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This information is current as of June 30, 2022.

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J Immunol 2019; 203:3-5; ;

doi: 10.4049/jimmunol.1900527

<http://www.jimmunol.org/content/203/1/3>

Supplementary Material

<http://www.jimmunol.org/content/suppl/2019/06/17/203.1.3.DC2>

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The Journal of Immunology is published twice each month by The American Association of Immunologists, Inc., 1451 Rockville Pike, Suite 650, Rockville, MD 20852
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Print ISSN: 0022-1767 Online ISSN: 1550-6606.



Complement in Motion: The Evolution of CD46 from a Complement Regulator to an Orchestrator of Normal Cell Physiology

M. Kathryn Liszewski* and Claudia Kemper^{†,‡,§}

The classic pathogen-fighting functions of our microbe sensing systems, such as the TLRs, the Nod-like receptors, and several proteins of the complement system, had been defined relatively rapidly after their discovery (1, 2). A more recent trend, however, clearly indicates that some of these evolutionarily ancient systems also serve additional, noncanonical roles in normal cell physiology.

In this article, we highlight how the functions of the complement component CD46 have expanded dramatically beyond its initial discovery as a regulator of complement activation. We now recognize this ancient molecule as a biological focal point for our continuously evolving understanding of the diverse roles of complement as a key orchestrator of (immunological) health.

Although identified in the early 1900s, complement traces its origins to more than a billion years ago, when primitive proteins evolved to protect cells from pathogens and to engage in other intracellular processes (reviewed in Refs. 3–5).

The contemporary complement system consists of three independently triggered activation pathways (classical, alternative, lectin) and a terminal cytolytic pathway common to all. It engages both innate and adaptive immunity. Complement component C3, the most abundant of its proteins, is the nexus where all three activation pathways converge. The proteolytic cleavage of C3 generates C3a (an anaphylatoxin) and C3b (an opsonin and critical component of the convertase complexes). Unbridled complement activation, however, would just as powerfully attack self-tissue as it does pathogens. Thus,

activation must be strictly controlled to maintain appropriate homeostasis while avoiding damage to self.

In this *Pillars of Immunology* article, Cole et al. (6) focused on the regulatory side of complement: in particular, on proteins that bind C3. During the 1980s, a family of structurally, functionally, and genetically related regulators was being elucidated as inhibitors of complement activation via their interactions with fragments of C3 (and/or C4). The regulators of complement activation (RCA) family, consisting of serum and cell-anchored proteins, employed two key processes: decay accelerating activity and cofactor activity. The former refers to the permanent dissociation of activating complexes (i.e., convertases), whereas the latter refers to a role as cofactor for the proteolytic cleavage of C3 (or C4) fragments in association with the serine protease, factor I.

The Atkinson laboratory had been studying polymorphisms of two such regulators, complement receptors (CR) CR1 and CR2 using C3 (i.e., C3b or iC3) affinity chromatography of surface-labeled peripheral blood cells (7). However, they routinely observed a third group of molecules when studying human leukocytes. The study by Cole et al. (6) delved into this phenomenon by examining the cell distribution, relative mobility, and antigenic specificity of "... a heretofore unrecognized group of 45,000–70,000 M_r C3-binding molecules."

The authors found that every tested cell population possessed this new factor as a broad band or doublet pattern. They dubbed the new protein gp45–70. A year later, Tsukasa Seya, of the same group, developed a purification scheme characterizing two distinct species, "upper" and "lower," each of which possessed cofactor activity for C3b cleavage (8). Interestingly, the C3b cofactor activity was unique when compared with CR1. To reflect the growing structure/function information, the Atkinson group renamed the molecule as "membrane cofactor protein (MCP)," later designated as CD46 (reviewed in Ref. 9).

Since these pioneering studies, we have learned that CD46 is ubiquitously expressed on all cells, except erythrocytes, and is a cofactor for C3b and C4b cleavage. Its cloning and characterization revealed that CD46 is a type 1 transmembrane glycoprotein coexpressed on most cells as four isoforms, which arise by alternative splicing of a single gene that lies within the RCA cluster on chromosome 1q32.2 (10–13). The structural heterogeneity is in part accounted for by alternative splicing in an extracellular region for O-glycosylation (BC region) and by having one of two intracellular cytoplasmic tails (tail 1 or tail 2;

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Work in the Kemper laboratory is supported by the Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health. M.K.L. support was provided by the National Institutes of Health (Grant R01 GM099111).

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Abbreviation used in this article: CR, complement receptor.

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termed CYT-1 or CYT-2, respectively). These isoforms are thus described as CD46-BC1, -BC2, -C1, and -C2.

An early indication that there is more to this molecule than mere complement regulative activity was the finding that CD46 plays a role in reproduction; specifically, in the interaction between the oocyte and sperm during fertilization (reviewed in Refs. 14, 15). Further, CD46 has been called a “pathogen magnet” because it is usurped by nine pathogens (four viruses and five bacterial species) [(16) and reviewed in Ref. 17].

Attention surrounding this intriguing molecule then gathered substantial traction beyond those with direct interest in complement after the first disease association was found by Richards et al. (18). A heterozygous CD46 mutation predisposed to a rare thrombotic microangiopathic-based disease (atypical hemolytic uremic syndrome) (18). Currently, there are more than 60 disease-associated CD46 mutations. Although most have been linked to atypical hemolytic uremic syndrome, new putative links to other diseases also have been identified (reviewed in Ref. 17).

As we gained a better understanding of the role of CD46 in endothelial biology, which protects vascular space against unwanted complement deposition, it was also realized that the signaling capacity of CD46 broadly impacts cellular behavior. Specifically, CD46-mediated intracellular signals 1) regulate autophagy during pathogen invasion of epithelial cells (19); 2) are important for macrophage activity, including cytokine and NO production, as well as Ag presentation (20); and 3) regulate T cell activation via providing costimulatory signals during TCR engagement (21).

This indicated that CD46, although initially discovered as a complement regulator, also functions as a complement receptor. Indeed, a closer look into the activities of CD46 during T cell activation demonstrated how central its signaling capacity is to normal cell homeostasis and effector function. Importantly, on T cells, CD46 is engaged and activated in an autocrine fashion by T cell-generated C3b, rather than via serum-derived C3b (22), suggesting compartmentalization of CD46's functions during serum complement activation and immune cell stimulation.

The Kemper laboratory then demonstrated that intrinsic CD46 stimulation is required for the upregulation of nutrient channels, including the glucose transporter GLUT1 (SLC2A1), the large neutral amino acid transporter LAT1 (SLC7A5/SLC3A2), and the cationic amino acid transporter CAT1 (SLC7A1), as well as the expression of metabolic enzymes, such as fatty acid synthase by human CD4⁺ and CD8⁺ T cells. In addition, CD46—and particularly the activity of CD46 CYT-1—mediates assembly of the key nutrient-sensing mammalian target of rapamycin (mTOR) machinery, which enables the high levels of glycolysis and oxidative phosphorylation that are needed for IFN- γ production and Th1 induction (23–25). Consequently, patients with CD46 deficiency cannot mount Th1 responses, have reduced cytotoxic CD8⁺ T cell activity, and suffer from recurrent infections (25, 26).

This work tightly connected CD46, rather unexpectedly, with key physiological pathways, particularly with those of a metabolic nature. Moreover, although a Th1-driving activity for CD46 was in line with the common understanding that complement underlies protective immunity, the discovery that signals mediated by CYT-2 then initiate the safe contraction of

Th1 responses through a “metabolic shutdown” demonstrated conclusively that CD46 also partakes in the T cell homeostasis (27, 28). These findings triggered a rethinking in the field about the tight relationship between pathogens and CD46, particularly because any given pathogen relies on the metabolic machinery of the cell it invades for its own propagation. Thus, there are ongoing studies assessing if pathogens may use CD46-driven metabolic reprogramming to their advantage.

Although these new noncanonical functions for CD46 have mostly been carved in human T cells, CD46 is ubiquitously expressed, strongly indicating that its regulation of metabolism occurs in a broad range of cells and, hence, may impact their respective effector functions (22).

However, conclusively probing the *in vivo* roles of CD46 has proven difficult because wild-type mice (and rodents in general) only express “membrane cofactor protein” (gene: *Cd46*) on the inner acrosomal membrane of spermatozoa and in the eye (29, 30). A functional homolog that mimics the activity of “human CD46” in mice remains to be defined—thus, there is currently no small animal model available to study CD46 biology *in vivo*. It is unclear why mice rid themselves of CD46 during evolution and what exact path rodent cells took to regulate the molecular mechanisms controlled by CD46 in humans. An intuitive possibility is, of course, that they aimed to protect themselves against CD46-binding pathogens, similar to New World monkeys that have modified their CD46 structure to avoid measles virus infections (31). Rooted in the observation that a direct interaction between the Notch ligand Jagged-1 and CD46 controls human CD4⁺ T cell homeostasis (26) and that murine Notch mimics the majority of CD46's functions, one viable possibility considered in the field is that Notch may have taken on CD46's roles in mice (24).

Thus, our understanding of the multifaceted roles played by CD46 continues to be an exciting journey that began with its initial discovery by Cole et al. (6) as a key complement regulator and has blossomed into an acknowledged conductor of cell metabolism. A key role for complement in cell physiology aligns well with the growing idea that ancient pathogen-sensing systems may have initially evolved on a single-cell level to detect and rectify nutrient/cellular stress and only acquired pathogen-fighting capabilities when life evolved into multicellular and multiorgan organisms. CD46 likely has more surprises in store for us, and it will be critical to create the needed new tools and models to understand its full range of biology in health and disease.

Disclosures

The authors have no financial conflicts of interest.

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