Complement dances with T cells

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Conventionally, complement is considered mostly a component of innate immune system; however, emerging data suggest that complement has pleiotropic effects impacting many aspects of the immune system. The modulation of T-cell responses and shaping of the overall immune response by locally produced/activated complement has far-reaching implications for therapeutic targeting of the complement system for the treatment of a variety of pathologic conditions.

The complement system consists of a set of soluble and cell surface proteins including components, receptors, and regulators. Complement activation is usually initiated by the interaction of several pattern-recognition receptors with foreign surface structures. Depending on the activation trigger, the complement cascade follows one of 3 pathways: the classical, lectin, or alternative pathway. Recently, however, additional activation pathways have been identified. For example, mannose-binding lectin (MBL)–associated protease-2 (MASP-2; of the lectin pathway) or thrombin (of the coagulation pathway) seems to directly cleave C3 or C5, respectively.

Traditionally, the complement system was thought to be mostly important in host defense functioning as a major component of the innate immune system. In recent decades, however, a considerable body of research has revealed that complement is also able to activate cells involved in both the innate and adaptive immune response, positioning it as an important link between the innate and the adaptive immunity. For example, complement provides a second signal to B lymphocytes that have recognized a complement-opsonized antigen. More recent work indicates that complement can also modulate T-cell responses during the induction, effector, and contraction phases of the immune response. Emerging data suggest complex and pleomorphic effects of complement activity on the production of key cytokines, T-cell effector differentiation, and function, as summarized in the figure. Medof, Heeger, and colleagues have previously demonstrated that, upon cognate interactions between antigen–presenting cells and T cells, locally produced complement not only functions integrally in co-stimulation leading to T-cell proliferation and cytokine production, but also operates constitutively in naive T cells to sustain their viability. The complement system has a sophisticated regulation mechanism that generally prevents the complement cascade from attacking host tissue. Such regulators, including factor H, decay accelerating factor (DAF/CD55), membrane cofactor protein (MCP/CD46), C4-binding protein (C4BP), and complement receptor 1 (CR1/CD35) either induce an accelerated decay of the convertases or degrade C3b to its inactive form. By reducing the complement activity, these complement regulators also, indirectly, regulate T-cell activation. A recently appreciated direct mechanism of regulation by complement of T-cell immune responses is the induction of T cells exhibiting characteristics of T regulatory 1–type (Tr1) cells. These cells secrete large amounts of IL-10, granzyme B, and perforin, inhibit proliferation of CD4+ T cells, and kill autologous targets when there is simultaneous ligation of CD3 and CD46 (a complement regulatory protein) on T cells. Furthermore, during the termination of an immune response, T cells enter a contraction phase where most of the cells undergo apoptosis, leaving a small number of viable T cells to constitute the memory pool.

Lalli and colleagues in this issue of Blood show that locally produced and activated complement enhances T-cell expansion by inhibiting apoptosis mediated through PI-3K–dependent enhanced Bcl-2 expression and prevention of Fas up-regulation. It is known that C5a inhibits apoptosis of neutrophils via PI-3K/AKT and increased Bcl-xL, extending their lifespan after recruitment to sites of inflammation in the caecal ligation and
puncture model of sepsis. However, intriguingly in the same model, T cells undergo intense apoptosis in a caspase-dependent manner and this effect can be blocked by anti-C5a antibody therapy. These data are at odds with those by Lalili et al and require further investigation. Guo and colleagues speculated that the contrasting effects on neutrophil and T-cell apoptosis in the sepsis model may be related to differences in C5aR density on neutrophils versus T cells, where T cells rapidly up-regulate C5aR. On the other hand, the differences may be due to variances in strength of the T-cell receptor (TCR) stimulation in these models, cytokine milieu, or due to utilization of distinct signaling pathways by neutrophils and T cells. Perhaps as a result, glucocorticoids have differential effects and inhibit apoptosis in neutrophils but promote thymocyte apoptosis.

Many inflammatory, autoimmune, neurodegenerative, and infectious diseases are thought to be caused, or at least perpetuated, by excessive complement activity. Therefore, inhibition or modulation of complement activity appears to be a promising novel strategy for their treatment and a number of clinical trials are already underway. Complement has also been shown to mediate graft rejection through increase in proinflammatory cytokine secretion by vessel walls and recruitment of effector T cells. Importantly, this immune-cell intrinsic phenomenon is independent of serum complement, indicating that local production and activation of complement makes a significant contribution to local tissue inflammatory injury and potentiation of adaptive immune response in many pathological conditions. For instance, in transplantation, C3 produced by a donor kidney allograft is a key mediator of experimental transplant rejection and markedly different kidney transplant outcomes are observed in humans based on kidney donor C3 polymorphisms. These findings and recent advances in understanding the novel role of complement in modulation of adaptive immunity and control of T-cell immune responses further support the need for continued efforts at better understanding the complex functions of complement. We can hope for the development of new therapies targeting specific pathways of the complement system in many immune-mediated diseases.

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REFERENCES

Comment on Farrar et al, page 1582

Diamond-Blackfan anemia: a new facet

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In this issue of Blood, Farrar and colleagues report the first mutations affecting the 60S large ribosomal subunit in DBA, providing further support for the concept of a central role for ribosome biogenesis in marrow failure.

Mutations in an increasing number of genes encoding 40S small ribosomal subunit proteins have been associated with marrow failure and leukemogenesis. RPS19 mutations have been identified in 25% of patients with Diamond-Blackfan anemia (DBA), with resulting impairment of 18S rRNA processing and 40S ribosomal subunit formation. The subsequent association between DBA and mutations in 2 additional 40S ribosomal subunit genes, RPS24 and RPS17, further supported the notion that the small ribosomal subunit plays an important role in DBA. Acquired defects in another 40S ribosomal protein gene, RPS14, were recently identified in patients with the 5q-myelodysplastic syndrome, suggesting that 40S ribosomal abnormalities constitute a general pathway underlying hematopoietic disorders. Nonetheless, the caveat remained that additional extra-ribosomal functions have been described for many ribosomal proteins and the possibility that these 40S subunit proteins might serve additional cellular functions could not be excluded. Hence, the relative contribution of ribosomal dysfunction to marrow disorders was unclear.

Now, Farrar et al have mapped a fourth DBA gene encoding a 60S large ribosomal subunit protein, RPL35A, in 5 out of a cohort of 150 patients with DBA (3.3%). They also confirmed that RPL35A sequence changes were not found in 180 healthy controls. The authors went further to test the functional consequences of RPL35A loss. They demonstrated that reduction of RPL35A expression by shRNAs resulted in decreased proliferation and viability of human hematopoietic cell lines. Impaired ribosomal 60S subunit biogenesis was observed following RPL35A knock-down and in DBA patient samples. These comprehensive findings together with prior studies of RPS19 convincingly demonstrate that disruption of either 40S or 60S ribosomal subunit biogenesis is associated with DBA. This new evidence lends considerable support for the role of ribosomal disruption as a fundamental factor in DBA.

Since mutations in the 4 known DBA genes are identified in only one-third of DBA patients, it is possible that additional 40S and 60S ribosomal protein genes might also contribute to DBA. In support of this hypothesis, Farrar et al also identified aberrant processing of the 60S subunit rRNAs in DBA patients for whom RPL35A mutations were not identified. Since the majority of DBA patients lack known mutations, it would be of considerable interest to determine whether impaired ribosome biogenesis constitutes a characteristic feature of all DBA patients. If true, functional assays for DBA-specific abnormalities in ribosome biogenesis might be useful diagnostically.

The molecular mechanisms whereby disruption of ribosome biogenesis results in marrow failure and malignant transformation remain to be defined. Several hypotheses have
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