comorbidities may be prevalent in many disorders because of exposure to any number of different forms of stress or other environmental factors. It is possible that microbiome involvement in schizophrenia is not causal to the disorder, but rather it contributes to or amplifies psychiatric and cognitive symptoms, perhaps in people with predisposing genotypes. A genetic template that makes the host susceptible to aberrant responses to immune challenges in a manner that alters synapse function is, however, consistent with both

a pathophysiological and etiologic role. To accelerate further traction, this field of study requires prospective and longitudinal cohorts with accompanying microbial biospecimens for use in population based studies. In so doing, it may be determinable whether certain microbial measures, GI conditions or exposures convey a future risk for schizophrenia. Ultimately, it is hoped that the microbial mechanisms affecting the gut-brain axis can be harnessed in such a way as to result in novel methods to treat and manage symptoms that currently compromise the mental health of so many people around the world.

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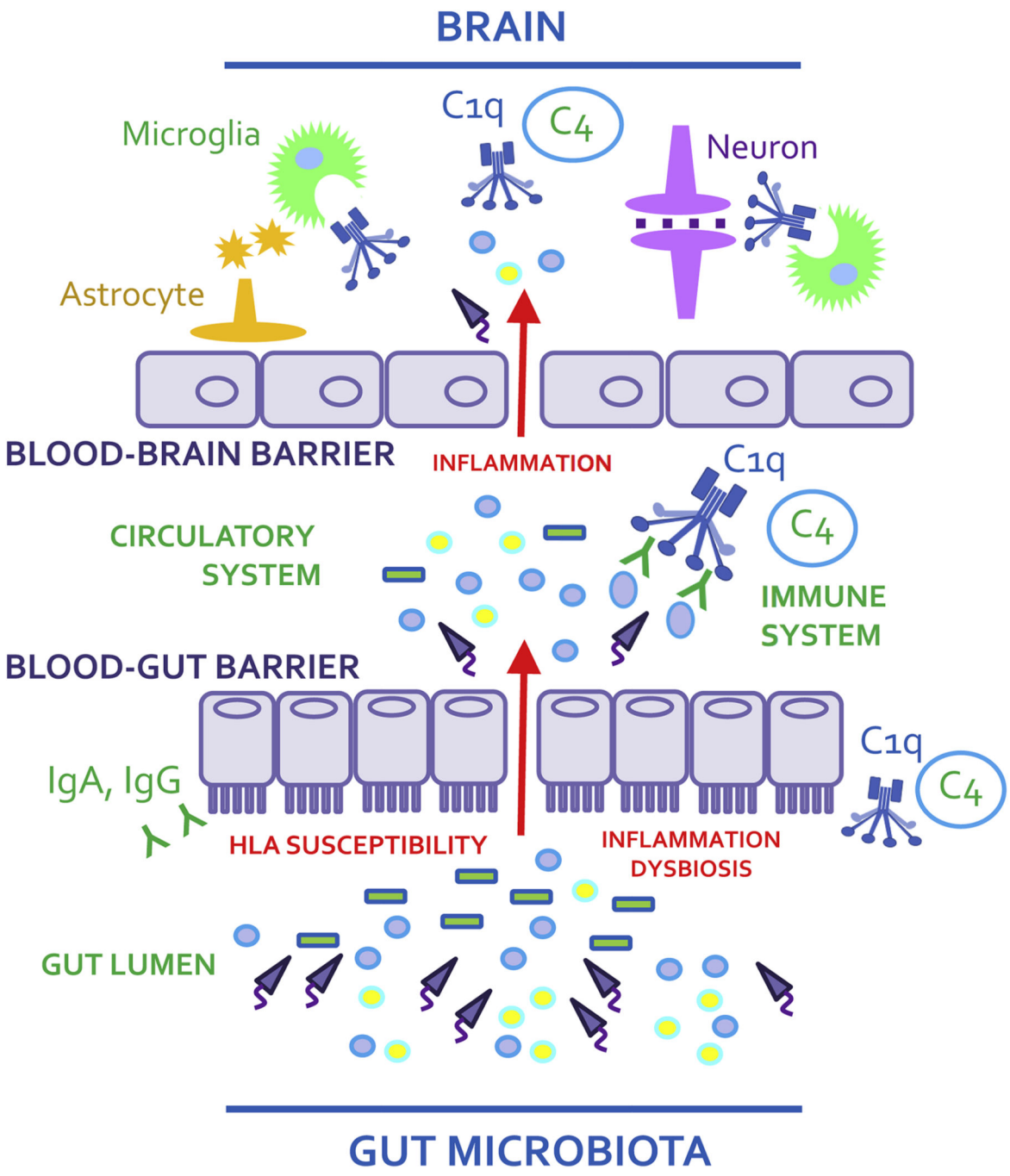

Figure 1.

The gut microbiome and immune gene pleiotropy along the gut-brain axis in schizophrenia. The proposed model illustrates an overview of microbial dysbioses leading to systemic inflammation and permeabilized blood-gut and blood-brain barriers in HLA-susceptible individuals. As resident microbes translocate into circulation, the immune response, as initiated by the complement pathway, is activated. With access to the brain, gut-derived molecules can enter, signaling astrocytes (orange) and microglia (green) to respond to

invaders. Subsequent complement expression in the vicinity of neurons (purple) may render susceptible synapses to inappropriate pruning.