Lupus: Open Access

OPEN ACCESS Freely available online

Commentary

Complement C5a/C5aR Signaling and CNS Lupus

Jessy J Alexander *

Department of Medicine, University of Buffalo, New York, USA

ABSTRACT

Systemic lupus erythematosus is a devastating disease with a therapeutic regimen that has toxic side effects. It affects 1.5 million Americans, 80% of whom have neuropsychiatric symptoms and finding an effective therapeutic target is an urgent need. One of the key inflammatory pathways altered in lupus is the complement system that forms a part of the clinical profile. Our lab has been systematically studying the role of complement in CNS lupus. Our work showed that pan complement inhibition using Crry-Ig is protective in experimental lupus. Inhibition of signaling by the complement byproducts C5a and C3a alleviated the lupus pathology. C5a causes the blood-brain barrier to become 'leaky'. Subsequent studies demonstrated that C5a caused the human brain microvascular endothelial cells to apoptose through the executioner caspases that could be prevented using the C5aR antagonist. These studies demonstrate the pharmacologic potential and clinical benefit of C5a receptor antagonist in lupus.

Keywords: C5a; Blood-brain barrier; Endothelial cells; Lupus

DESCRIPTION

Systemic lupus erythematosus is a devastating autoimmune disease that remains bereft of effective therapy. To identify transformative therapies, the critical pathways altered in the disease and the exact underlying mechanism causing the pathology needs to be understood. The disease lupus affects different organs that include from skin lesions to brain dysfunction. Neuropsychiatric symptoms occur in 80% of lupus patients [1]. The assessments for the change in brain is assessed by MRI, CT, X-rays and spinal tap and for brain function by cognitive tests. Lupus causes anxiety, altered social interactions and cognitive defects in both man and mouse indicating changes in brain. Brain is an immune-privileged organ protected from the circulating cells and toxins by the blood-brain barrier. In 2017, Carroll and his team showed that synaptic destruction occurred in lupus mice and post-mortem brains [2]. This synaptic destruction was associated with engulfment by type 1 interferon induced microglia. Cytokines normally have restricted access to the brain suggesting potential loss of blood-brain barrier integrity. More recently, using arterial spin labeling, diffusion-weighted brain MRI and voxel-based morphometry in a cross-sectional, case-control study Brunner and team demonstrated the increase in micro vascular permeability that negatively correlated with cognitive deficits in lupus patients [3] with regional specificity [4].

Small vessel disease and cerebral atrophy occurs in 25% of the lupus patients [5]. The microvasculature in brain is unique and made of astrocytic endfeet and pericytes interlaced with the endothelial cells. The endothelial cells lie closely apposed with adherent junctions in between.

The endothelial layer of the vasculature modulates the transport of metabolites, blood flow, and circulating cells to and from the brain. A critical mechanism that causes the blood-brain barrier to become leaky in an autoimmune setting such as lupus can be an immune mediated attack and complement activation. One of the cascades that are not regulated in lupus resulting in the generation of proinflammatory by products is the complement system. Elevated levels of complement byproducts are significantly correlated with poor outcome in lupus patients [6]. Therefore, the complement landscape is a part of the lupus clinical profile. The complement facet is very timely and important since the 'therapeutic tool box' for complement therapeutics including monoclonal antibodies and antagonists are rapidly on the rise with different products being tested, and in the pipeline.

Complement system consists of 3 different pathways that coalesce to a common end point, the formation of the membrane attack complex. Complement activation that occurs in lupus and other inflammatory settings generates small molecular weight by products such as C5a, C3a and C4a.

C5a is a 74 a.a fragment that is present on circulating cells and other cell types in different organs, and signals through the receptors, C5aR1 and C5aR2. C5a facilitates chemo taxis for movement of the cells, enhances the production of cytokines and reactive oxygen species and increases vascular permeability. In addition, it can

Correspondence to: Jessy J Alexander, Department of Medicine, University of Buffalo, 875 Ellicott Street, CTRC 8030D, Buffalo, NY 14203, New York, USA, Tel: 716-888-4852 ; E-mail: jessyale@buffalo.edu

Received: November 02, 2020; **Accepted:** November 16, 2020; **Published:** November 23, 2020

Citation: Alexander JJ (2020) Complement C5a/C5aR Signaling and CNS Lupus. Lupus: Open Access. 5:156.

cause neutrophil accumulation leading to occlusion of microvessels and thereby vascular injury. The critical role of C5a in maintaining BBB integrity was demonstrated *in vivo* in inflammatory settings such as sepsis and in the well-established lupus mouse model, MRL/MpJ-Tnfrsf6lpr (MRL/lpr) mice, and *in vitro* using cultures endothelial cells [7].

Our studies "C5a induces caspase-dependent apoptosis in brain vascular endothelial cells in experimental lupus" (8) using vascular casts revealed the loss of endothelial cells in experimental lupus brain. Increased expression of the 'executioner enzymes', the caspases and the proapoptotic kinases along with the DNA fragmentation observed in these cells suggest that apoptosis may be the mechanism resulting in the loss of these cells which could be alleviated using C5aR antagonist.

The open questions that remain include:

• On inhibition of C5aR1 what happens to C5a/C5aR2 signaling,

• Treatment was begun before clinical symptoms were observed, therefore the time for treatment initiation needs to be defined and lastly,

• Increased concentration of C5a suggests increase in other downstream complement proteins leading to the formation of the membrane attack complex that needs to be addressed.

CONCLUSION

In conclusion, although questions remain, our studies for the first time demonstrate the critical role of C5a/C5aR1 axis signaling in lupus. Preventing the detrimental effects of C5a/C5aR signaling could emerge as an effective therapeutic for lupus and the management of inflammatory vascular diseases.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGEMENT

This research is supported by NIH R01 Grant DK111222 to JJA.

REFERENCES

1. Futrell N, Schultz LR, Millikan C. Central nervous system disease in patients with systemic lupus erythematosus. Neurology. 1992;42(9):1649-1657.
2. Bialas AR, Presumey J, Das A, van der Poel CE, Lapchak PH, Mesin L, et al. Microglia- dependent synapse loss in type I interferon-mediated lupus. Nature. 2017;546(7659):539-543.
3. Gulati G, Jones J T, Lee G, Altaye M, Beebe, Meyers-Eaton J, Wiley K, et al. Altered blood-brain barrier permeability in patients with systemic lupus erythematosus: A novel imaging approach. Arthritis Care Res (Hoboken). 2017;69(2):299-305.
4. Di Francesco MW, Lee G, Altaye M, Beebe DW, Meyers-Eaton J, Brunner HI. Cerebral microvascular and microstructural integrity is regionally altered in patients with systemic lupus erythematosus. Arthritis Res Ther. 2020;22(1):135.
5. Goh YP, Naidoo P, Ngian GS. Imaging of systemic lupus erythematosus. Part I: CNS, cardiovascular, and thoracic manifestations. Clin Radio. 2013;68(2):181-191.
6. Sakuma Y, Nagai T, Yoshio T, Hirohata S. Differential activation mechanisms of serum C5a in lupus nephritis and neuropsychiatric systemic lupus erythematosus. Mod Rheumatol. 2017;27(2):292-297.
7. Jacob A, Hack B, Chiang E, Garcia JG, Quigg RJ, Alexander JJ. C5a alters blood-brain barrier integrity in experimental lupus. Faseb J. 2010;24(6):1682-1688.
8. Mahajan SD, Tutino VM, Redae Y, Meng H, Siddiqui A, Alexander JJ. C5a induces caspase-dependent apoptosis in brain vascular endothelial cells in experimental lupus. Immunology. 2016;148(4):407-419.