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CONNECTIVE TISSUES DISEASES

Do autoantibodies to C3 exacerbate autoimmunity in SLE?

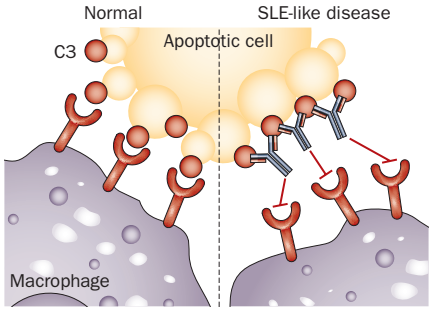
Defective clearance of apoptotic cells is a key factor in the pathogenesis of systemic lupus erythematosus (SLE). A new study by Karla Kenyon *et al*. suggests a role for autoantibodies to complement C3—a major serum opsonin—in this deficiency.

The researchers demonstrated *in vitro* that, unlike serum from wild-type mice, sera from Mer^{KD}, MRL^{lpr} or NZB/WF1 strains, which exhibit SLE-like disease, did not promote C3-dependent uptake of apoptotic cells by macrophages (efferocytosis). Furthermore, sera from these autoimmune animals actually inhibited efferocytosis when mixed with serum from wild-type mice.

Opsonization (binding of C3 to the surface of apoptotic cells) and total protein levels of C3 were not reduced, but flow cytometry-mediated detection of C3 on the surface of apoptotic cells was blocked, indicating that antibody binding sites on the protein were occupied. Accordingly, an inhibitor of efferocytosis was detected in the IgG-containing fractions of sera from these autoimmune mouse strains. Moreover, IgGs purified from the sera recognized C3 and prevented efferocytosis. Conversely, the inhibitory capacity of the sera in efferocytosis assays was reduced by IgG depletion.

In humans, the situation seems to be more complex. Patients with SLE had increased titres of anti-C3 antibodies, compared with healthy controls or patients with rheumatoid arthritis. Furthermore, sera from patients with SLE reduced detection of C3 on apoptotic cells, an effect that was replicated by isolated IgGs and reversed by IgG depletion. Nevertheless, efferocytosis was not inhibited.

The authors offer several explanations for this seeming inconsistency. One theory is that Fc receptor (FcR)-mediated clearance might be important in humans. In this regard, anti-C3 antibodies might promote a switch from immunosuppressive C3-mediated efferocytosis to proinflammatory and potentially immunogenic FcR-mediated phagocytosis.



Thus, autoantibodies to C3 might have a role in defective clearance of potentially immunogenic apoptotic cells; however, further investigation is needed to clarify whether these autoantibodies exacerbate autoimmunity in patients with SLE.

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Original article Kenyon, K. D. *et al.* IgG autoantibodies against deposited C3 inhibit macrophage-mediated apoptotic cell engulfment in systemic autoimmunity. *J. Immunol.* http://dx.doi.org/10.4049/jimmunol.1003468