Clinical Immunology

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Complement-dependent pathogenic mechanisms in systemic autoimmunity

Systemic Lupus Erythematosus (SLE) is the archetype of an autoimmune disease and can involve any organ system eventually leading to comorbidities that can also be observed independently of underlying SLE. The complex pathogenic mechanisms leading to and being involved in this autoimmune-inflammatory syndrome are not well understood. However, complement C1q, the first component of the classical pathway, seems to play a central role. By analysing the role of C1q as well as it's interaction with autoantibodies targeting C1q (anti-C1q) in SLE, we aimed at elucidating 1) mechanisms being involved in the initiation of autoimmunity, 2) mechanisms of secondary acceleration of inflammation, and 3) processes being associated with atherosclerosis and thromboembolism.

With regard to mechanisms being involved in the initiation of SLE, homozygous C1q deficiency is the strongest genetic risk factor for the development of SLE. Vice versa, in SLE patients without primary C1q deficiency, C1q is consumed during disease flares, deposited in affected tissues and becoming a target of autoantibodies (anti-C1q). The identification of a major linear epitope of C1q targeted by anti-C1q having a striking sequence homology with an antigenic site of Epstein Barr Virus (EBV) suggests cross-reactivity between anti-C1q and anti-EBV antibodies through molecular mimicry. This was an important observation since EBV infection is considered to be an essential step in the development of SLE. We now could demonstrate that EBV-derived antigenic peptides indeed can induce antibodies cross-reacting with complement C1q *in vivo*.

Secondly, C1q mediates and modulates the uptake of apoptotic cells, a mechanism that is defective in SLE patients. In the context of a defective clearance, dying cells can become antigenic and trigger the autoimmune response. In previous studies I could show that anti-C1q specifically recognize C1q when being bound to apoptotic cells and that anti-C1q induce a proinflammatory phenotype in macrophages being associated with reduced phagocytic capacity. We are currently exploring these mechanisms of secondary inflammation, in particular how C1q and anti-C1q affect macrophage-mediated T-cell activation.

Thirdly, our previous analyses of bone marrow-derived human anti-C1q identified sequence homologies with von Willebrand Factor (vWF). In striking analogy to anti-C1q, vWF also binds to C1q leading to consecutive platelet rolling and adhesion, and the lack of C1q is associated with increased bleeding *in vivo*, thus establishing a novel link between C1q and primary hemostasis. In addition, binding of vWF to C1q on cholesterol crystals substantially affects phagocytosing macrophages. This is of importance since both, C1q and vWF, have been shown to be implicated in atherosclerosis and thromboembolism, both being typical comorbidities in SLE patients.

Taken together, our projects elucidate the role of complement C1q and anti-C1q in interaction with EBV infection, macrophages, the clearance of apoptotic cells and primary hemostasis, all having been implicated in the pathogenesis of SLE. Our data improve the understanding of immune-mediated pathology occurring related to but also independently of autoimmunity.

Connection to Clinical Practice

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The role of complement in human disease

In clinical studies we were and still are analysing the role of anti-C1q as a biomarker in SLE patients and it's relation to previous Epstein Barr Virus infection. In addition and thanks to the participation in the Swiss SLE Cohort Study (SSCS) we are also studying the role of other autoantibodies and serum cytokines in SLE.

Independent from anti-C1q studies, we are studying the role of complement split products (i.e. activation parameters) and complement mannan-binding lectin (MBL) in clinical settings. MBL is strongly related to C1q and has been shown to play an important role in the defense against infectious agents. More recent studies suggest that MBL also binds to apoptotic cells and plays a pro-inflammatory role in experimental settings of ischemia-reperfusion injury. The high frequency of functional MBL deficiency in the general population (about 25 %) predestines MBL for clinical studies investigating its role in human disease.

Selected Publications

Donat C, Thanei S, Trendelenburg M. Binding of von Willebrand factor to complement C1q decreases the phagocytosis of cholesterol crystals and subsequent IL-1 secretion in macrophages. Front Immunol 2019; 10: 2712. doi: 10.3389/fimmu.2019.02712.

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Kölm R, Schaller M, Roumenina LT, Kremer Hovinga JA, Khanicheh E, Kaufmann BA, Hopfer H, Trendelenburg M. Von Willebrand factor interacts with surface-bound C1q and induces platelet rolling. J Immunol 2016; 197: 3669–3679.