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Back to the future – non-canonical functions of complement

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Protection against invading pathogens and environmental or selfderived antigens is critical to our survival and sustained health. The sensing of such dangerous or noxious entities is mediated by several germ-line encoded sentinel systems that detect highly conserved pathogen- or danger-associated molecular patterns (PAMPs or DAMPs) using several classes of innate immune receptors. These pattern recognition receptors (PRRs) include Toll-like receptors (TLRs), Nod-like receptors (NLRs), C-type lectin receptors (CLRs) and receptors of the complement system, among others. Because the PPRs of the complement system largely circulate in blood and the lymph, whereas TLRs, NLRs and CLRs are expressed within subcellular compartments or at the surface of cells, complement was and is generally considered the 'guardian of the extracellular space' [1]. In line with this view, deficiencies in serum complement components cause severe and recurrent infections, mainly with encapsulated bacteria. Based on its ability to opsonize or directly lyse invading microbes associated with general inflammatory reactions via innate immune cell mobilization and activation, complement was for a long time firmly and solely positioned within the innate arm of our immune system.

However, work over the past decades has demonstrated that complement, not just like the TLRs, NLRs and CLRs, but also in direct cross-talk with these systems, forms a central functional bridge with adaptive immunity and is now an acknowledged integral part of the 'innate sensor networks' that help controlling T and B cell activation and function [2,3]. A body of evidence has accumulated that local and often non-canonical complement activation impacts basically on all types of immune and non-immune cells suggesting that complement's functions in the tissue environment go beyond its role as a sensor and effector system [4]. There is a growing realization that complement functions exceed canonical immune functions and the system orchestrates normal (neuronal) cell and organ development and directs tissue repair and homeostasis. Furthermore, complement operates not only in the extracellular space but also within cells and subcellular compartments, where it is involved in the regulation of basic processes of the cell, particularly those of metabolic nature [5,6]. Importantly, the intracellular activity of complement engages in novel cross-talks between complement and intracellular innate sensor systems, such as the Pyrin

domains-containing protein 3 (NLRP3) inflammasome and the mitochondrial anti-viral signaling protein (MAVS), to direct a catered cellular response towards a perceived danger also from within [7].

These recent observations sparked a renewed interest in complement research and motivated scientists to re-visit and re-evaluate the role of complement activity – now with a fresh eye on its non-canonical functions - in diseases, where complement clearly plays a role but where the complement-driven molecular mechanisms remained elusive. This is paralleled by research efforts that focus on further exploring and understanding novel complement activities in normal cell physiology and diseases formerly not associated with canonical or non-canonical complement activation. The idea behind the current Seminars in Immunology topic is to introduce these emerging non-canonical and currently less well-known activities of complement. A classic canonical role of the complement system is the C3 activation fragment-mediated osponization of pathogens and immune complexes for their safe removal by Kupffer cells in the liver through the CR3/CR4 receptor system. Van Lookeren Campagne and Verschoor discuss in their review [8] the current knowledge about the more recently discovered complement receptor of the immunoglobulin superfamily (CRIg). CRIg emerged quickly as a key player during pathogen recognition and clearance with the discriminating ability to also bind non-opsonized pathogens [9] and to engage in the process of immune adherence (IA)[10]. Thus, CRIg mediates the innate removal of circulating pathogens by the liver, while allowing for the induction of longlasting immunity in the spleen. These features in combination with its ability to directly modulate adaptive immune responses suggests that this molecule is a complement protein ‘to watch’ when exploring new complement functions.

Neutrophils were among the first immune cells, on which the impact of complement activation fragments was studied. It is well appreciated that C5a receptor-mediated signals drive neutrophil activation via induction of the oxidative burst. Particularly, the uncontrolled complement-driven neutrophil activation that occurs during sepsis is recognized since decades as a major factor for the fatal outcome of patients suffering from this syndrome. Halbgebauer, Schmidt, Karsten, Ignatius, and Huber-Lang suggest in their review [11] that this notion was likely too simplistic. They discuss, how neutrophil activity during the course of sepsis can be rather ambivalent and how this Janus face is heavily driven by complement-mediated signals, which have major effects on the positive or detrimental outcome for sepsis patients.

Sadik, Miyabe, Sezin, and Luster also focus on neutrophils and examine the current knowledge about the central role of the anaphylatoxin C5a as an initiator of neutrophil-mediated autoimmune inflammation of the joint and skin [12]. It is well appreciated that C5a drives neutrophil recruitment into inflamed/infected tissues, but the exact mechanisms were not well understood. The authors discuss in their review the novel findings that C5a presented on the joint endothelium confers C5aR1-mediated neutrophil arrest via the β2-integrin. Subsequent production and release of leukotriene B4 (LTB4) [13] – a metabolite of arachidonic acid - by the neutrophils then directs their egress from the blood vessel lumen into the interstitium. This observation aligns very well with the idea tof complement as a critical regulator of different cell metabolic pathways in a broad range of cells. Similarly,

recent exciting work by the Pandey and Köhl laboratories [14] lends further support for a key non-canonical role of complement in cell metabolism. They discovered a novel role for C5a in Gaucher disease (GD), a lysosomal storage disease, where inherited mutations in GBA1 result in a functional defect of glucocerebrosidase, promoting excessive cellular accumulation of ß-glucosylceramide (GC) [15]. Pandey, Grabowski and Köhl discuss in-depth in their review, how C5aR1 activation fuels a cycle of cellular GC accumulation, innate and adaptive immune cell recruitment and activation in GD and how this vicious forward loop could possibly be interrupted therapeutically as an alternative therapeutic option in GD patients. In their contribution, Nording and Langer revisit platelets, an 'old friend' in the field of complement research [16]. It is well known that platelets can activate complement and that complement activation fragments can in turn impact on platelet 'behavior'. However, in the past, this functional cross-talk was mainly considered in the context of thrombosis [17]. Recently, several functions of platelets beyond thrombosis have been uncovered suggesting important immune functions of these cells in tissue homeostasis and remodeling. This review pays particular attention to the role of complement factors and receptors associated with platelet activation and regulation in this context with a particular emphasis on thrombo-inflammatory and cardiovascular diseases.

Also the review by Mödinger, Löffler, Markus Huber-Lang, and Ignatius adds to our growing understanding that complement not only drives degenerative pathways but actively partakes in regenerative processes [18]. It summarizes our current knowledge regarding the contribution of complement to bone erosion during inflammatory conditions such as rheumatoid arthritis or periodontitis, bone development and growth under homeostatic physiological conditions and to bone repair processes after injury or infections. Further, the authors discuss potential therapeutic interventions. A previously unappreciated role for complement, maintaining homeostasis at the host/environmental mucosal interface emerged during studies on complement activities in the intestine. Gut intraepithelial cells (IECs) express and secrete complement components, which are important for the resolution of chronic intestinal inflammation, as mice with defects in single complement components develop signs reminiscent of human inflammatory bowel disease (IBD) [19]. The exact mechanisms of this cross-talk between IECs, the gut microbiome and IEC-derived complement and its impact on IBD regulation awaits to be fully delineated. Sina, Kemper, and Derer summarize our current knowledge about this relatively young and fascinating complement research area [20].

Work particularly surrounding the understanding of neural development demonstrated that temporally and spatially controlled local and autocrine complement activity is required for normal brain development and activity [21]. Given that complement serves as an integral part of tissue integrity and functionality throughout the body, it not surprising that it also controls stem cell populations, from fertilization and implantation throughout embryogenesis and beyond post-natal development. Hawksworth, Coulthard, Mantovani, and Woodruff discuss, how complement-mediated control of physiological cell processes has been harnessed in stem cell populations throughout development and in adult homeostasis [22]. In the final contribution to this issue, Kolev and Markiewski share their ideas about potential new anti-cancer therapeutics [23]. Most previous complement-based anti-cancer strategies focused on increasing complement-mediated cytotoxicity towards

tumors [24]. The authors, however, suggest to rather tap into our increasing knowledge about complement's role in metabolism and modulation of immune cell effector functions and to target complement-mediated immunoregulation for cancer immunotherapy – similar to the ongoing successful developments of 'immune checkpoint modulators'.

Taken together, innovative basic and clinical research has markedly broadened our narrow view of complement as an innate sensing and defense system. This broadened view is inherently complex, not only requiring detailed knowledge of the intricate biochemical framework of the complement system, but equally of the local physiology of the cells, tissues, organs and wider biological systems it intersects with. The complexity of the complement system itself, combined with its still emerging intricate connections to other biological systems, calls for an integrative, multidisciplinary approach that brings together complement researchers with different scientific backgrounds to gain a holistic view on the networks underlying complement-mediated cellular regulation in health and disease. While complement was discovered over hundred years ago, it has managed to sustain its scientific attractiveness well into the 21st century with clearly many exciting discoveries about its non-canonical activities still ahead of us.

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