**Intersection Between Complement and Transfusion Medicine**

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Early attempts to understand immunity demonstrated that both cellular and serological factors provide protection against pathogen re-challenge[1]. Subsequent efforts to understand how serological factors contribute to immune defense demonstrated that heating serum to 55°C eliminated the *in vitro* ability of serum to kill microbes. However, infusion of heat inactivated serum isolated from animals previously exposed to an infectious organism provided effective protection for naïve animals when challenged with the same organism. These foundational studies suggested that serological immunity consists of heat labile and heat stable components that work in concert to provide immunological protection. Paul Ehrlich subsequently coined the term “complement” to describe the heat-labile component of immunity, which he postulated worked in concert with the heat-stable “amboceptor” that provided target specificity. Later studies demonstrated that a complex pathway of complement activation and regulation occurs following “amboceptor” (antibody) engagement of antigen(2).

Following the discovery of complement, elegant biochemical studies further elucidated key pathways that regulate its activation. Early experiments primarily focused on antibody-mediated complement activation (classical pathway), while later work contributed to the discovery of other activation pathways, including the lectin and alternative complement pathways. Complement-fixing antibodies activate complement after pathogen engagement and also after alloantigen recognition, which can occur in the context of transfusion. For this reason, detecting complement deposition on the surface of red blood cells (RBCs) quickly became a routine test to evaluate the activity of a RBC-bound antibody in transfusion candidates or in recently transfused individuals[3]. Although complement deposition tests are now routine, the full complexity of complement activation following antibody engagement is still emerging. Intriguingly, only a subset of antibodies fix complement following engagement of an RBC surface antigen. In this special issue of *Transfusion Medicine Reviews,* Arthur and colleagues review the factors that regulate complement activation following antibody engagement. As alloantibodies can also induce platelet refractoriness, Peter Hoglund provides an excellent overview of the role of complement in antibody-mediated platelet refractoriness and HLA sensitization.

Despite a wealth of knowledge regarding the biochemical basis of complement regulation, including the mechanisms by which antibodies fix complement, more research is needed to develop a complete understanding of complement activation in the pathophysiology of disease and the methods to modulate the activation process. In this issue, Sunny Dzik provides a comprehensive review of recent research regarding the axis between complement and hemostasis and how activation of either pathway may influence the pathophysiology of disease marked by exuberant complement or hemostatic activation. Although complement inhibitor replacement has provided a way to treat angioedema, nicely reviewed by Marcel Levi, no specific therapeutic approach was available for many years to otherwise favorably manipulate complement activity in patients. The recent development of complement inhibitory drugs has led to a resurgence of interest in complement biology, including new research into the potential role of complement in a broad range of diseases.

In addition to paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), myasthenia gravis and a growing number of other indications(4), recent studies suggest that complement inhibition may play a direct role in abating the disease pathophysiology of transfusion-related complications. Perhaps one of the most promising examples of this is the treatment of hyperhemolysis in the setting of delayed hemolytic transfusion reactions (DHTRs). Lubka Roumenina and colleagues provide a compelling overview of the potential mechanisms of complement activation during a DHTR with hyperhemolysis, in addition to providing recommendations on how complement inhibition may be used to treat this potentially fatal condition. Similar complement activation may be critical in the development of transfusion associated-acute lung injury (TRALI), an equally fatal transfusion complication, which is detailed in an excellent review by Rick Kupar and colleagues.

In addition to eculizumab, other complement inhibitors are currently in trial, some of which will likely be available in the near future. Given this changing pharmacological landscape of complement regulatory therapeutics, Kevin Kuo and Chris Patriquin provide a nice overview of the different complement inhibitory approaches currently available and under study, including their potential advantages and limitations. In addition, indirect approaches aimed at targeting pathophysiological processes that likely involve complement, such as the use of Caplicizumab to treat thrombotic thrombocytopenic purpura, are outlined by Marhsall Mazepa. Despite the promise of new complement inhibitory drugs, one of the significant challenges remaining in the field is the accurate diagnosis of complement-driven effects in a given disease process. Novel tests are in development to accurately assess complement activation. Lillemor Skattum provides an outstanding overview of the status of currently available and upcoming assays that may aid clinicians who are considering complement inhibitory approaches in patients.

Despite successes, the clinical use of complement inhibitors brings formidable challenges. The exceptionally high cost of currently available drugs, which can exceed US$500,000 annually per patient, severely restricts their availability in certain markets. Generics will partially solve the cost issue after patent protections expire. However, in the interim, healthcare administrators need to facilitate price negotiation on the national and international levels in order to enable broad accessibility to these drugs.

Taken together, this is an exciting time to examine the intersection of transfusion medicine and complement. The series of review articles in this issue, which we outlined here, provide a wealth of information about the pathophysiology, diagnosis, and treatment of complement-related disorders in the context of transfusion medicine. These timely articles will be useful to a wide array of individuals, from those studying the role of complement in the development of disease to those seeking to leverage this information to treat patients.

References:

[1] A.M. Silverstein, A.A. Bialasiewicz. History of immunology. A history of theories of acquired immunity, *Cell Immunol* 1980; 51:151-167.

[2] E.S. Reis, D.C. Mastellos, G. Hajishengallis, J.D. Lambris. New insights into the immune functions of complement, *Nat Rev Immunol* 2019.

[3] C.P. Engelfriet. The immune destruction of red cells, *Transfus Med* 1992; 2:1-6.

[4] D.C. Mastellos, D. Ricklin, J.D. Lambris. Clinical promise of next-generation complement therapeutics, *Nat Rev Drug Discov* 2019.