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Editorial

## Complement in leucocyte development and function

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The complement system is a critical part of vertebrate innate immunity and, as has become increasingly clear over the last decade, also of adaptive immunity. Complement comprises about 20 soluble components, many of which are initially produced as inactive proteases, and several membrane components that prevent self-damage or potentiate complement function. Microbial polysaccharides not present in mammals, immune complexes and apoptotic cell debris can all activate complement by starting a cascade-like process, with each protease activating the next one in the pathway. As a result of complement activation, pathogens may be completely covered by complement-activated fragments (a process termed opsonization), stimulating their phagocytosis by macrophages and neutrophils. Opsonization can also trigger direct pathogen lysis by complement-mediated insertion of the membrane-attack complex. At the same time, complement activation releases small peptide fragments, or anaphylatoxins, that recruit macrophages and neutrophils to sites of infection through direct chemotaxis or indirectly, by activation of local mast cells. Thus, the three-pronged action of complement (enhancing phagocytosis, lysing pathogens and recruiting leucocytes while maintaining innate self-tolerance) is vital for survival. Complement deficiency or dysfunction can give rise to infections (immunodeficiency) or self-damage (autoimmunity, inflammation) in susceptible tissues such as red blood cells, kidney, brain or retina. Research in complement-targeted therapies is an expanding field that has already improved the prognosis of severe diseases such as atypical Hemolytic Uremic Syndrome (aHUS) or Paroxysmal Nocturnal Hemoglobinuria (PNH). A thorough account of the most important methods used in the clinic to assess the complement system of healthy and diseased individuals is central to understand the potential role of complement in diagnostics and therapeutics [1].

The distinct pathogen-fighting functions of complement provide a formidable barrier for most pathogens, which have evolved numerous immunoevasion mechanisms in an attempt to hide and escape from or subvert the complement system [2]. Complement activation also results in cross-talk with the adaptive immune system. Indeed, it is currently appreciated that a full-fledged cellular immune response de-

pends, at least in part, on molecular cues generated by complement components. This is reflected by the participation of nearly all complement components in signaling pathways that connect with cellular immunity. Complement receptor (CR) 3 and 4 recognize complement-activated fragments attached to surfaces, thereby providing a direct physiopathological link between complement activation and immune cell detection and signaling [3]. Despite their structural homology, CR3 and CR4 show functional segregation in myeloid cells for phagocytosis, cell adhesion and podosome formation, and clear species-specific differences [3]. Soluble complement regulators like factor H (FH), the main modulator of the alternative pathway of complement activation, and the closely related proteins FHL-1 and FHR-1 to FHR-5, can also engage cell surface receptors on leucocytes and regulate their activation and inflammation. The outcome of such receptor-mediated interactions is context-dependent and can range from pro- to anti-inflammatory activities. A better understanding of these non-canonical functions of FH and related proteins may in the future contribute to the arsenal of therapeutics available for the management of complement-associated diseases. A state-of-the-art account of receptor-mediated activities of FH, FHL-1 and FHR-1 to FHR-5 is presented in this volume [4]. Lymphocytes display differential subset-specific CR and membrane complement regulators (CReg) expression patterns and regulate their surface expression levels after activation, further supporting the concept of cross-talk between innate and adaptive immunity. Complement also contributes directly to adaptive immunity by enhancing antibody generation, immunological memory (it is essential for the development of memory B cells) and T-cell responses, although CReg-induced signaling in T cells requires validation using complement-dependent engagement. Lastly, it has now become established that complement is also activated intracellularly (i.e. the “complosome”). In this unsuspected location, complement activation has profound implications for lymphocyte development and function by promoting T-cell survival and induction of T helper 1 (Th1) responses [5]. The discovery of cross-talk mechanisms between complement effectors/regulators and dendritic cells (DCs) promises to open up new avenues for the development of innovative complement therapeutics [6]. In particular, the capacity of various complement components to induce a tolerogenic, anti-inflammatory phenotype in DCs may usher in new possibilities for the management

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of autoimmune diseases including type 1 diabetes mellitus, rheumatoid arthritis and systemic lupus erythematosus.

Recent work on the C3a and C5a anaphylatoxins has unveiled that both peptides have functions that transcend their classical roles as chemotactic signals for polymorphonuclear leukocytes and inducers of vascular permeability. In fact, it is now recognized that locally-produced C3a and C5a bind to antigen presenting cells and T cells and control antigen uptake, costimulation and Th cell differentiation into Th1, Th2, Th17 and regulatory T cells (Treg). C3a and C5a can also maintain chronic inflammation, promote an immunosuppressive microenvironment, induce angiogenesis and increase the motility and metastatic potential of cancer cells [7]. These properties can induce tumour progression, thus raising the question whether anaphylatoxins and their receptors may play important roles in cancer. In this light, the inhibition of the C5a-C5aR1 and C3a-C3aR axes appears as a viable treatment option to maximize the effect of current immunotherapies that target immune checkpoints. Metabolic disturbances associated with insulin resistance and obesity represent an area of intense medical investigation where complement dysregulation appears to play important roles. Complement activation is manifest in adipose tissue from obese subjects, in conjunction with subclinical inflammation and alterations in glucose metabolism. Thus, the possible contribution of the complement system to the physiology of adipose tissue and the pathophysiology and therapy of obesity and associated metabolic disease is also reviewed [8].

The picture that emerges is one of a tightly integrated, exquisitely regulated joint venture between the complement system and the innate and adaptive cellular immune defences, which act in concert to fight off infections, maintain homeostasis and modulate inflammation

to serve a variety of functional outcomes. New insights on the repercussions of the cross-talk between complement components will likely have a powerful impact on the development of novel diagnostic and therapeutic tools for the better management of inflammation, autoimmunity, cancer and metabolic disease (Figure).

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