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Editorial

Complement therapeutics

The proverb that "we must learn to walk before we can run" appears particularly fitting for the field of complement-targeted drug discovery. Although the complement system was initially described more than a century ago as part of our innate host defense system that helps to clear pathogens, it soon became clear that it also had a "dark side" as an initiator and exacerbator of inflammatory diseases [1]. Although the therapeutic potential of interfering with complement activation was widely recognized and sparked commercial interest, the initial excitement was dampened by slow drug development progress and discouraging clinical trial results in early indications such as arthritis. Evidently, the pathological involvement of complement is often more complex than would be anticipated from disease models. In addition, despite the availability of druggable targets in circulation, the complement system itself has proved to be a challenging pathway to conquer using traditional approaches of drug discovery, thereby slowing the pace toward complement-directed therapeutics.

Thanks to remarkable research efforts over the past few decades, we have learned a lot about the complement system, both in terms of the molecular aspects of complement activation and its involvement in health and disease [2]. Many of the more than 50 proteins that constitute the complement network have been characterized on a structural level, and assays for measuring complement activity have been refined. At the same time, the list of clinical disorders with contributions from complement has been steadily growing, largely fueled by insight from genome-wide association studies and elegant disease models. As a consequence of these efforts, the first complement-specific drugs finally became broadly available almost a decade ago and have reshaped the field. The anti-C5 antibody eculizumab (Soliris, Alexion Pharmaceuticals), in particular, has already changed the treatment landscape of two rare diseases, and its off-label use has revealed other promising indications. The clinical success and good long-term experience with the first complement drugs has reignited interest in therapeutic complement inhibition, with both small biotechnological and large pharmaceutical companies entering the arena [3].

Clearly, the running shoes are on now, and the race to discover the most rewarding targets and indications has only just begun. In our own review in this special issue of *Seminars in Immunology*, we highlight major developments in complement-targeted drug discovery and discuss the many creative and promising strategies that are currently being pursued [4]. Candidate drugs in the pipeline and in clinical trials cover a broad range of targets within the complement cascade and involve highly diverse approaches, including small molecules, peptides, antibodies, and nucleotides. This diversity may prove critical for enabling a more tailored and disease-specific therapeutic modulation of the complement cascade. Although almost any condition that involves the exposure of foreign, diseased, or injured cells to the blood may potentially benefit from pharmacological complement modulation, several key therapeutic areas have emerged as particularly promising in recent years and are reviewed here by leading scientists in the field.

In view of the clinical success of eculizumab in paroxysmal nocturnal hemoglobinuria (PNH) [5], this ultra-rare disease has evolved into a highly common indication for complement-focused research and drug development alike. However, it is still not clear which of the many new potential treatment options will translate into a real benefit for PNH patients. In their review, Risitano and Marotta reveal the unmet clinical needs in PNH and critically discuss novel therapeutic approaches [6]. Moreover, they illustrate the potential of complement-targeted therapy in other hemolytic diseases, such as antibody-mediated hemolytic anemias and thrombotic microangiopathies (TMA).

One of the disorders belonging to the TMA spectrum, atypical hemolytic uremic syndrome (aHUS), is largely fueled by complement dysregulation and already benefits from therapeutic C5 inhibition. For another family of complement-driven kidney disorders referred to as C3 glomerulopathy (C3G), treatment options have unfortunately remained scarce. Nester and Smith survey the puzzling variety of genetic and autoimmune factors affecting complement activity that can contribute to the progression of C3G, and they discuss the promises and limitations of therapeutic approaches in this severe condition [7]. It is becoming increasingly evident that the kidneys are particularly susceptible to complement-mediated tissue damage, with potential consequences for acute kidney injury, end-stage renal disease, and kidney transplantation [1,8].

The implications of complement activation in adverse clinical reactions after solid-organ transplantation, the promise of using complement-targeted inhibitors to prevent such complications, and the value of complement biomarkers for monitoring therapeutic success are the focus of the review by Montero et al. [9]. Transplantation has been among the first proposed indications for complement therapy, and this strategy has only gained more traction with the realization that complement contributes to

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ischemia-reperfusion injury as well as cellular and antibody-mediated graft rejection [10]. Complement-targeted therapies are therefore considered very attractive in transplantation, and several strategies are intended to inhibit complement in circulation or directly on the cell surface of the donor organ.

Cell surface-directed complement inhibition indeed appears promising in many indications beyond transplantation that may allow for tissue/site-specific intervention [11]. In their review, Holers and other experts in targeted complement inhibition provide the historic background for this approach and introduce an elegant concept for directing complement regulators to sites of tissue injury by addressing damage-associated molecular patterns [12]. Importantly, some of these targeting strategies may also be used for diagnostic purposes to determine the localization and extent of complement activation and monitor therapeutic progress.

Complement is typically not the only defense system that is triggered during transplantation or tissue damage or after exposure of blood to biomaterials. Concomitant activation of the coagulation and contact systems is typically observed, and these systems engage in crosstalk with complement that can contribute to thrombo-inflammatory complications [13]. The review by Ekdahl et al. explains the molecular mechanisms behind thromboinflammation, explores therapeutic strategies for taming defense systems on affected surfaces, and discusses the benefits of controlling complement and coagulation at the same time [14].

Whereas complement and other defense pathways can be initiated in many diseases, traumatic injury often leads to a particularly devastating adverse reaction [15]. In a body overwhelmed by the sudden exposure to damage markers and invading microbes, massive complement activation may fuel a hyperinflammatory response, with severe or even fatal consequences. Huber-Lang and colleagues illustrate the promises and challenges of complement modulation in systemic inflammatory reactions during trauma, hemorrhagic shock, and sepsis and discuss the potential implications for the clinical management of such acute situations [16].

The intricate interplay between infection, host defense, and inflammation also becomes obvious in the case of periodontal disease, in which the activation of complement and Toll-like receptors by the keystone pathogen *Porphyromonas gingivalis* fuels an inflammatory milieu that fosters dysbiosis and contributes to tooth bone loss [17]. Periodontitis has therefore evolved into an interesting indication for complement-targeted intervention. With a focus on C3 inhibition, Hajishengallis and colleagues discuss these novel therapeutic options and their evaluation in animal models of periodontal disease [18].

Another fascinating frontier for complement therapeutics encompasses neurological and neurodegenerative disorders. Although comparatively little is known to date about the physiological involvement of complement in the central nervous system (CNS), it is becoming increasingly evident that erroneous or insufficiently controlled complement activation contributes to neuroinflammation, with potential pathological consequences for a broad spectrum of conditions ranging from Alzheimer's disease, schizophrenia, and amyotrophic lateral sclerosis to stroke and traumatic brain injury [19]. In their review, Brennan et al. summarize the current knowledge of complement's complex role in CNS disorders and discuss the potential for using complement therapeutics in neurological conditions [20].

A similarly complex role for complement is anticipated in the case of cancer development, with complement mechanisms potentially contributing to both the control of tumor growth and the maintenance of the inflammatory milieu that facilitates progression [21]. Owing to complement's cell-directed effector functions, the potential of directing complement attack toward cancer cells has long been recognized and is clinically harnessed in the form of complement-dependent cytotoxicity (CDC) in antibody-mediated cancer therapy. Despite its successful use in the clinic, many underlying mechanisms and therapy-defining properties of CDC are only now becoming evident. In their review, Taylor and Lindorfer explore the lessons that have been learned from using the CDC principle in cancer therapy, share novel mechanistic and clinical insights, and provide an outlook on how the knowledge we have gained may influence the development of future antibody-based cancer therapeutics [22].

The complement therapeutics field had indeed come a long way and is thriving in a way that would not have been expected a few decades ago. Current progress not only opens new potential therapeutic options for many patients suffering from a broad spectrum of diseases but also critically contributes to our understanding of complement's role in health and disease. Despite the increasingly commercial aspects of the complement therapeutics field, development is fortunately still being fueled by innovation from and close interactions between academic, clinical, and industrial partners. This collaboration is particularly evident in cross-disciplinary scientific meetings such as the International Conference on Complement Therapeutics (www.aegeanconferences.org), which has not only provided a platform for discussing emerging concepts but also acted as a nucleus for compiling this special issue of *Seminars in Immunology*. We consider ourselves fortunate that we could engage many key players in the field of complement therapeutics and hope that you will enjoy reading these excellent reviews as much as we did.

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