The Synapse: Intercollegiate science magazine

Volume 8 | Issue 1 Article 6

2016

The Complement System and Schizophrenia: What if a psychological disorder could be treated by targeting part of the innate immune response?

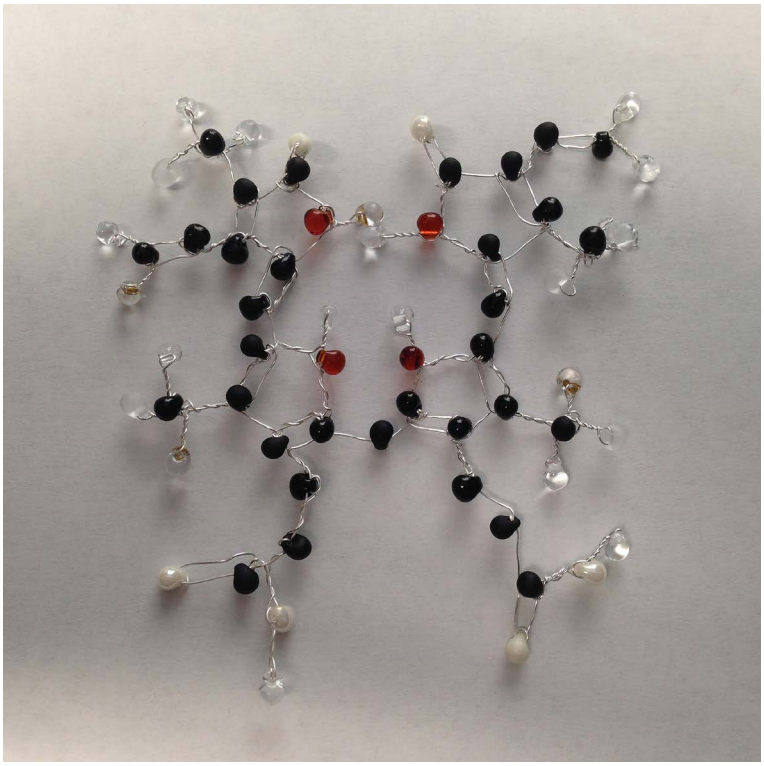
Sarah Hughes

The Complement System and Schizophrenia

What if a psychological disorder could be treated by targeting part of the innate immune response?

By Sarah Hughes
Artwork by Megan Lee

A recent publication in Nature reports schizophrenia to be linked to alleles of the complement system's component 4 genes, which produce and transcribe for the C4 protein (a member of the complement system). Sekar et al. found that the complement system's component 4 alleles generate diverse levels of C4A and C4B, which are two functionally and structurally distinct types of C4. In humans, this protein attaches to neuronal synapses, dendrites, axons, and cell bodies and limits their activity. Although the pathogenesis of schizophrenia is unknown, it is understood that characteristics of the disease include both reduced numbers of synapses on neurons and excessive loss of grey matter — all of which are affected by the C4 protein. Interestingly, in schizophrenic patients, greater expression of C4A has been found. This is a crucial discovery because it may provide a possible explanation of the pathogenic mechanisms which contribute to the disease — and may aid in the production of new therapies which will target components of the complement system, drastically changing current treatment practices.



Schizophrenia is a mental disorder that is categorized by abnormal social behavior, hallucinations, delusions, and jumbled speech and thinking. Scientists have not yet uncovered the origins of the disease, however, they have noted several morphological differences in the brain such as enlarged ventricles, reduced amounts of gray matter, and synaptic pruning.

The complement system is a phylogenetically conserved arm of innate immunity which functions together with the adaptive immune response. The latter works in a specific manner through antigen-antibody interactions while the former has been long credited as the main contributor to the innate immune response — essentially unchanging in its reaction cascade. It consists of a complex group of about 30 serum proteins which play important roles in the defense against infections. Working non-specifically, they bind to microbes, foreign objects, and pathogens among other foreign bodies, to eliminate anything they recognize as "non-self". Essentially, the complement system works with the adaptive immune system by serving as an important infl ammatory mediator. Moreover, the complement system is more active in the brain than the adaptive immune system due to the blood-brain barrier, which restricts the passage of certain substances, i.e., antigens and antibodies. Under normal circumstances, the complement system provides protection from the aforementioned pathogens and accumulating debris. However, excessive activity in the system coupled with the presence of excessive amounts of specific proteins can tip the balance between health and disease.

Now, why is the increased amount of C4A in schizophrenia important? In essence, there is a growing desire to understand the role of the complement system in pathological processes and to exploit its targets in developing therapies. Since C4 is a critical component to the system's classical cascade (being a precursor to one of the three pathways that result in the system's activation) it has been the focus of many studies. Thus, its imperative to understand that the increased expression of the protein C4A in schizophrenia patients may stimulate continual amplification of the complement system's cascade — possibly accounting for the increased elimination or 'pruning' of synapses in the brain of schizophrenic patients. This synapse elimination or 'pruning' in humans normally occurs between early childhood and the onset of puberty — the same period when schizophrenia, in most cases, becomes clinically apparent. In summary, new findings have confirmed that the human C4 gene suggests a critical relationship between an overabundance of C4A and risk for schizophrenia.

Meanwhile, since the direct causes of schizophrenia are relatively unknown, therapy focuses on eliminating symptoms through a combination of anti-psychotics, which target dopamine and serotonin, and psychosocial talk-therapy. However, because C4 has been found in excess in schizophrenia patients and is known to contribute greatly to excessive complement system activation, and thus to synaptic pruning, loss of cortical grey matter, etc., complement system inhibitors or other targeted therapies may enhance treatment of the disease. Currently, these types of inhibitors are used to treat known complement system disorders, such as paroxysmal nocturnal hemoglobinuria, and are in clinical trials as promising alternatives to transplant rejection drugs (which intensely compromise the immune system by placing a time limit on the transplanted organ). Furthermore, understanding the complement system and its roles in not only schizophrenia, but also in complement-related diseases may provide information about the management and understanding of disease infiltration as a whole.