The present issue of Seminars in Immunopathology is dedicated to a branch of the innate immune system that is more commonly associated with host protection rather than disease. And indeed, the complement system offers a broad and rapidly acting layer of host defense against microbial intruders and endogenous threats, which is particularly important when the adaptive immune system is still in development. Yet as the title of this special issue suggests, i.e., “Complement & Disease: Out of the Shadow into the Spotlight,” there is also a destructive side to the complement system, in which the effector and crosstalk functions that enable the removal of pathogens can turn against host cells and contribute to a broad range of clinical conditions. Within only a few decades, the list of complement-associated disorders has grown substantially and meanwhile covers several autoimmune, hemolytic, thrombo-inflammatory, and age-related diseases that affect various organs (e.g., kidneys, CNS, eyes) and range from local to systemic and from hyperacute to chronic manifestations. Moreover, complement often mediates adverse reactions to transplants, biomaterials, and liposomal drugs and exerts dual roles in cancer progression. Owing to this broad disease involvement, it is not surprising that the complement system has been raising both the awareness of the clinical community and the interest of the pharmaceutical industry. After initial skepticism about the feasibility and safety of any therapeutic intervention in the complement system as a host defense system, the clinical and commercial success of the anti-C5 antibody eculizumab (Soliris, Alexion) in the treatment of paroxysmal nocturnal hemoglobinuria (PNH) initiated this current era of complement-targeted drug development, which finally appears to provide the much-needed diversity regarding targets, indications, and treatment modalities. While enabling a clinical validation of therapeutic complement inhibition in various diseases, the endeavor has seen its fair share of setbacks with various clinical trials not reaching the anticipated outcome. These experiences served as painful but necessary reminders that the disease involvement of complement is often complex and that a successful expansion of the approach relies on a detailed understanding of the disease mechanisms and on careful patient stratification. The articles in this special issue provide a timely and clinically relevant update on selected indication areas and highlight opportunities and challenges in the detection and treatment of complement-related disorders.

Both the extraordinary versatility as immune surveillance system and the broad disease involvement of complement are largely defined by its reliance on a highly dynamic network of close to 50 activating, regulating, and effector components. In our review article [1], we show that even though the contribution of complement to different pathologies can be highly specific and diverse, it is typically a simple summation of activating and regulating stimuli that determines whether complement acts as an initiator, contributor, exacer - bator, or even protector in any given disorder. Using relevant examples, we discuss how excessive or misguided activation and/or insufficient regulation of complement responses may drive pathologies in a context- and tissue-specific manner. Finally, we provide an overview of recent developments in complement-targeted drug discovery, including the recent approval of the C3 inhibitor pegcetacoplan (Empaveli, Apellis) as a second complement-specific drug class, and discuss late-stage clinical candidates.

The recent pandemic crisis with thousands of patients suffering from a severe form of COVID-19 that caused extensive inflammatory and thrombotic complications raised the awareness that hyperactivation of our host defense pathways can rapidly turn from protective into destructive functions. In their review, Mannes et al. show that such massive complement activation events reach far beyond COVID-19 but
are at the center of many systemic inflammatory response syndrome (SIRS) disorders, including sepsis, trauma, and burn injury [2]. In such cases, complement is performing its designated function by reacting to pathogen- and/or damage-associated molecular patterns but to such an extent that the generated effector causes host tissue damage and contributes to organ failure. The authors provide an overview about the underlying mechanisms and discuss potential therapeutic avenues.

Complement’s contribution to adverse outcomes of organ transplantation, as covered in the review by Howard et al. [3], is another example in which complement activation is an expected yet unwelcome reaction. Tissue damage and immune activation in the donor, the hypoxic conditions during organ transportation, and the recognition of non-self-tissue by the recipient’s innate and adaptive immune system can all lead to complement activation. Alongside hyperacute rejection, such complement responses may also contribute to chronic rejection or reduced organ function. While an association between complement and transplantation outcome has long been made, we only recently began to understand the intricacies of the adverse reactions and appreciate the role of local complement components provided by the donor organ and infiltrating immune cells. As the authors show, such insight may guide efforts to render transplantation more efficient and successful and may enable transplantation across barriers to address the organ shortage.

Owing to their abundance and close contact with the vascular complement system, erythrocytes are particularly susceptible to complement-mediated damage. In their review [4], Jalink et al. compare two hemolytic diseases with major complement involvement yet highly distinct mechanisms. Whereas PNH is driven by insufficient regulation and damage driven by the alternative pathway of complement activation, autoantibodies lead to misguided activation of complement via the classical pathway in autoimmune hemolytic anemia. The authors not only discuss the molecular mechanisms underlying the diseases but also existing and emerging treatment options for these hemolytic disorders. As mentioned above, PNH served as an important gateway to the renewed interest in complement as a therapeutic target and still provides the go-to model to compare different intervention strategies.

In contrast to hemolytic diseases, the contribution of complement to the development and/or progression of neurological diseases has long remained less well investigated. In recent years, however, substantial progress has been made in deciphering the pathomechanisms of complement in diseases of both the central and peripheral nervous system. In their review [5], Lee and Woodruff focus on neuromuscular disorders, including amyotrophic lateral sclerosis, Duchenne muscular dystrophy, and myasthenia gravis. Whereas anti-C5 therapy is already approved for certain forms of the latter disease, several clinical trials have been initiated for other neuromuscular indications. The authors review the progress in such treatment options and discuss it in the context of disease models and mechanisms.

Although a connection between inflammation and the development of metabolic disorders (aptly termed “metaflammation”) is increasingly appreciated, the association with complement activation has only emerged rather recently. The review by King and Blom discusses the different and sometimes counteracting mechanisms with which the complement interferes with metabolic control in a tissue-specific manner [6]. The authors also provide insight into potential involvement of complement in obesity and diabetes and hint at complement-targeted interventions as part of personalized medicine approaches in the future.

When viewed as a collection, the review articles in this special issue provide a fascinating insight into the intricate and diverse involvement of a host defense pathway in a broad spectrum of clinical conditions. It also reiterates the value of complement-targeted therapies in severe disorders with major complement contribution as long as potential infectious risks are monitored and mitigated. Yet the overview provided here marks only the tip of the iceberg in a rapidly evolving area that has recognized the shady side of an ancient immune branch and moved it into the spotlight of clinical research and drug discovery effort alike. With new pathway-specific treatment options becoming available and enabling the clinical validation and extension of indication areas, we will very likely hear much more about the role of complement in health, disease, and therapy in the years to come.

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