Universität Basel

Research Project

Antibodies against complement C1q in systematic lupus erythematosus (SLE)

Third-party funded project

Project title Antibodies against complement C1q in systematic lupus erythematosus (SLE)
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Our major goal is to understand pathogenic mechanisms in Systemic Lupus Erythematosus (SLE) in which a number of factors and systems have been shown to play an important role. Studying the origin and consequences of autoantibodies against the first component of the classical pathway of complement (C1q) offers the exceptional opportunity to elucidate the interplay of some of them, i.e. complement, apoptosis, Ebstein-Barr-Virus (EBV) and the coagulation system.

A major hypothesis of the pathogenesis of SLE assumes that the disease is driven by a defective clearance of dead and dying cells. In the context of an altered clearance, dying cells could become antigenic and initiate an autoimmune response. Complement has been shown to play an important role in the clearance of apoptotic cells and the deficiency of one of the early components of the classical pathway of complement is strongly associated with the development of SLE. However, most SLE patients have no primary complement deficiency. In contrast, hypocomplementemia in SLE patients is a secondary event and most often associated with autoantibodies against C1q (anti-C1q). As we could show, anti-C1q strongly correlate with severe lupus nephritis suggesting that the occurrence of anti-C1q is necessary for the development of proliferative lupus nephritis.

1) Recently, we identified a major linear epitope targeted by anti-C1q. The dissection of its core amino acid sequence revealed a striking sequence homology with EBV suggesting cross-reactivity through molecular mimicry. This is a particularly interesting observation since EBV infection is considered to be essential for the occurrence of SLE and might be an important driver for the development of anti-C1q. 2) We could also demonstrate that binding of anti-C1q to C1q leads to complement activation via the classical pathway. However, since our previous studies showed that bone marrow-derived, affinity matured anti-C1q specifically bind to C1q bound on early apoptotic cells, it is likely that they interfere not only with the activation but also with other important functions of complement, e.g. the clearance of apoptotic cells. 3) Independently, our analyses of bone marrow-derived anti-C1q identified sequence homologies with von Willebrand Factor (vWF) suggesting that, at least in specific situations, vWF might also bind to C1q. In fact, we could demonstrate binding of vWF to bound C1q. Considering the binding characteristics of anti-C1q, C1q bound to apoptotic cells might allow the binding of vWF and consequently trigger platelet aggregation. Such a finding would for the first time demonstrate a direct link between an activating molecule of the complement cascade and a component of primary hemostasis.

As a consequence, in this proposal we aim to examine 1) whether EBV-derived peptides can induce antibodies cross-reacting with C1q through molecular mimicry in vivo and to compare phage display derived anti-C1q and anti-EBV from SLE patients on a molecular level. 2) We will study the consequences of the binding of anti-C1q to C1q for phagocytic cells by the analysis of characteristics of macrophages

and immature dendritic cells exposed to C1q-coated apoptotic cell material in the presence or absence of anti-C1q. 3) We will investigate the binding characteristics of vWF to C1q and its functional relevance.

Taken together, the proposed projects based on the analysis of anti-C1q will help to understand the role of complement C1q, apoptosis, EBV and primary hemostasis in SLE. Considering the important role of these factors in SLE, data generated in this project will significantly improve the understanding of pathogenic mechanisms of the disease, including the understanding of driving factors and alterations in coagulation as frequently observed in SLE patients.

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