Complement Regulation in Renal Disease Models

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Summary: Activation of the complement system is tightly regulated by plasma and cell-associated complement regulatory proteins (CRPs), such as factor H (fH), decay-accelerating factor, and membrane cofactor protein. Animal models of disease have provided considerable insights into the important roles for CRPs in the kidney. Mice deficient in fH have excessive fluid phase C3 activation and inactivation, leading to deposition of inactivated C3b in glomerular capillary walls (GCW), comparable with dense deposit disease. In contrast, when fH lacks C-terminal surface targeting regions, local activation on the GCW leads to a disease reminiscent of thrombotic microangiopathy. The uniquely rodent protein, CR1-related y (Crry), has features analogous to human membrane cofactor protein. Defective Crry leads to unrestricted alternative pathway activation in the tubulointerstitium, resulting in pathologic features ranging from thrombotic microangiopathy (TMA), acute kidney injury, and tubulointerstitium nephritis. In the presence of initiators of the classic or lectin pathways, commonly in the form of immune complexes in human glomerular diseases, complement regulation is stressed, with the potential for recruitment of the spontaneously active alternative pathway. The threshold for this activation is set by CRPs; pathology is more likely when complement regulation is defective. Within the endocapillary region of the GCW, fH is key, while decay-accelerating factor and Crry are protective on mesangial cells and podocytes. Arguably, acquired alterations in these CRPs is a more common event, extending from pathologic states of cellular injury or production of inhibitory antibodies, to physiological fine tuning of the adaptive immune response.

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Activation through classic, alternative, or lectin complement pathways leads to the cleavage of C3 and C5 and generation of C3a, C3b, C5a, and C5b. The latter can combine with C6, C7, C8, and C9 to form C5b-9 in any receptive cell membrane; although this is fairly promiscuous, the effects of such C5b-9 formation appear to have some specificity in terms of cellular pathways that become activated (see article in this issue).[1–3] In contrast, C3a, C3b, and C5a have specific cellular and plasma protein ligands. Anaphylatoxin receptors C3aR and C5aR (CD88) are in the rhodopsin family of seven-span transmembrane proteins. C3b-binding proteins include the regulators of complement activation (RCA) proteins (discussed later), and β_2 integrin (CD18) heterodimers with α_M (Itgam, CD11b) and α_x (Itgax, CD11c), also termed complement receptors 3 and 4 (CR3 and CR4) because they bind C3b products. C3aR and C5aR couple to G-proteins to transduce their signals, whereas the β_2 integrins may generate outside-in signals via immunoreceptor tyrosine-based activation motif proteins and spleen tyrosine kinase. Despite the limited ligand-receptor systems, the net effect of complement activation can vary considerably depending on the context.

The vestiges of the alternative complement pathway were present 1 billion years ago in sea anemones of the phylum Cnidaria. Over time, genome, chromosome, and individual gene duplications have resulted in more than 40 complement genes in higher vertebrates.[4,5] It is presumed that evolutionary pressure from infectious microorganisms led to an increasingly active complement system. The benefits of this protective system were limited by the negative effects of complement activating the body's own tissues, which led to the evolution of a multitude of regulatory checkpoints. There is considerable genetic, structural, and functional variability within the complement system proteins.[6,7] This level of complexity is very relevant when considering the mechanics of complement activation; for example, antibody-mediated complement activation beginning with the classic pathway, recruiting the alternative pathway, and ending in the terminal pathway, requires 14 activating proteins, and can be affected by 11 regulatory proteins (Fig. 1). This led Harris et al[8] to propose the term "complotype" to reflect the pattern of genetic variants in complement genes inherited by an individual, which alters the risk for both inflammatory disorders and infectious diseases involving complement.

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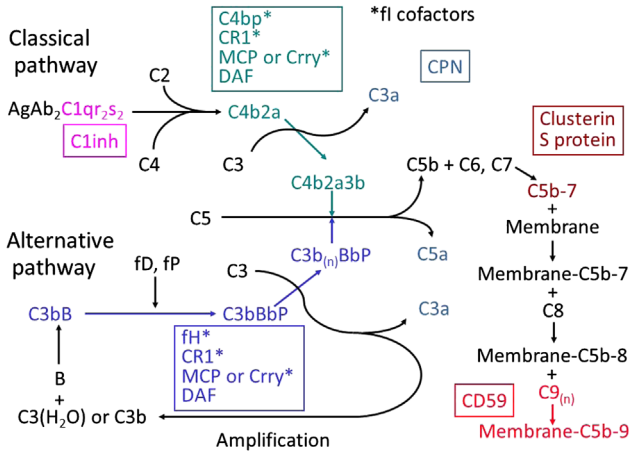

Figure 1. Complement activation and regulation. The proteins relevant to complement activation beginning with ICs in the classic pathway are shown. Regulators of complement activation are in the boxes adjacent to their site(s) of action. Classic pathway activation can recruit the alternative pathway; if intrinsic regulation is overwhelmed, activation and generation of C3a, C3b, C5a, and C5b-9 ensues, each of which has pathophysiologic relevance in kidney diseases. CPN, carboxypeptidase N.

COMPLEMENT REGULATION

The complement system is heavily regulated, including by time and space; several complement intermediates have little time to find particular acceptor sites before inactivation. For example, in the fluid phase, the exposed thioester in C4b and C3b must find a receptive carbohydrate or amino group within 0.1 seconds before inactivation by hydrolysis.[9] Similar constraints occur upon formation of the trimolecular C5b-7 complex, in which the exposed hydrophobic domain must find an acceptor lipid membrane in approximately 0.1 seconds.[10]

There are also dedicated complement regulatory proteins (CRPs), the majority of which block C3 and/or C5 activation, presumably reflecting the importance of their activation.[11] These are the RCA family members, C4 binding protein (C4bp), factor H (fH), decay-accelerating factor (DAF, CD55), membrane cofactor protein (MCP, CD46), complement receptors 1 and 2 (CR1 and CR2), and the rodent-specific CR1-related y (Crry). Proteins that prevent formation of C5b-9 include plasma clusterin and S protein, and cellular CD59. The complement inhibitory properties of all these CRPs are conferred by their fairly low affinity binding for C3, C4, and/or C5 products.

In contrast, the plasma proteins, factor I (fI), and carboxypeptidase N structurally inactivate complement intermediates, C3b and C4b, and C3a and C5a, respectively.[11] Here again, the importance of the C3/C5 step is evident. Both are produced in their active forms; fI requires a cofactor from among C4bp, fH, MCP, CR1, or Crry, which facilitates fI binding and also allows full expression of its catalytic domain.[12]

In a physiological sense, the distinction between complement regulation and its activation is exploited by the adaptive immune system by using C3-/C5-binding proteins on lymphocytes and dendritic cells. For example, the B lymphocyte signaling complex contains CR2, which can be activated by immune complexes (ICs) containing natural antibodies, foreign antigens, and activated C3, thereby facilitating an adaptive humoral response to that antigen.[13] More recent evidence has shown complement impacts cellular immunity (covered in detail in another article in this issue). Here, it appears the T cell and its antigen-presenting dendritic cell partner both generate complement proteins and down-regulate DAF, the net result being local complement activation. Signals through C3aR and C5aR affect T-cell proliferation and differentiation in normal T-cell responses, as well in autoimmunity and alloimmunity.[14–18] The relevance of these largely in vitro observations has held up in correlative human studies.[19,20]

All RCA proteins are composed of short consensus repeat (SCR) domains of approximately 60 amino acids, and are highly related within and between even distant species.[21–23] Human, mouse, and rat fH are very similar, containing solely 20 SCRs arranged in tandem.[24–26] DAF and MCP each have only 4 SCRs along with membrane proximal O-glycosylated regions. DAF is linked to the plasma membrane through a glycosyl-phosphatidylinositol anchor, whereas MCP is a type I transmembrane protein. Although mouse *Crry* was first discovered with a human *CR1* complementary DNA probe (giving rise to its unique name), it is a short transmembrane protein most similar to MCP.[27–29]

The functional activities of each RCA family member are attributable to their binding to C3 products, with the exception of C4bp, which has limited binding to C3b in physiological conditions. Most other RCA members also can bind C4b, which expands their repertoire to classic and lectin pathway C3 convertases. Importantly for some of the conclusions reached to date, fH is not a C4b-binding protein, and therefore is limited to inhibiting the formation and accelerating the decay of intermediates with C3b. Factor H serves as a cofactor for fI-mediated cleavage and inactivation of C3b to inactivated C3b (iC3b) (which should be distinguished from C3bi, which occurs from hydrolysis of C3b).[30] Despite their similar SCR compositions, DAF, MCP, and Crry have distinct functions as complement regulators. DAF has decay-accelerating activity toward C3 and C5 convertases of all pathways, while MCP is a fI-cofactor only. Interestingly, Crry has the features of DAF and MCP, and hence is a versatile and potent complement regulator.[31]

Factor H is produced primarily in the liver and circulates in human and rodent plasma at relatively high concentrations (~500 μg/mL or 3.3 mmol/L),[26,32]