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Complement and the Regulation of T Cell Responses

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Abstract

The complement system is an evolutionarily ancient key component of innate immunity required for the detection and removal of invading pathogens. It was discovered more than 100 years ago and was originally defined as a liver-derived, blood-circulating sentinel system that classically mediates the opsonization and lytic killing of dangerous microbes and the initiation of the general inflammatory reaction. More recently, complement has also emerged as a critical player in adaptive immunity via its ability to instruct both B and T cell responses. In particular, work on the impact of complement on T cell responses led to the surprising discoveries that the complement system also functions within cells and is involved in regulating basic cellular processes, predominantly those of metabolic nature. Here, we review current knowledge about complement's role in T cell biology, with a focus on the novel intracellular and noncanonical activities of this ancient system.

INTRODUCTION

Complosome: components of the complement system that are intracellularly activated and act primarily on intracellular complement receptors and regulators

The immune system perpetually orchestrates a broad range of effector pathways to detect and remove pathogens and self-derived dangerous entities, such as infected, apoptotic, or malignant cells. Microbe-derived antigens, so-called pathogen-associated molecular patterns (PAMPs), and noxious self-derived antigens, termed damage-associated molecular patterns (DAMPs), are recognized by different pattern recognition receptors (PRRs) expressed on or secreted by immune cells (1, 2). The complement system is among the most ancient of the preformed mediators of host defense, and several of its more than 50 serum-circulating proteins and cell surface receptors function as PRRs (3). The role of liver-derived serum complement as a vital PRR system is demonstrated by the fact that a large proportion of complement deficiencies cause recurrent infections (4, 5). Additionally, and similar to the Toll-like receptor (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) PRR systems (6, 7), complement is required for the efficient sensing and removal of DAMPs and particularly for the clearance of apoptotic cells and immune complexes (ICs) (8–10). Furthermore, it is now broadly acknowledged that complement's activity goes well beyond these innate functions during the early phases of the host response to infection, noxious antigens, and dangerous, altered self and that this system forms a functionally critical bridge between innate and adaptive immunity by directly controlling both B and T cell responses (11–13).

More recent discoveries that (*a*) complement components are secreted by a wide range of (immune) cells and function in an autocrine fashion and (*b*) complement activity is not confined to the extracellular space but occurs within cells represent paradigm shifts in the field (14). Subsequent queries into the functional implications of these novel modes and locations of complement activation then demonstrated that complement unexpectedly regulates basic physiological pathways [particularly those of metabolic nature (15, 16)] that are key to general cell homeostasis and effector functions. The intracellular complement system (the so-called complosome) impacts cell physiology via direct cross talk with other intracellular innate sensor systems, such as the inflammasomes (17, 18), and governs, for example, human T helper type 1 (Th1) responses by driving the signaling pathways and metabolic reprogramming necessary for effector responses (16, 19). In this review, we first briefly cover the known roles of liver-derived serum-circulating complement in orchestrating the early stages of an immune response against a pathogenic invader (the canonical functions of complement). We then discuss in depth the emerging roles of immune cell–derived complement, with a focus on the complosome (the noncanonical functions of complement) as an independent arm of the complement system that is vital for the cellular machinery underlying the normal initiation and regulation of effector T cell responses.

THE COMPLEMENT SYSTEM

Canonical Functions of Serum-Effective Complement

Complement was discovered by Jules Bordet and Paul Ehrlich more than a century ago and was defined as a "system of serum-circulating proteins *complementing* antibody-mediated immune responses" (20, our translation and our emphasis; 21). The complement system is composed of >50 proteins that either circulate in the fluid phase or are cell membrane bound. It is commonly recognized as the prime sentinel for the detection and removal of pathogens that have breached the host's protective barriers. The complement components circulating in the blood, the lymph, and the interstitial fluid are secreted mostly by the liver; these include the PRR components and the effector molecules. Serum complement effector proteins exist in inactive proforms but are rapidly activated in a cascade-like fashion when one or more of the three main activation

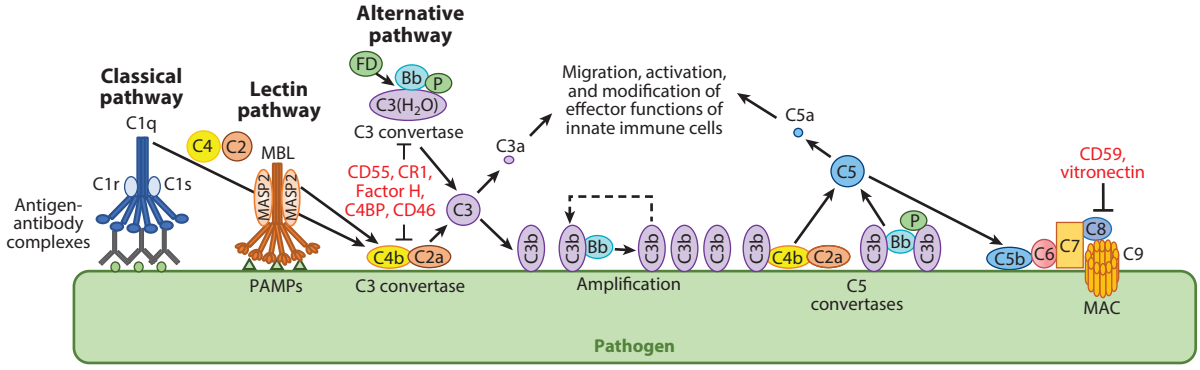

Figure 1

Activation and functions of serum-circulating complement. Liver-derived, systemically circulating complement can be activated through the classical pathway, the lectin pathway, and the alternative pathway. Through the formation of classical (C4b2a) and alternative (C3bBb) C3 convertases, these pathways lead to the generation of C3a and C3b. Upon subsequent generation of C5 convertase (C4bC2aC3b for the classical and lectin pathways and C3bBbC3b for the alternative pathway), C5b and C5a are produced, with surface-bound C5b initiating the formation and insertion of the MAC on pathogens (or other target membranes), and the generated anaphylatoxins act on innate immune cells to foster an inflammatory reaction. Complement activation is regulated by multiple inhibitory proteins (*red font*), such as CD46, CD55, CR1, Factor H, and C4BP, which aid in the inactivation of deposited C3b and C4b (CD46, Factor H, C4BP, and CR1) and/or disassemble the convertases (CR1 and CD55), and CD59 and vitronectin, which inhibit MAC formation. Abbreviations: C4BP, C4b-binding protein; FD, Factor D; MAC, membrane attack complex; MASP2, mannose-binding lectin serine protease 2; P, properdin (C3 convertase stabilizer); PAMP, pathogen-associated molecular pattern.

pathways—the classical pathway, the lectin pathway, and the alternative pathway—are triggered via PAMP sensing (4, 5, 22–24) (**Figure 1**).

The classical pathway is initiated by the binding of C1q to complement-fixing antibodies (primarily of the IgM type and IgG1, IgG2, and IgG3 subtypes) bound to pathogen surfaces. The lectin pathway components mannose-binding lectin, ficolins, and collectins recognize specific carbohydrate moieties on pathogenic surfaces, and activation of the alternative pathway is initiated when C3b-like molecules that are continuously generated in blood through spontaneous hydrolysis ($C3[H_2O]$) attach to microbial surfaces via a covalent thioester bond (**Figure 1**). All activation pathways lead to the formation of C3 convertases (C4bC2a for the lectin and classical pathways and C3bBb for the alternative pathway), which cleave C3 into the bioactive opsonin C3b and the anaphylatoxin C3a. C3 convertases then seed the rapid formation of C5 convertases (C4bC2aC3b for the lectin and classical pathways and C3bBbC3b for the alternative pathway), which process C5 into the anaphylatoxin C5a and into the fragment C5b. Deposition of C5b onto a pathogen surface induces the assembly of the pore-forming terminal complement complex (TCC) [also known as the membrane attack complex (MAC)], which is composed of complement proteins C5b-C6-C7-C8-polyC9, and subsequent direct lytic killing of the microbe. The alternative pathway is also termed the amplification pathway or loop, because it dramatically potentiates the activity of the lectin and classical pathways (14, 22, 23).

Of note, C3 and C5 can also be activated in a convertase-independent fashion by specific proteases that belong mostly to the coagglutination system and to the granzyme and cathepsin enzyme families. Such nonclassical complement activation modes have recently received much attention, as they have clear physiological importance not only in the orchestration of human Th1 responses (see below) but also in several disease conditions such as trauma and sepsis (14, 25–27).

Aside from direct pathogen killing, additional canonical key roles of activated complement are mediated by cell membrane–bound complement receptors. During the initiation and propagation

Opsonins: proteins binding the surface of particles and enhancing their uptake by phagocytes; include IgG and complement activation fragments

Anaphylatoxins: the proinflammatory complement activation fragments C3a and C5a, which mediate inflammatory responses through cell activation, chemotaxis, and histamine release

Cathepsins: an evolutionarily conserved family of 12 proteases that play important roles in cell turnover (e.g., cancer) and degradation of the extracellular matrix

of the inflammatory reaction, these receptors are engaged by activation fragments that transmit instructive signals into the cell. For example, C3b mediates the opsonization and subsequent phagocytic uptake of pathogens by scavenger cells such as neutrophils and macrophages via engagement of receptors specific for C3 activation fragments, including complement receptor 1 (CR1, or CD35), CR3 (CD11b-CD18), and CR4 (CD11c-CD18) (28, 29). Furthermore, C3a and C5a induce migration, activation, and effector functions in innate immune cells such as neutrophils, mast cells, and macrophages, as well as increasing permeability of small blood vessels via engagement of their specific G protein–coupled receptors—C3aR and C5aR1 (CD88), respectively (30–33)—and hence drive a broad inflammatory reaction (**Figure 1**).

The critical role of serum-circulating complement in the protection against pathogen invasion is undisputed and emphasized by the fact that deficiencies in key complement components cause severe and recurrent infections (34). However, serum-circulating complement-derived PRRs, similar to the NLRs, the TLRs, and the inflammasomes, are instrumental in the recognition and removal of DAMPS, and normal functioning complement is therefore also required to prevent autoimmune responses. For example, opsonization of ICs with C3 activation fragments is required for their removal (35, 36), and the C1 complex (composed of C1q-C1r-C1s) detects danger molecules appearing on the surface blebs of apoptotic cells and induces the safe elimination of such potentially dangerous self-derived entities. Consequently, C3 and C1 deficiencies cause failure in the efficient removal of ICs and dying cells and are therefore associated with IC disorders (36, 37) and the autoimmune disease systemic lupus erythematosus (SLE), respectively (8, 38, 39).

Because C3b and C4b proteins bind to hydroxyl and amine groups that are ubiquitously present on pathogen and host cell surfaces, complement, once activated, is basically nondiscriminative and needs to be tightly regulated to prevent unwanted host tissue damage (22, 23). This desired control is achieved through several fluid-phase and membrane-bound complement inhibitors and regulators (40) (**Figure 1**). These regulators are expressed by all cells and aid in the proteolytic inactivation of deposited C3b and C4b [membrane cofactor protein (MCP), also known as CD46; Factor H; C4b-binding protein (C4BP); and CR1], induce disassembly of C3 and C5 convertases [decay-accelerating factor (DAF), also known as CD55, and CR1], or inhibit MAC formation and insertion (CD59, also known as vitronectin) (41, 42). Importantly, all membrane-bound complement regulators have, similar to the classic complement receptors, signaling capacity. This combined functional activity of complement regulators (in conjunction with their respective cross talk with other sensor and effector systems; see below) on host immune and nonimmune cells substantially contributes to the broad functional repertoire of this ancient system (12, 14, 15).

Noncanonical Functions of Autocrine Complement

It is now widely acknowledged that controlled engagement of complement receptors and regulators in both serum-circulating and tissue-resident cells is required for normal immunity (22, 24). For decades it was also considered established that the complement activation fragments driving such receptor/regulator stimulation were liver and serum derived. However, in the late 1990s, studies of C3 and C7 allotype conversion in patients that had received bone marrow or liver transplants hinted that the liver is the main, but not sole, source of systemic complement (43, 44). Today we know that complement components can be produced by almost all cell populations and that local complement synthesis occurs in a range of diverse tissues and organs, including the kidney, intestine, heart, and synovial tissues of joints (45, 46). Moreover, in some immune-privileged organs such as the brain and eye, local generation by astrocytes and epithelial cells is the prime complement source (47). Importantly, the local production of complement can be modulated negatively and positively by cytokines and growth factors, and conversely, changes

in local complement activation impact cytokine production by tissue-resident immune cells (48, 49). These findings imply that extrahepatic complement activity may have evolved to respond to environmental cues that signal the requirement for or the presence of an immunological response.

Indeed, there were early indications of an important role for serum-independent, immune cell–derived local/tissue complement activity: Gadjeva and colleagues (50) showed in 2002 that C4 generated by monocytes restores the impaired humoral response against tumor-derived antigens in serum C4–deficient mice. Additionally, Pratt et al. (51) demonstrated in 2002 that local synthesis of C3 by donor kidney epithelial cells mediates rejection of the grafted organ. Finally, in a series of elegant studies utilizing mouse strains with appropriate complement deficiencies in models of heart and kidney transplantation as well as pathogen infections, work by the Song (52, 53), Heeger (54, 55), and Medof (56) laboratories demonstrated unequivocally that normal antigen-presenting cell (APC) function and T cell function are largely independent of serum-derived complement but rely on complement activation fragments generated by these immune cells themselves.

Specifically, these groups observed that both cell types not only secrete C3 and C5 upon cognate interaction but also express and secrete Factor D and B proteins, resulting in local extracellular C3 and C5 convertase formation. C3a and C5a generated in such fashion in the extracellular space then engage their respective receptors, C3aR and C5aR1 (CD88), expressed on $CD4^+$ and $CD8^+$ T cells and on APCs in an autocrine fashion (**Figure 2**), and mediate APC maturation and T effector cell responses (see below) (52–57). In humans, concurrent autocrine engagement of CD46 by T cell–generated C3b is an additionally required event for successful Th1 induction (see below) (58, 59) (**Figure 2**).

Mechanistic target of rapamycin (mTOR): a core nutrient sensor complex regulating transcription; protein synthesis; and cell survival, proliferation, growth, and motility

Noncanonical Functions of Intracellular Complement: The Complosome

Just when the concept that immune cell–derived and autocrine-functioning complement acts as a key instructor of cellular effector functions became more mainstream, it was discovered that complement activation is not confined to the extracellular space, as originally thought, but also occurs intracellularly (60, 61). Importantly, the stimulation of intracellular complement receptors (for example, stimulation of C3aR and C5aR1) induced signaling pathways and cellular responses distinct from those elicited by the same receptors when present on the cell surface (**Figure 3**).

Specifically, human $CD4^+$ T cells contain intracellular stores of C3, intracellular C3aR (on lysosomal membranes), and the protease cathepsin L (CTSL). CTSL continuously processes intracellular C3 into bioactive C3a and C3b in resting T cells, and the engagement of lysosomal C3aR by intracellular C3a mediates homeostatic T cell survival through tonic mechanistic target of rapamycin (mTOR) activation. Thus, when intracellular C3 activation is abrogated by CTSL inhibition, T cells succumb to apoptosis (60). T cells also constantly generate intracellular C5a from internal C5 sources (61), likely via intracellular C5 convertase formation (N. Niyonzima, T.E. Mollnes, T. Espevik & C. Kemper, unpublished data). Upon T cell receptor (TCR) activation, intracellular C5a engages the intracellular C5aR1 (located on a yet-to-be-defined subcompartment) and impacts oxygen metabolism by triggering the increased generation of mitochondrial reactive oxygen species (ROS) that supports cell activation (61) (**Figure 3**). At the same time, C3a and C3b generated intracellularly rapidly translocate to the cell surface, where they engage their receptors, C3aR and CD46, respectively, and these events together drive optimal IFN-γ production and Th1 induction (14, 60, 61) (**Figure 3**). T and B cells can also transport the hydrolyzed form of C3, $C3(H_2O)$, from the extracellular milieu into the cell and process it intracellularly via CTSL into C3b and C3a; the biological implication of this observation remains to be established (62).

Although the functional importance of the intracellular complement system has been best studied in human $CD4^+$ T cells, this system is present in all cells analyzed thus far. Therefore, this

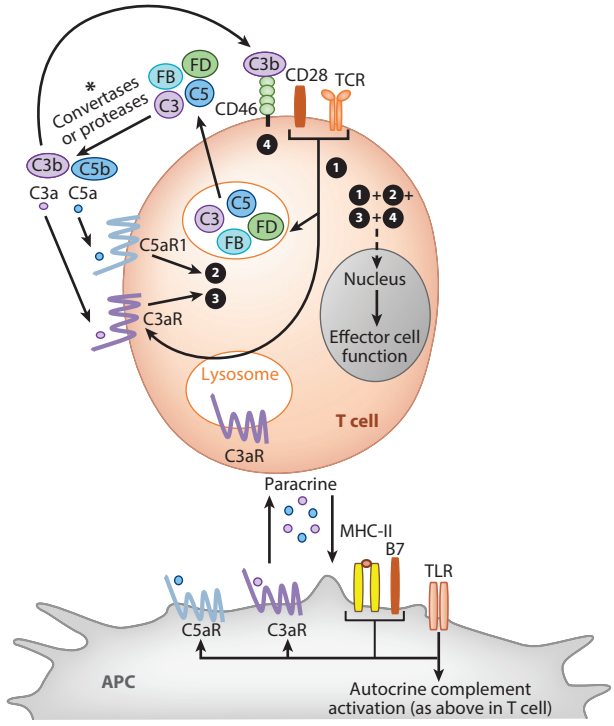

Figure 2

Noncanonical functions of immune cell–derived local complement. Local complement activation is triggered when (❶) activating signals (TCR stimulation on T cells and TLR activation on APCs) initiate the generation and secretion of C3, C5, Factor B, and Factor D, leading to C3 and C5 convertase formation in the extracellular space and on the cell surface and ultimately the generation of the complement activation fragments C3a, C3b, C5b, and C5a (C3 and C5 can also be cleaved by proteases in the extracellular space). TCR stimulation also (❷ +❸) induces the shuttling of C3aR from the lysosome to the cell surface, allowing these complement fragments to bind to their respective receptors on the cell surface and induce cellular responses [in conjunction with (❹) CD46 activation signals in T cells]. Autocrine activation is also supported by preformed C3 and C5 activation fragments that are generated intracellularly (**Figure 3**) and rapidly transported to the cell surface to mediate autocrine signaling from that location. C5aR1 expression is limited to the intracellular space in human T cells, and its expression pattern in mouse T cells is controversial. The asterisk denotes that C3 and C5 convertases or C3- and/or C5-activating proteases operate in parallel with intracellularly generated C5 and C3 activation fragments (**Figure 3**). Abbreviations: APC, antigen-presenting cell; FB, Factor B; FD, Factor D; MHC-II, major histocompatibility complex class II; TCR, T cell receptor; TLR, Toll-like receptor.

intracellular complement system, which we have coined the complosome, somewhat in analogy to the inflammasome, with its novel activities within cells, is likely of broad biological relevance (17, 60, 63). Indeed, researchers recently showed that intracellular C3 within gut epithelial cells drives intestinal tissue damage during mesenteric ischemia (60, 64).

In summary, although liver-derived (serum-circulating) complement is undoubtedly vital for its classic sentinel function and the rapid elimination of blood-borne pathogens, local complement and intracellular complement serve noncanonical roles: Immune cell–derived and autocrine functioning complement is a key instructor of cell effector functions, and the complosome surfaces as a critical regulator of basic cellular processes.

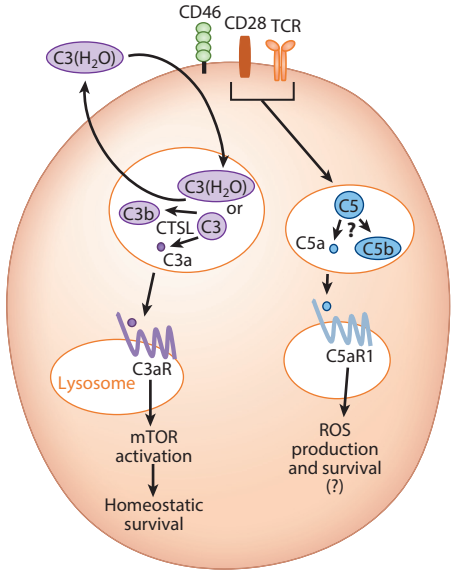

Figure 3

Noncanonical functions of intracellular complement. Intracellular complement activation in $CD4^+$ T cells (and possibly other cells) occurs through the cleavage of intracellular C3 and C5 stores [or imported hydrolyzed C3-C3(H_2O)] by action of the C3-cleaving protease CTSL [for C3 and C3(H_2O)] or a currently undefined protease for C5. The resulting C3a and C5a fragments engage their intracellular receptors (C3aR and C5aR1, respectively) and mediate mTOR activation and homeostatic survival (C3aR) and ROS production and possibly survival (C5aR1). Intracellular C3aR signaling occurs on lysosomes, although the intracellular compartment or compartments expressing C5aR1 are not yet defined. Abbreviations: CTSL, cathepsin L; mTOR, mechanistic target of rapamycin; ROS, reactive oxygen species; TCR, T cell receptor.

COMPLEMENT AND THE INSTRUCTION OF ADAPTIVE IMMUNITY: B CELL RESPONSES

The first realization that complement also forms a critical bridge between innate and adaptive immunity was instigated by work from Pepys and colleagues in the 1970s that showed that complement receptor 2 (CR2; also known as CD21) functions as a strong costimulator during B cell activation (65): During B cell receptor (BCR) stimulation, coengagement of CR2 through C3d-coated antigens reduces the threshold for BCR signaling, thereby providing important additional signals for optimal antibody production (66–68). Thus, C3 plays the role of a natural adjuvant during B cell function (69–72), and this explains why serum C3 deficiency often causes common variable immunodeficiency (73). CD21-mediated signals also directly control positive selection and the expansion and maintenance of a subset of B cells termed B-1 cells (74) and contribute to the maintenance of memory B cell responses by tethering complement-opsonized antigens to follicular dendritic cells (FDCs) for long-term retention in germinal centers and its (re)presentation to previously primed B cells (75). Furthermore, and aligning with the growing understanding that complement also contributes to the negative control of immune responses and even immune cell homeostasis (14, 22), CD21 partakes in the negative selection of self-reactive B cells, as mice deficient in either *C4* or *Cr2* fail to induce B cell anergy toward self-antigens (76) [of note, whereas humans express CR1 and CR2 as single molecules derived from two separate genes, mice express a hybrid CR1/CR2 protein encoded by a single gene (36)]. The exact underlying molecular mechanisms for this

B-1 cell: a B cell subtype that is distinct in phenotype, distribution, and function from classical B cells and considered part of innate immunity

observation are not fully understood, but they may operate in humans through CD21-driven lowering of the threshold in B cells for apoptosis induction during the negative selection process (77).

The effects of complement activation fragments on normal B cell activity have so far been attributed solely to complement derived from serum or generated locally in tissues, for example, the lymph nodes. However, given that intracellular complement is so essential to normal T cell function (see below) and that B cells harbor a so-called B cell complosome (60, 63), the latter may also be an integral part of B cell responses.

COMPLEMENT AND T CELL RESPONSES

Indirect Effects

In view of the impressive repertoire of complement activities in B cell biology, involvement of this system in $CD4^+$ and $CD8^+$ T cell responses was anticipated. Work by several groups over the past few years has indeed confirmed this suspicion. T cell activation is triggered through the presentation of antigen by mature APCs in lymph nodes or secondary lymphoid organs. The nature of the antigen, the APC, and the surrounding microenvironment mostly determines which effector functions (cytotoxic, Th1, Th2, Th17, regulatory, etc.) are induced by the signal-receiving T cells. Complement controls both the induction and contraction of T cell responses (14, 78–80), and its regulatory impact can be mediated directly through modulation of the T cell itself and/or indirectly via affecting APC function (**Figure 4**). APCs, including dendritic cells (DCs), FDCs, and macrophages, express the full repertoire of complement receptors and regulators and are hence ideally suited to integrate and respond to virtually all incoming complement activation–derived signals (3, 12, 53). The engagement of these complement receptors and regulators (often in a paracrine and/or an autocrine fashion; see **Figure 2**) subsequently modulates their maturation status and cytokine and chemokine expression profile, which in turn dictates the nature of the T cell response during the cognate APC–T cell interaction.

The first evidence that complement exerts control over protective T cell responses was delivered through experiments in influenza and lymphocytic choriomeningitis viral infection models utilizing mice treated with cobra venom factor (which leads to C3 consumption in the blood) or deficient in *C3* (81, 82). In both models, $CD4^+$ and $CD8^+$ T cell responses to the viruses were strongly reduced, accompanied by increased mortality. The need for complement during the induction of protective T cell immunity against a broad range of pathogens is now also well documented. For example, C5aR-deficient mice have reduced virus-specific $CD8^+$ T cell responses during influenza type A infection (83), whereas C3aR and C5aR1 double-deficient strains are highly susceptible to herpes simplex keratitis (84) and *Toxoplasma gondii* infection with substantially dampened T cell immunity (56). Subsequent work using animals lacking additional key complement components demonstrated a strong involvement of the alternative pathways and strict requirement for anaphylatoxin-mediated signals for normal and efficient DC maturation, with optimal upregulation of major histocompatibility class II (MHC-II), CD80 and CD86 costimulator upregulation, and production of the polarizing cytokines that orchestrate T cell differentiation. DCs from *C3*, complement factor B (*Cfb*), complement factor D (*Cfd*), and *C5ar1* and *C3ar* knockout mouse strains, but not from *C4*-deficient strains, fail to upregulate MHC-II, show reduced expression of costimulatory molecules, and have defective T cell priming and reduced IFN-γ secretion upon encounter of alloantigens expressed by the DCs (55, 56, 85). Conversely, APCs and T cells from mice lacking DAF expression ($Cd55^{-/-}$ mice) have unrestrained C3 and C5 convertase formation with increased local anaphylatoxin production and, thus, hyperactive Th1 induction (52, 54). Moreover, investigators recently showed that C3 activation fragments bound to ingested apoptotic cells

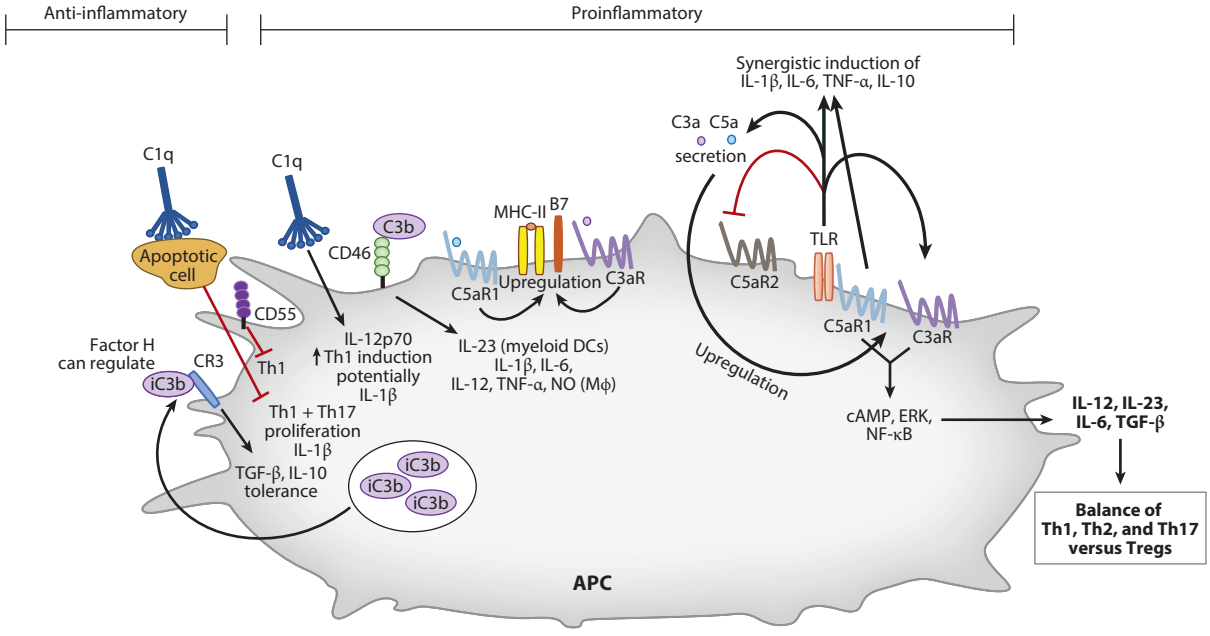

Figure 4

Direct effects of complement receptor activation on antigen-presenting cells. On APCs (DCs), signaling of C5a and C3a through their receptors (C5aR1 and C3aR, respectively) upregulates MHC-II and costimulatory B7 molecules and cAMP, ERK, and NF-κB signaling, leading to the secretion of IL-12, IL-23, IL-6, and/or TGF-β. TLR signals enhance secretion of C3a and C5a, which both act as ligands for their respective receptors and enhance receptor expression in a positive feedback loop. TLR signals, in conjunction with C5aR1 and C3aR signals, lead to the synergistic induction of IL-1β, IL-6, TNF-α, and IL-10, which are important cytokines for Th1 and Th17 induction. In human DCs and macrophages, CD46 stimulation also induces proinflammatory cytokine and NO production. C1q both positively and negatively regulates the inflammatory response, which depends partially upon the context/environment: C1q increases IL-1β and IL-12p70 and potentiates Th1 responses, whereas C1q bound to apoptotic cells inhibits IL-1β secretion and Th1 and Th17 proliferation. Additional anti-inflammatory signals are potentiated by CD55 (DAF), which reduces Th1 induction potential of APCs, and iC3b bound to CR3 results in TGF-β and IL-10 secretion and tolerance, which can be further regulated by Factor H and intracellular stores of iC3b. Red lines denote inhibitory activities of respective receptors. Abbreviations: APC, antigen-presenting cell; cAMP, cyclic adenosine monophosphate; DAF, decay-accelerating factor (CD55); DC, dendritic cell; ERK, extracellular signal–regulated kinase; MΦ, macrophage; MAC, membrane attack complex; MHC-II, major histocompatibility complex class II; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; TLR, Toll-like receptor.

regulate the intracellular routing and shunting of cargo into lysosomes and delay phagosome maturation in DCs, thereby enhancing antigen presentation and overall T cell expansion in mice but not impacting a specific effector subpopulation (86). Furthermore, sensing of pathogen-introduced C3b in the cytosol activates signaling cascades dependent on mitochondrial antiviral signaling and induces proinflammatory cytokine production and cell-autonomous immunity in cells (87). These data indicate that the engagement of intracellular complement receptors within DCs, as has been shown for T cells, induces distinct signaling pathways that modulate DC activity.

Engagement of the anaphylatoxin receptors C3aR and C5aR1 on DCs induces the downstream activation of cyclic adenosine monophosphate (cAMP) (88), extracellular signal–regulated kinases (ERKs) (89), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (90), which in turn drive the secretion of interleukin (IL)-12, IL-23, IL-6, and transforming growth factor (TGF)-β, which are cytokines instrumental in generating Th1, Th2, or Th17 responses

(91, 92). Specifically, C5aR1 activation drives IL-12 production by DCs (93), and both the production of this cytokine and Th1 induction were blunted in *C5*-deficient mouse macrophages upon challenge with *Staphylococcus aureus* (94). Furthermore, *C5*-deficient mice have enhanced Th2 immune responses in models of experimental allergic asthma, but this is only in part due to reduced Th1 activity, suggesting that C5 can also directly suppress the development of Th2 lineage commitment via the C5aR1 axis (94, 95). Importantly, C3- and C5-derived signals received by monocytes are also required for normal human Th1 activity, as blockage of C5aR1 in human monocytes during *S. aureus* infection inhibited Th1 induction (94) and monocytes from C3-deficient human patients have diminished ability to induce IFN-γ secretion in $CD4^+$ T cells (96).

Anaphylatoxin receptor–mediated signals have also emerged as key regulators of Th17 responses via direct regulation of TLR activity on APCs: Upon stimulation with the TLR ligand Pam_3Cys, *C5ar1*$^{-/-}$ splenic DCs produce augmented amounts of IL-6 and IL-23 relative to C5aR1-sufficient DCs (97). Aligning with this observation, Lajoie and colleagues (98) demonstrated that C5a suppresses house dust mite–induced IL-23 production from bone marrow–derived DCs in a mouse model of asthma. In contrast, bone marrow–derived DCs from *C5ar1*$^{-/-}$ mice are unable to produce IL-1β, IL-6, and IL-23 when activated with ovalbumin and lipopolysaccharide (91), indicating that the specific impact of C5aR1 activation on Th17 induction depends on the APC type that senses the C5a generated and the TLR that is coengaged. A similar role for the anaphylatoxins in the regulation of human Th17 is suggested by the findings that *Candida albicans* triggers IL-6 secretion in human monocytes in a C5a-dependent fashion (99) and that C3aR stimulation prompts IL-1β production in human monocytes, which in turn specifically promote Th17 induction in activated human $CD4^+$ T cells without affecting Th1 and Th2 cytokines (100). The human-specific complement regulator CD46, which is engaged by C3b or C4b deposited on cells, positively regulates the expression of IL-23 by human myeloid DCs (101) and induces IL-12 and the production of nitric oxide in macrophages (102). In line with an APC-instructing role for CD46, monocytes from mice transgenic for human CD46 transition faster into the macrophage state, with a strong bias toward proinflammatory M1-type differentiation, including the production of high amounts of IL-1β, IL-6, IL-12, and tumor necrosis factor (TNF) (103). Similarly, CR1 activation on human macrophages supports increased IL-12 secretion and a proinflammatory APC phenotype (104). However, these studies did not explore the downstream effects of CR1- or CD46-induced regulation of DC and macrophage activity on T cell responses.

C1q (in a form not complexed with C1) is now emerging as an important regulator of APC function. C1q increases surface expression of CD83, CD86, HLA-DR, and CCR7 on DCs, and C1q-experienced DCs produce more IL-12p70 than do immature DCs, with C1q-primed mature DCs inducing Th1 bias in cocultured $CD4^+$ T cells (105). In contrast, in humans, C1q bound to apoptotic cells suppresses macrophage- and DC-mediated Th17 and Th1 T cell subset proliferation (106, 107), demonstrating that the functional outcome of C1q-driven signals on APCs regarding subsequent T cell instruction is, similar to the observations pertaining to anaphylatoxin receptors, strongly context dependent. This finding aligns well with the increased understanding that complement also controls the resolution phase of immune responses. For example, blockage of C3aR and C5aR1 signals in mouse and human DCs transitions these cells into a default TGF-β-producing state upon activation, which leads to the generation of inducible Foxp3-positive regulatory $CD4^+$ T cells (108–110). Moreover, several complement receptors and regulators actively contribute to the generation of APCs with an anti-inflammatory phenotype: The ligation of CR3 by its ligand, iC3b, on APCs results in the sequential production of TGF-β and IL-10; such production is essential for the induction of T cell contraction and for the maintenance of tolerance (111). Also, the fluid-phase complement regulator Factor H (FH) can induce a tolerogenic state in human monocyte-derived DCs (112), is actively internalized by human apoptotic

cells, and enhances processing and cell surface shuttling of endogenously expressed C3 into iC3b via this suppressive CR3 engagement in DCs (113). In addition, internalized FH forms complexes with nucleosomes, facilitates their phagocytosis by monocytes, and induces an anti-inflammatory-biased cytokine profile (via a currently undefined mechanism), suggesting that FH diminishes the immunogenic and inflammatory potential of autoantigens via APC modulation (113).

Various comprehensive, expert reviews provide further in-depth information on the roles of complement in APC biology (3, 9, 53, 114).

Recent thymic emigrants: the youngest T cells in the periphery; have not diluted their T cell–receptor–excision–circle (TREC) copies by division

Direct Effects

For many years, it was thought that T cells express a limited repertoire of complement receptors and regulators. Recent work by several groups, however, indicates that T cells express almost all complement proteins, albeit in much lower amounts compared to APCs, and—at least in the resting state—often chiefly intracellularly (14) (**Figure 5**). Although CR1 and CR2 have a central role in the induction and regulation of B cell activity, there does not seem to be a similar costimulatory role for these receptors in T cell biology. CR1 is expressed by ~12% of blood-circulating human $CD4^+$ and $CD8^+$ T cells and is strongly upregulated upon TCR engagement (115, 116). As CR1 stimulation during $CD4^+$ T cell in vitro activation inhibits proliferation and IL-2 production and induces IL-10 secretion (117), CR1 is considered to be a negative controller of T cell activity. However, ligation of CR1 on HIV-infected T cells enhances viral replication, suggesting that CR1 may have an additional, not-yet-defined signaling capacity in T cells (118). This understanding aligns well with a current study demonstrating that human recent thymic emigrants express CR2 and CR1, produce predominantly IL-8 upon activation, and are precursors of a long-lived tissue-homing lineage of memory cells (119), indicating a potential role for these receptors in T cell lineage development. Although murine T cells also express CR1/2 (120), no studies have addressed the in vivo functional role of CR1/2 on these cells. CR3 and CR4 are detected on ~5% of circulating $CD4^+$ and $CD8^+$ T cells and can be upregulated upon T cell stimulation, but no direct T cell function has yet been attributed to these receptors.

C1q also directly impacts T cell function. C1q-opsonized ICs bind to T cells through a C1qR and induce cell activation, with concurrent IFN-γ and TNF secretion but with or without concurrent TCR stimulation (121). However, the responsiveness of T cells toward C1q depends on the timing of C1qR activation, as preincubation of T cells with C1q-opsonized ICs prior to TCR stimulation reduces production of IFN-γ and TNF (122). Because Jiang and colleagues (122) have also shown that C1q can induce an antiproliferative signal in T cells, the direct impact of C1q during T cell responses is not well understood and requires further investigation (123).

Similar to their vital role in normal APC activity, the anaphylatoxin receptors have surfaced as central complement components in the direct regulation of T cell responses (**Figure 5**). Engagement of C3aR and C5aR on mouse $CD4^+$ T cells induces IL-12 receptor expression, activates phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and inhibits protein kinase A activation by decreasing cAMP generation; these events allow for protein kinase B (PKB) phosphorylation and the subsequent mTOR complex 1 (mTORC1) and rbS6 activation required for IFN-γ and IL-2 production (55, 56). Thus, $CD4^+$ T cells from *C3ar* and *C5ar1* double-knockout animals have a reduced capacity to generate Th1 responses and thus induce less pathology in mouse models of experimental autoimmune encephalomyelitis (56). $CD8^+$ T cells from these mice have diminished cytotoxic activity and IFN-γ secretion during antigraft responses in heart transplant models (124). Furthermore, C3aR and C5aR1 double-knockout T cells secrete enhanced amounts of the anti-inflammatory cytokines IL-10 and TGF-β1 (108). In addition, the frequency of suppressive $Foxp3^+$ regulatory T cells was significantly increased in cultures of $C3ar^{-/-}C5ar^{-/-}$

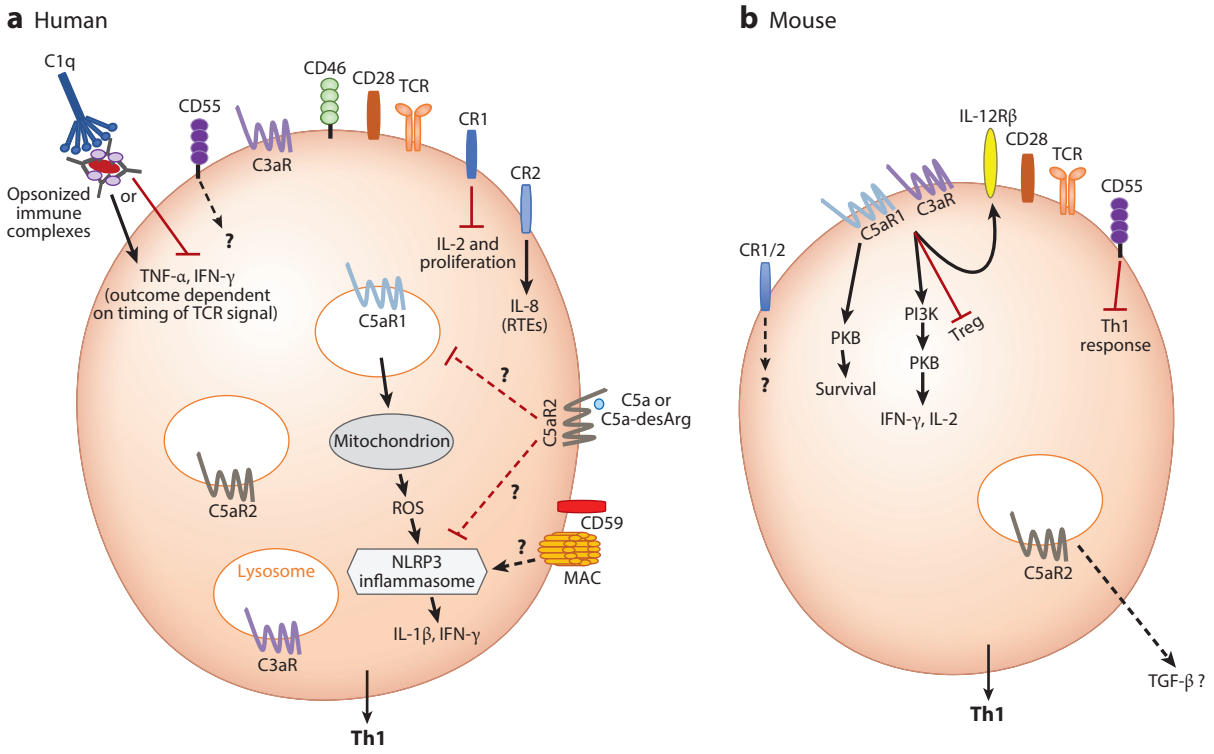

Figure 5

Direct effects of complement receptor signaling on human and mouse T cells. (*a*) In humans, activated T cells express C3aR and C5aR2 both intracellularly and extracellularly, whereas C5aR1 is observed only intracellularly. Intracellular C5aR1 signaling results in mitochondrial ROS production and activation of the NLRP3 inflammasome, culminating in autocrine IL-1β signaling and enhanced Th1 function, which is inhibited by extracellular C5aR2 activation (through a yet-undefined mechanism). NLRP3 inflammasome activity and Th1 induction may be sustained by sublytic MAC formation on the T cell surface, with CD59 being a negative regulator of MAC formation and hence possibly Th1 induction. C1q bound to opsonized immune complexes can be both a positive and a negative regulator of Th1 responses, as it regulates TNF-α and IFN-γ production in either a positive or a negative manner, depending upon the timing of the TCR signal. CR1 ligation inhibits IL-2 production and proliferation in activated T cells, whereas CR2 induces IL-8 production in RTEs. The potential signaling role of CD55 activation in human T cells is not understood. (*b*) In mice, activated T cells express surface C5aR1 (although its expression is controversial) and C3aR, but C5aR2 is expressed only intracellularly. C5aR1 and C3aR ligation results in PI3K and PKB activation, leading to increased IFN-γ and IL-2 production, increased IL-12Rβ expression and Th1 effector responses while inhibiting FoxP3 Treg generation. Additionally, C5aR1 stimulation results in increased T cell survival through PKB activation. In contrast, C5aR2 and CD55 appear to be negative regulators of Th1 responses, where C5aR2 may induce TGF-β secretion and CD55 inhibits convertase formation. Mouse cells express a hybrid CR1/2 molecule, although its function is unknown. TCR and CD28 signals are not shown, as we focus on the signaling of complement receptors and regulators. Red lines denote inhibitory activities of receptors. Dashed lines denote observed effects with the underlying mechanisms not yet defined. Abbreviations: C5a-desArg, "desarginated" form of C5; MAC, membrane attack complex; NLRP3, NACHT-, leucine-rich repeat–, and pyrin domain–containing protein 3; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKB, protein kinase B; ROS, reactive oxygen species; RTE, recent thymic emigrant; TLR, Toll-like receptor; Treg, regulatory T cell.

double-knockout T cells compared with cultures derived from *C3ar*$^{-/-}$ or *C5ar*$^{-/-}$ single-knockout or wild-type animals, suggesting that the inhibition of anaphylatoxin receptor signaling in CD4^{+} T cells paves the way for regulatory function (108, 110). A subsequent study demonstrated that the pharmacological blockage of C3aR and C5aR1 also prevents in vitro induction of Th1 effector function and induces regulatory capacity in naive human CD4^{+} T cells (125). Of note, C5aR1 in

DIFFERENCES BETWEEN MOUSE AND HUMAN COMPLEMENT IN T CELL BIOLOGY

Although complement activity is needed for normal T cell immunity in both mice and humans, there are substantial differences in the exact complement-driven contributing signals between these species. Whereas CR1 and CR2 are two separate proteins in humans, mice express these complement receptors as one protein derived from a single gene. Moreover, the complement regulators CD55 and CD59 are present in mice as two different spliced protein forms, whereas humans express only one protein form (174). Thus, activation of these proteins on APCs and T cells will likely not follow the same modes and/or trigger the same downstream molecular pathways. Furthermore, (surface) expression of the C3aR and C5aR1 on mouse cells is still debated, with some groups observing expression on activated T cells (55, 56) and others—using C3aR and C5aR1 reporter mice—failing to confirm expression on resting or activated T cells (175–177). In addition, Th1 induction in mice currently does not integrate the C3b portion produced after C3 activation, as mice do not express CD46 and another closely related protein, complement receptor–related protein (also known as Crry or p65, which can replace the role of CD46 as a cofactor in the cleavage of C3b and C4b), does not induce Th1 induction or contraction in mouse $CD4^+$ T cells (178, 179). Finally, intracellular C3 activation, driven in humans by CTSL in T cells and monocytes, is not CTSL dependent in mouse cells (60). Thus, we need to be conscious of these differences when translating findings in mouse models to human T cell biology.

mouse T cells also regulates T cell survival by inducing PKB and thereby inhibiting programmed cell death (55, 126).

Although the importance of complement receptor and regulator signaling directly on T cells is now—at least among complementologists—commonly accepted, there is an ongoing debate in the field about the similarities and differences in complement signaling events driving T cell responses between mice and humans (see sidebar titled Differences Between Mouse and Human Complement in T Cell Biology).

For example, we found that C5aR1 expression in both human resting $CD4^+$ T cells and human activated $CD4^+$ T cells is restricted to intracellular compartments and is not present on the cell surface, unlike what is observed in mice (61). Also, the alternative C5a receptor C5aR2 (also known as C5L2 or GPR77) is expressed both on the cell surface and intracellularly in resting and stimulated human T cells (61), whereas it has been detected only intracellularly in mouse T cells (108) (**Figure 5**). C5aR2 is often considered the alternative C5a receptor and can bind C5a, but it has stronger binding affinity for the "desarginated" form of C5a (C5a-desArg) generated by carboxypeptidase processing. The function of C5aR2 varies with cell type, and C5aR2 can act either as a nonsignaling decoy receptor antagonizing C5aR1 or as an active transducer of pro- or anti-inflammatory signals (31, 32, 127).

In human T cells, intracellular C5aR1 signaling induces ROS production by mitochondria. Such production triggers the assembly of the canonical NLRP3 (NACHT-, leucine-rich repeat–, and pyrin domain–containing protein 3) inflammasome. This event initiates caspase-1-dependent IL-1β secretion, thereby promoting IFN-γ production and Th1 differentiation in an autocrine fashion. Secretion of intracellularly generated C5a/C5a-desArg engages the surface-expressed C5aR2, which negatively controls NLRP3 activation (through a currently undefined mechanism) (17, 61). The importance of this new intracellular cross talk between these ancient danger sensor systems—complement/C5 and the inflammasomes—for normal Th1 regulation is demonstrated by the fact that its dysregulation affects inflammatory responses in autoimmune disease and infection. $CD4^+$ T cells from patients with cryopyrin-associated periodic syndromes (CAPS),

who have constitutively active NLRP3, exhibit overactive Th1 responses that can be normalized by NLRP3 inhibition. Furthermore, IFN-γ production is impaired in T cells from *Nlpr3*$^{-/-}$ mice (but is increased in T cells from *C5ar2*$^{-/-}$ animals) upon viral infection, and the extent of IFN-γ production alters disease outcome in a colitis model (61).

This finding that the T cell–intrinsic NLRP3 inflammasome contributes to normal Th1 induction could also explain why cross-linking the TCC/MAC regulator CD59 on human T cells augments cell proliferation and IL-2 secretion (128). Specifically, because the sublytic MAC induces NLRP3 inflammasome assembly in monocytes via mediating K^+ and Ca^+ influx (129), increased MAC formation on the T cell surface (via CD59 blockage) may sustain NLRP3 inflammasome activity also in these cells and hence amplify Th1 induction.

Interestingly, we owe a large part of our current knowledge about the vital roles of complement in T cell immunity to studies on the complement regulator CD46, which is present in humans and primates but is not found in rodents. CD46 not only is a critical driver of human Th1 induction (see below) but also is required for the successful contraction of Th1 responses and the prevention of autoimmune disease. Furthermore, work on defining the signaling pathways of CD46 in T cells established an unexpected novel and critical link between the complement system and immunometabolic adaptations driving human $CD4^+$ T cell effector function.

THE KEY ROLE OF CD46 IN HUMAN TH1 RESPONSES

Th1 Induction

CD46 is a transmembrane protein and was initially discovered as a complement regulator that functions as a cofactor in the proteolytic inactivation of C3b and C4b deposited on self-tissue (130). Shortly after the discovery of CD46 as a complement regulator, it became clear that this molecule may also act as a functional hub, involved in a rather broad range of distinct activities. For example, CD46 is required for normal sperm-egg interaction (131, 132) and serves as a cell entry receptor for a range of important human pathogens, including viruses and bacteria (133). Important for this review, CD46 is a key costimulatory molecule on human $CD4^+$ T cells, where it specifically regulates Th1 responses (58, 134–136). CD46 is absent on hematopoietic cells in rodents, and an exact functional homolog has not yet been identified (131, 137, 138). In humans, CD46 is ubiquitously expressed on all nucleated cells in four distinct isoforms that arise through alternative splicing of a single gene. The four isoforms differ in the extent of *O*-glycosylation of the extracellular region of the protein and in the expression of either one of two distinct cytoplasmic tails, termed CYT-1 and CYT-2 (139), with each isoform mediating distinct signaling events in a broad range of cells (138). CD46-transduced signals are required for the induction of IFN-γ in human $CD4^+$ T cells, with CYT-1 principally driving Th1 polarization (58, 140). Simultaneous engagement of CD3 and CD46 results in increased levels of adaptor proteins involved in TCR signaling, such as $p120^{CBL}$ and linker of activation of T cells (LAT) (134), as well as phosphorylation activation of the mitogen-activated protein kinase (MAPK) family members ERK1 and ERK2 and of Rac; ERK1, ERK2, and Rac are key regulators of cell cycle progression (141).

Importantly, coengagement of CD46 during TCR activation is largely independent of serum-derived C3b but relies on C3b generated by the T cell, both intra- and extracellularly via CTSL-mediated cleavage of C3 (**Figure 6*a***). TCR activation induces the shuttling of the intracellularly generated C3 activation fragments C3b and C3a to the cell surface [and CD28-mediated signals further potentiate this process (60)], and C3b then engages CD46 while C3a binds to cell surface–expressed C3aR. Hence, patients deficient in either CD46 or C3 are unable to mount productive Th1 responses and suffer from recurrent infections (58, 59). Of note, $CD4^+$ T cells from these

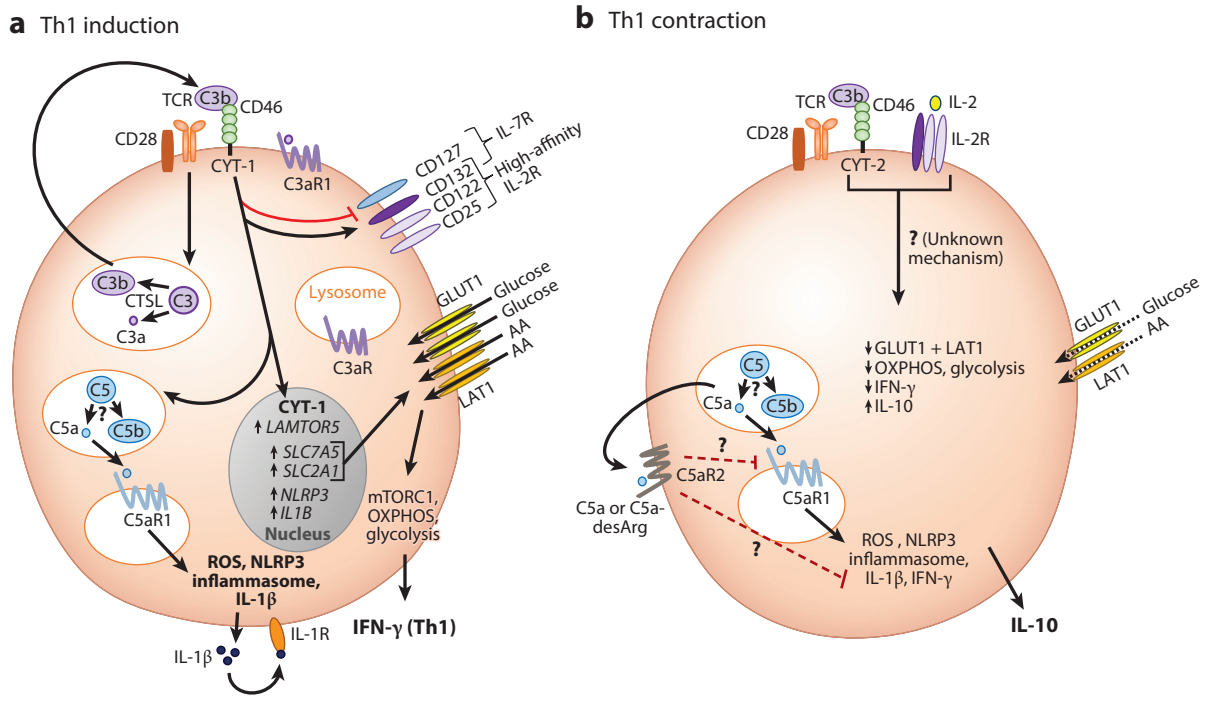

Figure 6

The role of the complosome in Th1 cell induction and contraction. (*a*) TCR activation and CD28 costimulation of resting T cells induce the intracellular generation of the CD46 ligand C3b by CTSL cleavage and the increased expression of CD46 isoforms bearing CYT-1. Nuclear translocation of CYT-1 upon autocrine CD46 activation upregulates *CD25* and *CD132* gene expression, allowing for the enhanced IL-2 receptor signaling important for Th1 induction while decreasing *CD127* gene expression. Autocrine CD46 CYT-1-driven signals also induce expression of the glucose transporter GLUT1 and the AA channel LAT1, allowing for increased glucose and AA influx. In parallel, CD46 CYT-1-mediated signals induce increased expression of LAMTOR5 and, via this, the assembly of the lysosome-based mTORC1 machinery, which senses AA influx and drives the high levels of glycolysis and OXPHOS required for IFN-γ secretion. CD46-mediated signals also trigger increased intracellular C5a generation, which supports the mitochondrial metabolic activity and ROS production critical to normal Th1 induction. C5aR1-driven ROS production and mTORC1 activity also activate the NLRP3 inflammasome in TCR-stimulated T cells, a process that supports Th1 expansion via IL-1β functioning in an autocrine fashion. (*b*) During Th1 contraction and induction of IL-10 coexpression, CD46 isoform expression reverts to a CYT-2-predominant pattern (through an unknown mechanism), and this development, in conjunction with IL-2 receptor signaling (also through an unknown mechanism), results in reduced expression of GLUT1 and LAT1, downregulation of glycolysis and OXPHOS, and reduced IFN-γ production. Moreover, autocrine engagement of the surface-expressed C5aR2 via C5a or C5a-desArg secreted upon T cell activation contributes to negative regulation of mitochondrial activity and reduction of ROS (through inhibition of intracellular C5aR1 activity and/or a yet-undefined mechanism). Red lines denote inhibitory activities of receptors. Dashed lines denote observed effects with the underlying mechanisms not yet defined. Abbreviations: AA, amino acid; C5a-desArg, "desarginated" form of C5a; CTSL, cathepsin L; GLUT1, glucose transporter 1; LAMTOR5, late endosomal-lysosomal adaptor, MAPK, and mTOR activator 5; LAT1, neutral amino acid transporter 1; mTORC1, mechanistic target of rapamycin complex 1; NLRP3, NACHT-, leucine-rich repeat–, and pyrin domain–containing protein 3; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCR, T cell receptor.

patients proliferate normally, despite the fact that CD46 regulates proteins involved in cell cycle progression, and have no defect in Th2 effector cell induction (58, 59).

The autocrine engagement of CD46 during T cell stimulation leads to the cleavage of the intracellular domains CYT-1 and CYT-2 of CD46 via γ-secretase and to their translocation into the nucleus, where they contribute to CD46-driven specific gene expression. For example, CD46

stimulation regulates the expression of *CD25*, *CD127*, and *CD132*, which are genes coding for key components of the IL-2 receptor (IL-2R) family of cytokine receptors (142). Thus, CD46 allows for productive signaling through the high-affinity IL-2R that is required for Th1 cell induction (142, 143). Importantly, in addition to enabling cells to respond to environmental cues such as growth factors, CD46 is required for the metabolic remodeling that underlies successful Th1 induction and contraction (**Figure 6**). The metabolic inventory of immune cells is composed of metabolic enzymes (the steady-state signature), nutrient sensors and metabolic checkpoint kinases (the adaptation signature), and the epigenetic landscape of metabolic genes (the memory signature). The activation of T cells drives specific remodeling of key metabolic pathways, and each T cell subset (helper, cytotoxic, regulatory, memory, etc.) is characterized by a distinct metabolic profile (144, 145). Whereas naive T cells are metabolically quiescent and depend primarily on oxidative phosphorylation (OXPHOS) for homeostatic ATP generation (146–149), activated T cells strongly upregulate aerobic glycolysis and glucose influx and enhance mitochondrial biogenesis, OXPHOS, and uptake of amino acids to accommodate the biomolecular synthesis needed for cell proliferation and effector function (148, 150). mTOR senses and integrates nutrient influx to then regulate metabolic adaption in cells by driving glycolysis, OXPHOS, and lipid synthesis (151–153).

Metabolic remodeling: the process of making metabolic adjustments in cellular bioenergetics to accommodate the need for increased or decreased energy demand

Oxidative phosphorylation (OXPHOS): the mitochondrial enzymatic oxidization of nutrients; releases energy that is used to replenish ATP pools

Glycolysis: a metabolic process in which glucose is converted stepwise to pyruvic acid for energy generation in the form of ATP

Interestingly, the production of IFN-γ by $CD4^+$ T cells requires particularly high levels of glycolysis (154). CD46 stimulation and the subsequent nuclear translocation of CYT-1 are required to drive the expression of the glucose transporter GLUT1 (encoded by *SLC2A1*) and the L-type amino acid transporter LAT1 (encoded by *SLC7A5*), and blockade of both glycolysis and amino acid uptake results in decreased IFN-γ production (19). Furthermore, CD46 also induces increased expression of LAMTOR5 (late endosomal-lysosomal adaptor, MAPK, and mTOR activator 5), a component of the Ragulator complex. LAMTOR5 is essential for amino acid sensing by mTORC1, which in turn is needed for LAT1 expression.

Thus, upon activation, $CD4^+$ T cells from CD46-deficient patients (which have normal TCR and CD28 signaling pathways) display severely decreased LAMTOR5, LAT1, and GLUT1 expression, and this decreased expression is critically linked to these cells' inability to produce IFN-γ (19). Therefore, in humans, CD46 delivers the signals driving the very high levels of glycolysis and OXPHOS specifically needed for Th1 induction, whereas in mouse T cells, these pathways are driven mostly by CD28 (15, 16, 155, 156). Importantly, we observed pathologically increased CD46 stimulation via unregulated intracellular CTSL-mediated C3 activation in $CD4^+$ T cells in the inflamed joints of patients with juvenile idiopathic arthritis (JIA). This uncontrolled generation of intracellular C3 contributes to exaggerated mTOR activity and IFN-γ secretion in these patients' T cells. Of note, augmented intracellular C3 activation in T cells from patients with JIA can be normalized with a cell-permeable CTSL inhibitor, demonstrating that this pathway is amenable to therapeutic intervention (60).

The nature of incoming environmental signals and threshold levels and differences in the exact metabolic programs triggered during T cell activation heavily impact the differentiation of effector T cell subpopulations (145). In line with this concept, decreased CD46 expression on $CD4^+$ T cells specifically impacts mTORC1 activity and Th1 cell induction, whereas Th2 cell and $Foxp3^+$ regulatory T (Treg) cell responses remain unaffected. Furthermore, only the complete absence of CD46 leads to a reduction in Th17 induction, suggesting that the complosome indeed interlinks with metabolic threshold differences underlying T cell polarization (19).

Autocrine CD46 activation during T cell activation also controls oxygen metabolism and the maintenance of high levels of IFN-γ secretion by Th1 cells via regulation of the intracellular C5 system. CD46 signals amplify low-level steady-state intracellular C5a generation during T cell

stimulation, with C5a increasing the production of mitochondrial ROS needed for the generation of Th1 responses (157) in an intracellular C5aR1–dependent fashion (61). This C5aR1 stimulation also induces the expression of genes coding for *NLRP3* and *IL1B* and the subsequent assembly of an NLRP3 inflammasome in T cells. Activation of the NLRP3 inflammasome prompts caspase-1-mediated activation and secretion of IL-1β by T cells, which further supports Th1 induction in an autocrine fashion (61) (**Figure 5**). Because APCs usually provide larger quantities of IL-1β during the cognate APC–T cell interaction than T cells make themselves, we were initially surprised that T cell–derived IL-1β is needed for normal IFN-γ production. We suggest, however, that APC-derived IL-1β supports Th1 priming but that successful imprinting and maintenance of the Th1 phenotype during differentiation and migration into tissues require complement-driven autocrine NLRP3 activity. Because T cells can live as long as 15 years, it is logical that they would have to develop specific machinery that enables self-sufficiency over this extended life span. It is now important to assess whether CD46 also contributes to the epigenetic changes and DNA landscape that define Th1 cells.

Th1 Contraction

Successful pathogen clearance has to be accompanied by the concurrent contraction of Th1 responses, as uncontrolled or ongoing Th1 activity causes a range of autoinflammatory diseases (158). In line with our increasing understanding that complement actively partakes in the resolution phase of immune responses, CD46, together with IL-2, also coordinates IL-10 coexpression in expanded Th1 cells and thus the transition toward a (self-)regulatory contraction phase (60, 136) (**Figure 6*b***). Indeed, perturbations in CD46 signaling contribute to the hyperactive Th1 responses and the reduced IL-10 switching observed in T cells from patients with rheumatoid arthritis, JIA, or multiple sclerosis (60, 159). The CD46-mediated signals that induce this switch in cross talk with IL-2R are not well understood but seem to be driven mostly by the CYT-2 domain of CD46 and again involve modulation of the metabolic profile in these cells. Resting T cells predominantly express CD46–CYT-2. Upon TCR activation, CYT-1-bearing CD46 isoforms are upregulated and engaged via autocrine C3b production and specifically induce the metabolic changes required for IFN-γ production described above (19). During Th1 contraction and induction of IL-10 coexpression, the CD46 isoform expression in $CD4^+$ T cells reverts back to a CYT-2-predominant pattern, accompanied by reduced expression of GLUT1 and LAT1 and downregulation of OXPHOS and glycolysis. Interestingly, natural Treg cells do not upregulate CD46–CYT-1 isoforms upon activation. Furthermore, CD46 does not induce, or abrogate the suppressive capacity of, IFN-γ or IL-10 in these cells, and CD46-deficient patients have normal numbers of fully functional Treg cells (60). These data suggest that although Treg cells express all complement components required for proinflammatory cytokine production and generate intracellular C3a (60), CD46–CYT-1 signaling is particularly disengaged in Treg cells, enabling this T cell population to remain in an anti-inflammatory state. Cellular phenotype switching by CD46 could hence be critically dependent on alternative splicing, and it may be therapeutically valuable to define the molecular pathways regulating such *CD46* mRNA splicing events in T cells (160), particularly because novel CD46 splice variants have previously been associated with pathological bone remodeling in osteosclerosis (161).

Not only does CD46-driven modulation of intracellular C5 activation support Th1 maintenance, but C5a also contributes to the negative control of human Th1 responses. As mentioned above, CD46-activated T cells use intracellularly generated C5a to engage the exclusively intracellularly expressed C5aR1, but they also simultaneously secrete a fraction of C5a to the cell

surface (**Figure 6*b***). The surface-shunted C5a, or C5a-desArg, engages cell surface–expressed C5aR2; this interaction exerts negative control over C5-driven NLRP3 inflammasome activation and autocrine IL-1β secretion and, hence, the levels of IFN-γ produced by human $CD4^+$ T cells (61). The C5aR2-triggered signaling pathway or pathways leading to its suppressive effects are not yet defined but could include inhibition of intracellular C5aR1 signaling or direct effects on inflammasome assembly. Because IL-1β is a strong suppressor of IL-10 production (162), it is important that local IL-1β levels be tightly regulated, as too much of this cytokine could block CD46-induced IL-10 coexpression. Indeed, T cells from CAPS patients (which produce increased IL-1β) have significantly reduced switching from IFN-γ to IL-10 (61); this reduction can be remedied by activating C5aR2 on the cell surface. The concept that proinflammatory effector T cells integrate environmental cues, and particularly growth factor–mediated signals, to actively induce a self-regulatory switch and thereby prevent exuberant tissue injury during infection clearance has also been demonstrated in Th9 and Th17 effector T cells (163). What remains to be investigated is whether CD46 and the complosome are also involved in fatty acid metabolism, as changes in fatty acid metabolism are considered a key driver in the contraction of T cell responses.

Jagged-1: ligand for Notch-1 receptor which induces the nuclear translocation of the Notch-1 intracellular domain and activation of target genes

Notch-1: a member of the conserved Notch receptor family that controls cell-cell communication, cell fate decisions, and hence development

T Cell Homeostasis

Autocrine complement activity also directly sustains T cell homeostasis. For example, CD46 on the surfaces of resting human T cells functions as a homeostatic brake (58) via its interaction with the Notch protein family member Jagged-1. Because the binding affinity of CD46 for Jagged-1 is stronger than that of the Jagged-1 receptor Notch-1, CD46 sequesters Jagged-1 on resting T cells and prevents a Jagged-1–Notch-1 interaction that would normally lead to $CD4^+$ T cell activation (**Figure 7**). Upon TCR engagement, however, T cell–derived C3b engages CD46 (the C3b and Jagged-1 binding sites within CD46 do not overlap); such engagement induces CD46 signaling and shedding of CD46 from the T cell membrane via metalloproteinases (164, 165). This event sets Jagged-1 free and enables the concurrent Jagged-1–Notch-1 interaction that is also required for optimal Th1 induction (58, 166). In consequence, patients with mutations in Jagged-1 [Alagille syndrome (167)] have, similar to CD46-deficient patients, defective Th1 responses and suffer from recurrent bronchopulmonary viral infections (58). Furthermore, dysregulation of matrix metallopeptidase 9–mediated shedding of CD46 on the $CD4^+$ T cells of patients with SLE contributes to defective autocrine Notch signaling and the failure of normal IL-10 coexpression in Th1 cells (168). Of note, there are many intriguing parallels between human CD46 and murine Notch-1, giving rise to our speculation that Notch may be the functional CD46 homolog in mice (see the sidebar titled Is Notch the Functional Homolog to CD46 in Mice?).

CD46-mediated regulation of the IL-7 receptor (**Figure 7**) likewise contributes to the maintenance of the peripheral T cell pool, as this receptor provides important survival signals for circulating nonactivated T cells by sustaining low-level expression of GLUT1 and the glucose-mediated activation of PKB that supports the expression of antiapoptotic B cell lymphoma 2 in circulating T cells. Furthermore, the intracellular tonic generation of C3a via CTSL cleavage is required for T cells to survive in the resting and circulating states. C3a binds to the C3aR expressed on lysosomes and sustains the low levels of mTOR required for such survival (**Figure 3**). Neither the exact intracellular C3aR signaling pathway mediating this function nor the modes of regulation of intracellular CTSL–mediated C3 activation are currently defined (14). We have noted that complete knockdown of C5aR1 in human T cells is accompanied by cell death (G. Arbore & C. Kemper, unpublished data). This finding aligns with the known survival signal delivered by C5aR1 stimulation in mouse T cells (although this involves C5aR1 surface activation) via sustenance of the PI3K-PKB-mTOR pathway, which inhibits apoptosis (55, 56, 169). Interestingly, we found

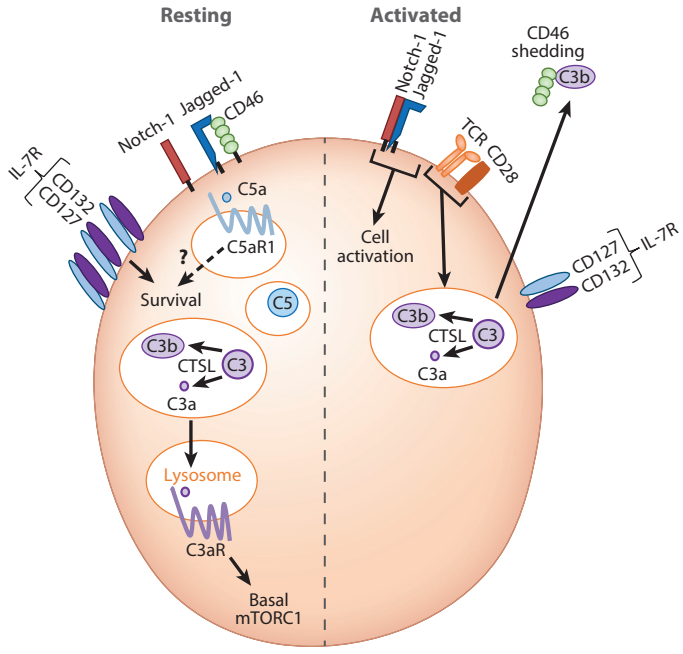

Figure 7

The role of complement in T cell homeostasis. In resting cells, intracellularly generated complement fragments sustain T cell self-regulation through the fine-tuning of basal metabolic activity via C3a generated by CTSL or the recycling pathway (shown in **Figure 3**), and cell survival by C5a binding intracellular C5aR1 (through an unknown mechanism). This quiescent state is supported by complement-driven assembly of the IL-7R and by CD46 sequestration of Jagged-1, thus restraining Notch activity (*left side* of the cell). The brake imposed by CD46 and Jagged-1 is released in activated cells, when TCR stimulation drives CD46 shedding through metalloproteases, allowing for the release of Jagged-1 and, thus, increased Notch activity. The CD46-driven decrease in CD127 expression then also reduces incoming IL-7 signals (*right*). Dashed arrow denotes observed effects with the underlying mechanisms not yet defined. Abbreviations: CTSL, cathepsin L; mTORC1, mechanistic target of rapamycin complex 1; TCR, T cell receptor.

that immune cells from patients with serum C3 deficiency generate sufficient intracellular C3a from the mutated C3 protein to survive. However, these immune cells fail to secrete C3 or activation fragments and hence cannot engage surface C3aR and CD46 for productive Th1 induction (60). We have noted a similar picture for immune cells from patients with serum C5 deficiency: Cells from these individuals generate intracellular C5a and engage intracellular C5aR1 pathways but cannot secrete C5 and its activation products (T.E. Mollnes, P. Garred, K. Lappegard, A. Fara, N. Niyonzima & C. Kemper, unpublished data). These data support the notions that serum C3 and C5 deficiencies associated with recurrent infections clearly occur (34, 170, 171) but that intracellular C3 and C5 may not be completely absent in humans.

Thus, our current knowledge about the role of complement and the complosome in T cell immunity provides a molecular framework that links this ancient system with other danger sensors (e.g., inflammasomes, TLRs) and with basic cellular processes such as survival pathways and immune-metabolic reprogramming to the direct regulation of the normal (Th1) T cell life cycle.

IS NOTCH THE FUNCTIONAL HOMOLOG TO CD46 IN MICE?

The functional mouse homolog for human CD46 has not been identified (see the sidebar titled Differences Between Mouse and Human Complement in T Cell Biology). However, on the basis of the many intriguing structural and functional parallels between CD46 and the Notch system, an attractive (but not formally proven) hypothesis is that in mice, Notch may play similar roles during T cell activation as CD46 does in humans. For example, like complement, the Notch system is evolutionarily old, is highly conserved among species, and mediates key cell-cell communication and developmental processes (180, 181). Furthermore, the normal function of CD46 and of Notch family members (Notch receptors Notch-1 through Notch-4 and ligands Jagged-1, Jagged-2, and delta-like 1, 3, and 4) requires the cleavage of their extracellular protein portions by specific proteases and the γ-secretase-mediated cleavage and nuclear translocation of their intracellular domains (60, 138, 140, 180). Likewise, Notch-1 plays a crucial role in the control of Th1 and Th2 lineage differentiation (166) and in the coexpression of IL-10 in human Th1 cells (182). Moreover, Notch is suspiciously involved in regulating the same metabolic pathways, including nutrient uptake and regulation of OXPHOS, as CD46 is in humans (183–185), and recent work identified Glut1 as a direct transcriptional target of Notch-1 in mice (186). Why rodents do not express CD46 is still debated. The fact that CD46 is a pathogen magnet (133) may have added evolutionary pressure in mice to avoid its expression and reduce risk of infection, whereas in humans, the beneficial contributions of CD46 to host homeostasis seem to (currently) outweigh the possible risks.

CONCLUDING REMARKS

PRRs were initially discovered as pathogen detection and elimination systems; however, their early evolutionary appearance and extensive functional involvement in normal cell metabolic processes argue that they may have initially evolved as sensors of metabolic changes and imbalances. Consistent with this notion, dysregulation in these systems is often connected with metabolic disease, e.g., inflammation is linked with metabolic syndrome (172, 173). Conversely, because these PRRs both identify and respond to cell metabolic changes, it makes sense that they represent important nodes that control cell-autonomous immunity, as well as other innate and adaptive immune cells. Given this background, along with the recent finding that the complement system also has an intracellular sensor arm—the complosome—it is not surprising that complement has emerged as an integral part of normal T cell biology. Although our current focus has been on the noncanonical role of complement in the induction of T cell effector responses, given the tight connection between the complosome and cell metabolism and the directive impact of cell metabolism on all stages of T cell life, it is now important to explore whether intracellular complement is required for normal T cell development itself and/or T cell memory induction (see the section titled Future Issues).

The existence of a complosome and its ability to directly regulate cell metabolism (and most likely other basic cellular processes such as DNA transcription and mRNA translation) (**Figure 8**) sparked two important new lines of thought in our laboratory. First, we suggest that complement may have originally functioned as an intracellular sensor system and may have become a secreted and systemic component only when life evolved from unicellular to multicellular and then multiorgan entities. Thus, the function of complement may have evolved from regulation of normal intracellular physiological homeostasis, via orchestration of cell-autonomous immunity to induction and contraction of effector function during cell stimulation, to its role as we know it today—prime guardian of the extracellular space. Such a revised view of complement and

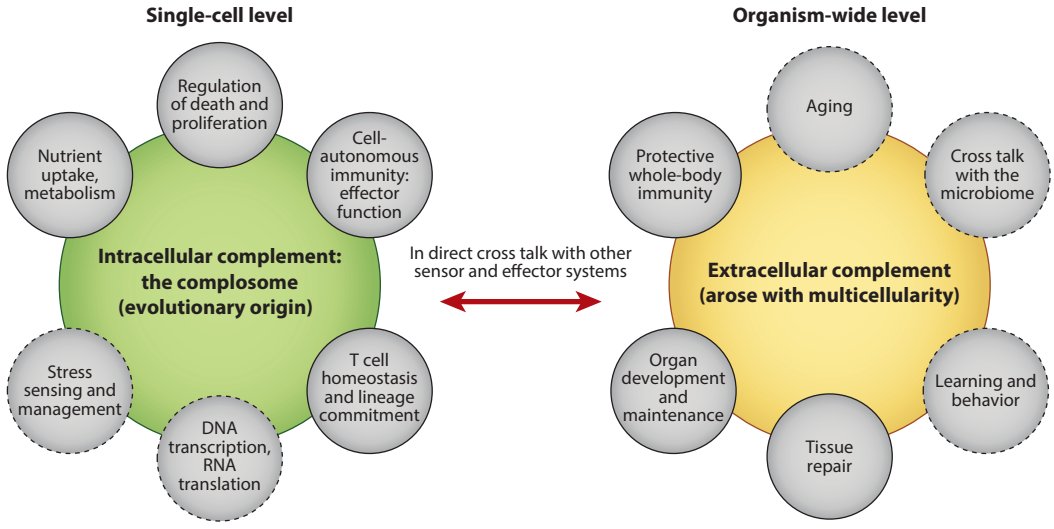

Figure 8

The evolution of complement from an intracellular driver of cell homeostasis and effector function to a serum sentinel system orchestrating host integrity. The ancient origin of complement and its coevolution and tight connection with basic cellular processes suggest that complement may have originally appeared as an intracellular system regulating single-cell homeostasis and may have functioned to mostly recognize and rectify danger derived from the self/within the cell (*left*). When life evolved into multicellular organisms, complement also became a secreted system and adopted an additional function of being a protector of the extracellular space against pathogens (*right*). Today, this dual role of complement likely explains why this ancient system in direct intra- and extracellular cross talk with other sensor and effector systems (such as TLRs, inflammasomes, and growth factors; not shown here) has such profound effects on normal cell and host function in immunity and beyond. Circles with solid outlines depict functions for complement that have been clearly demonstrated, whereas circles with dashed outlines are processes that we anticipate complement will contribute to. For many of the activities currently solely attributed to the liver-derived, extracellular complement, possible contributions from the intracellular complement system, the complosome, have not yet been assessed.

general PRR biology is supported by the recent findings that the NLRP3 protein can also act as a transcription factor and directly initiate *Gata3* gene expression in mouse T cells, leading to Th2 lineage induction, and that the intracellular domains of CD46 regulate gene activity, also likely through modulation of transcription factor complexes.

Second, given our observation that the complosome exists in other cells as well, the core role of complement in cell physiology likely has broad physiological relevance to human health. Thus, it may be worthwhile to (re)assess the role of complement in normal and aberrant cell function during both disease states such as infection and autoimmunity and diseases such as metabolic disorders, including diabetes and cancer. Efforts to better understand the role of complement in malignancies may be rewarding, as unleashing antitumor T cell responses while simultaneously suppressing cancer metabolism via modulation of complosome activity could become a powerful new therapeutic avenue.

Moreover, a central role for the complosome in the pathways and processes underlying normal learning, behavior, and aging is also probable (**Figure 8**). For example, complement is needed for normal synaptic pruning in the developing brain, and recent work has connected unwanted increased activity of the classical complement pathway in particular with inappropriate synaptic pruning and neurodevelopmental disorders such as schizophrenia and autism (187). Based on our published and ongoing work, we argue that deviations in complement-regulated metabolic

pathways in the brain will also emerge as key contributors to neurological disease. Of course, if perturbations of intracellular complement activity indeed transpire as core drivers of aberrant (immune) cell activity in a wider range of diseases, rectifying these perturbations pharmacologically in specific tissues, in specific cells, and possibly even in specific subcellular compartments will be a major challenge.

FUTURE ISSUES

1. What are the exact composition and function of the complosome in distinct (T) cell populations, and are the composition and function across populations the same or are they distinct?
2. Which particular cellular subcompartments contain complement components and/or receptors for activation fragments, and how are their controlled intracellular interactions and the cell surface shuttle (secretion) of this system orchestrated?
3. How is the complosome regulated? Are complement regulators expressed intracellularly, and what surface receptor signals regulate complosome component expression?
4. Does the complosome engage in additional cross talk with other sensor systems such as the retinoic acid–inducible gene I system and extracellular complement?
5. Does the complosome also indirectly affect T cell responses via metabolic reprogramming of APCs?
6. Are CD46 or other components of the complosome required for normal T cell lineage induction in the thymus, the generation of T cell memory, and the phenotype of tissue-resident T cells?
7. What is the role of CD46 and the complosome in human $CD8^+$ T cells and in natural killer T cells (as well as in FDCs and innate lymphoid cells)?

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