SYSTEMIC LUPUS ERYTHEMATOSUS

T cell metabolism connects complement and autoimmune regulation

C1q functions as a metabolic regulator of CD8⁺ T cells to restrain responses to self-antigens and limit autoimmunity, according to new research published in *Science*. “In this study, insight is provided as to why C1q deficiency and not C3 deficiency is associated with the development of systemic lupus erythematosus (SLE),” reports Leendert Trouw, a complement expert who was not involved in the study.

A number of theories exist to explain the association between C1q deficiency and SLE development, including the ‘waste-disposal’ theory that C1q deficiency leads to inadequate clearance of apoptotic cells, and hence increased exposure to self-antigens, resulting in autoimmunity. However, the lack of an association between C3-deficiency and SLE development, and the existence of other redundant clearance pathways, indicates that other mechanisms are involved.

To study the protective function of C1q, Ling et al. used a chronic

graft-versus-host disease (GVHD) model of SLE in wild-type and C1q-deficient mice. As expected, the mice developed an autoimmune syndrome resembling SLE, with high levels of autoantibodies. By 10 weeks, mice lacking C1q had more severe glomerulonephritis and increased IgG and C3 glomerular deposition compared with wild-type mice.

Notably, following GVHD induction, CD8⁺ T cells constituted a greater proportion of leukocytes in the spleen and blood of C1q-deficient mice compared with wild-type mice. Interestingly, the relative proportions of short-lived effector cells (SLECs) and memory precursor effector cells (MPECs) in this expanded CD8⁺ T cell population were increased and decreased, respectively.

By using antigen-specific T cells or depleting CD8⁺ T cells in the GVHD model, the investigators found evidence that in the absence of C1q, CD8⁺ T cells had exaggerated responses and that these cells were responsible for maintaining the autoimmune response.

To understand whether the effects of C1q on CD8⁺ T cells occurred via intracellular or extracellular pathways, the investigators co-transferred wild-type and C1q-deficient CD8⁺ T cells into wild-type recipients prior to GVHD induction. The two CD8⁺ T cell populations had similar proliferative responses, indicating a cell-extrinsic effect. Similarly, in a lymphopenia-induced proliferation model, the expansion of donor CD8⁺ T cells was greater in C1q-deficient recipients than in wild-type recipients.

Following GVHD induction, CD8⁺ T cells had increased surface expression of complement C1q

binding protein (C1qBP) — a mitochondrial protein also present on the cell surface of some cells. Strikingly, C1q bound preferentially to MPECs and the data suggested that C1q regulated the survival and turnover of these cells. Furthermore, a higher proportion of MPECs (but not SLECs) secreted granzyme B in C1q-deficient mice compared with wild-type mice.

As activation of CD8⁺ T cells involves metabolic reprogramming, Ling et al. sought to measure the metabolic activity of MPECs and SLECs in this model. The MPECs from C1q-deficient mice had impaired mitochondrial spare respiratory capacity and reduced mitochondrial mass compared with wild-type MPECs. Furthermore, in vitro evidence indicated that C1q is internalized in activated CD8⁺ T cells and co-localizes with C1qBP in the mitochondria, providing a possible link between C1q binding and regulation of mitochondrial function in CD8⁺ T cells.

“The authors have shown that there are small metabolic differences in CD8⁺ T cells in the presence or absence of C1q, but whether this mechanism has a crucial role and is the sole mechanism by which C1q effects these cells remains unknown,” says Trouw. He thinks that the next steps should aim to determine the critical level of circulating C1q needed to maintain proper CD8⁺ T cell regulation and to clarify why the effect of C1q is so prominent in CD8⁺ T cells when other cells also express C1q receptors.

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C1q restrains autoimmunity and viral infection by regulating CD8⁺ T cell metabolism. *Science* **360**, 558–563 (2018)

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