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Lymphocyte integration of complement cues

Ana V. Marin, Paula P. Cárdenas, Anaïs Jiménez-Reinoso, Miguel Muñoz-Ruiz [1,2], Jose R. Regueiro [*,2]

Department of Immunology, Ophthalmology and ENT, Complutense University School of Medicine and 12 de Octubre Health Research Institute (imas12), Madrid, Spain

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ABSTRACT

We address current data, views and puzzles on the emerging topic of regulation of lymphocytes by complement proteins or fragments. Such regulation is believed to take place through complement receptors (CR) and membrane complement regulators (CReg) involved in cell function or protection, respectively, including intracellular signalling. Original observations in B cells clearly support that complement cues through CR improve their performance. Other lymphocytes likely integrate complement-derived signals, as most lymphoid cells constitutively express or regulate CR and CReg upon activation. CR-induced signals, particularly by anaphylatoxins, clearly regulate lymphoid cell function. In contrast, data obtained by CReg crosslinking using antibodies are not always confirmed in human congenital deficiencies or knock-out mice, casting doubts on their physiological relevance. Unsurprisingly, human and mouse complement systems are not completely homologous, adding further complexity to our still fragmentary understanding of complement-lymphocyte interactions.

Contents

Abbreviations: aHUS, atypical haemolytic uremic syndrome; BCR, B-cell receptor; CTSL, cathepsin-L; CFP, complement factor P or properdin; CR, complement receptor; CReg, membrane complement regulator; GOF, gain-of-function; GPI, glycosylphosphatidylinositol; IFN, interferon; IL, interleukin; ILC, innate lymphoid cell; KO, knock-out; LOF, loss-of-function; LPS, lipopolysaccharide; MAC, membrane attack complex; NCR, natural cytotoxicity receptors; NK, natural killer; PID, primary immune deficiency; PIGA, phosphatidylinositol *N*-acetylglucosaminyltransferase subunit A; PNH, paroxysmal nocturnal hemoglobinuria; RCA, regulation of complement activation; SLE, systemic lupus erythematosus; Tc, cytolytic T cell; TCR, T-cell receptor; Th, helper T cell; TLR, toll-like receptor; TNF, tumor necrosis factor; Treg, regulatory T cell.

* Corresponding author at: Department of Immunology, Ophthalmology and ENT, Complutense University School of Medicine and 12 de Octubre Health Research Institute (imas12), 28040, Madrid, Spain.
E-mail address: regueiro@med.ucm.es (J.R. Regueiro).
[1] Current address: The Francis Crick Institute, London NW1 1AT, United Kingdom.
[2] Joint last authors.

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1. Introduction

The complement system is a complex network of glycoproteins that interact among them in a cascade fashion and with either non-self-molecules on pathogens and toxins or self-molecules on immune complexes and cells. The system is composed of more than 50 proteins, some of them soluble and produced by the liver mainly and others are membrane-bound, distributed in a wide range of cell types. Their aim is to identify and label for elimination foreign material informing surrounding cells through complement receptors (CR), while remaining self-tolerant by means of soluble and membrane (CReg) complement regulators. To that end, complement activation can take place by three different routes: the classical, the lectin or the alternative pathway [1].

Certain cells receiving complement signals through CR can profoundly change their behaviour, as granulocytes do by triggering chemotaxis or phagocytosis in response to different complement fragments. Similarly, lymphoid cells such as B lymphocytes lower their B-cell receptor (BCR) activation threshold when their cognate antigen is opsonized by C3-derived fragments and detected by CR2. CReg involved in self-tolerance such as CD46 also show intriguing T lymphocyte regulation activities when engaged, although most of these activities have been revealed by antibody crosslinking rather than by complement engagement.

Complement regulation of lymphoid cell function has evolved humongously in the last decade, as information accumulates on the nature, signals and subset distribution of classic and new CR and CReg that perceive a growing range of complement proteins or fragments both extracellularly and intracellularly, since lymphocytes synthesize most soluble complement components [2]. Intracellular complement interactions, including the inflammosome, have led to the term 'complosome' [3]. Thus, it will be of substantial interest to investigate the complex interactions between the complosome and intracellular pathogens or inflammatory signals in a broad range of cells, and their impact on cell physiopathology.

Here we will review the range of CR and CReg used by lymphoid cells for the interpretation of direct complement cues, the human or animal models of complement deficiencies and their main consequences in lymphoid cell development or function. We have excluded indirect effects of complement in lymphoid cells through antigen presenting cells.

1.1. Lymphoid cell types

Lymphoid cells are normally classified as innate or adaptive depending on whether they rearrange antigen receptor (i.e. TCR or BCR) genes (Table 1, left). Under this classification, innate lymphoid cells (ILC) are clearly distinct from adaptive lymphoid cells (T and B lymphocytes). ILC comprise various types of bone-marrow-derived tissue lymphocytes that contribute to immune responses to microbes and stressed cells, including tumour cells, and promote tissue repair. They are classified as group 1 (natural killer or NK cells and ILC1), group 2 (ILC2), and group 3 (ILC3 and lymphoid tissue-inducer cells) depending on their cytokine and microbe recognition profile (Th1-like, Th2-like and Th17-like, respectively). Only NK cells are cytolytic. Besides their capacity to respond to and secrete cytokines, ILC express several cell surface receptors to recognize two types of relevant ligands: non-self-molecules from microbes and stress self-molecules on other cells. The biological significance of both receptors and ligands remains unclear, limiting our understanding of ILC biology.

Among T lymphocytes, γδ T cells may be considered adaptive as they rearrange TCR genes. However, they may also be considered innate as they use their restricted TCR repertoire as pattern recognition receptors, rapidly secrete cytokines in response to infectious agents with rapid, innate-like responses that place them in the initiation phase of immune reactions. For the purpose of this review, we have thus considered them closer to innate lymphoid cells.

αβ T lymphocytes derive from haematopoietic stem cells that colonize the thymus. Developing thymocytes undergo a series of maturation steps by interaction with thymic stromal cells, characterized by the expression of different cell surface markers such as CD4 and CD8. The former become Th lymphocytes, which are classified as effector (Th1, Th2 and Th17) or regulatory (Treg) depending on their functional profile, while the latter become cytolytic T lymphocytes (Tc), capable of specific cytolysis.

The generation and differentiation of B lymphocytes occurs in two steps that take place in different tissues. Firstly, B cell precursors differentiate into naïve B cells in the bone marrow, and, secondly, the immature B cells reach secondary lymphoid organs, where they mature into memory or effector cells [4].

1.2. Lymphoid complement receptors (CR) and membrane complement regulators (CReg)

CR and CReg expression levels are quite heterogeneous (– or + in Table 1) in different lymphoid cell types or subsets, and can be induced, increased or reduced after activation. Recently, other unexpected receptors have been reported (NKp46) [5]. Experiments designed to evaluate CR/CReg roles include knock-out (KO) mice, human congenital deficiencies (due to loss-of-function or LOF mutations) or dysregulations (due to gain-of-function or GOF mutations) and triggering using either natural ligands (i.e. complement fragments) or antibodies. Therefore, the conclusions vary widely. In this review, we have considered genetic experiments and natural ligands as more reliable than antibody crosslinking.

Despite many unknowns (ND in Table 1), lymphocytes are well prepared to detect complement cues, because they express several CR or CReg on their surface, which are frequently up- or down-regulated by activation.

1.2.1. Human vs mouse CReg discrepancies (Table 2)

The complement system is quite similar in humans and mice, but evolutionary gene rearrangements in their regulators of complement activation gene cluster has caused some notable differences affecting CReg, thus making comparisons difficult [46]. First, humans have single CD55 and CD59 genes whilst mice have two functional copies of *Cd55* and *Cd59*, respectively, albeit with dif-

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Table 1
CR and CReg expressed by lymphoid cells. Most data are from human. [1]Other ligands are HMGB-1 (high-mobility group box 1) and LPS (lipopolysaccharide). [2]+/r=constitutive but reduced after activation. [3]+/i = constitutive but increased after activation (in $CD56^{dim}$ cells). [4]ND=not determined. [5]Only expressed by a small population of cells. [6]Data from mice. [7]–/i = negative but induced after activation. [8]Imm.: immature. [9]PIGA deficiency reported (GPI link-deficiency). [10]The Cr2 gene encodes both CR2 and CR1 by alternative splicing; thus $Cr2^{-/-}$ mice lack CR1 and CR2. Intracellular signalling data from [6,7]; NK cell data from [8,9]; of ILC1,2,3 from [10–12]; γδ T lymphocyte data from [13–16]; αβ T lymphocyte data from [7,8,17–24]; B lymphocyte data from [8,25,26]; human congenital deficiencies data from [27–33]; mice KO data from [34–44]. C1qR/CD93 was excluded based on recent data [45].

Lymphocytes		CReg	CReg	CReg	CReg/CR	CR	CR	CR	CR	CR	CR	CR	Other
	Names	CD46	CD55	CD59	CR1	CR2	CR3	CR4	C3aR	C5aR1	C5L2		NKp46
		MCP	DAF	–	CD35	CD21	CD11b/CD18	CD11c/CD18	–	CD88	C5aR GPR77		CD335
	Gene	*CD46*	*CD55*	*CD59*	*CR1*	*CR2*	*ITGAM/ITGB2*	*ITGAX/ITGB2*	*C3AR1*	*C5AR1*	*C5AR2*		*NCR1*
	Complement ligands	C3b, C4b	C4b2b, C3bBb	MAC	C3b, C4b	iC3b, C3dg, C3d	iC3b	iC3b	C3a, $C5a^{desArg}$	C5a, $C5a^{desArg}$	C5a		CFP
	Other ligands	Jagged1	CD97	CD2	–	CD23, EBV	ICAM-1, fibrinogen[1]	–	–	–	–		*M. Tuberculosis*, vimentin
	GPI link	No	Yes	Yes	No	No	No	No	No	No	No		No
	Intracellular signaling	ND	ND	ND	ND	ND	ND	ND	Yes	ND	Yes		ND
Innate	NK	+/r[2]	+/r[2]	+/r[2]	+	–	+/i[3]	+	+	+	+		+
Innate lymphoid cells	ILC1,2,3	ND[4]	ND	ND	ND	ND	ND	ND	–[5]	–[6]	ND		+[6]
Innate / adaptive	γδ T lymphocytes	+	ND	ND	ND	ND	+	ND	ND	+	ND		+
Adaptive	αβ T lymphocytes	+	+	+	+	+	–	–	+	+/i	ND		ND
	Thymocytes	+/i	+	+	+/i	+	–/i[7]	–/i[7]	+	+/i	–/i		–/i
	$CD4^+$	+/i	+	+	+/i	+	+/i	+[6]	–/i	+/i	+		–/i
	$CD8^+$	+/i	+/i	+	+/i	+	+/i	–	ND	ND	ND		–
	Pro-/Pre-B/Imm.[8]	+	ND	ND	–	–	–	–	ND	ND	ND		–
	B lymphocytes												
	Transitional	+	+	+	+	+	–	–	ND	ND	ND		–
	Mature	+	+	+	+	+	+	+	+	+	ND		–
	Plasma cells	+	+	+	+	+	–	–	+	ND	ND		–
	Human	Yes	Yes[9]	Yes[9]	No	Yes	Yes (CD18)	Yes (CD18)	No	No	No		No
	Congenital deficiencies												
	Mouse	Yes	Yes	Yes	Yes[10]	Yes[10]	Yes	Yes	Yes	Yes	Yes		Yes

ferential tissue expression and/or structure [47,48]. Second, the functional murine homologue of *CD46* is *Crry*, as rodent *Cd46* is poorly expressed in leukocytes. Third, human CR1 and CR2 are encoded as splicing transcripts from a single *Cr2* gene in mice [49].

1.3. Primary immunodeficiencies of CR, CReg or their ligands

Human primary immunodeficiencies (PID, [53]) have been reported for several CR, CReg or their ligands (see Table 1), offering the possibility to address if their lymphoid cells are affected. Patients show disparate clinical phenotypes as summarized below, essentially similar to their respective KO mouse models. Unlike CR, CReg protect cells from complement lysis, thus their deficiencies cause tissue damage.

1.3.1. CR deficiencies

CR show different functions ranging from immune complex clearance (CR1) or co-BCR activity (CR2), to phagocytosis (CR3, CR4) or inflammation (C3aR, C5aR1, C5L2). Therefore, their deficiencies are associated with disparate dysfunctions.

CR1 clears immune complexes due to its high affinity for C3b and C4b, but it is also a CReg due to its decay-accelerating and co-factor activity for C3b/C4b cleavage. Complete CR1 deficiency has not been reported, but reduced CR1 expression has been associated with autoimmune diseases such as glomerulonephritis [54] or systemic lupus erythematosus (SLE, [55]), in concordance with its immune complex clearance function.

As mentioned above, C3-opsonized antigens allow B lymphocytes to lower their BCR activation threshold for such antigens. Thus, complete CR2 deficiency is a mild PID reported in two adult patients to date [27,30] that debuts with B cell dysfunction. Both exhibited hypogammaglobulinemia and impaired naïve to memory B cell differentiation, but unexpectedly normal antibody responses to protein vaccination. Recurrent infections were only present in one of them during early adulthood, but not in childhood.

Isolated CR3 or CR4 deficiencies have not been reported. These defects occur together with leukocyte adhesion deficiency type 1, a severe PID caused by CD18 deficiency, shared by both CR and CD11a/CD18 or LFA-1. This PID is mainly characterized by recurrent bacterial infections, skin ulcers and impaired leukocyte adhesion to the vascular endothelium [56]. The role of CR3 + 4 deficiency in the clinical phenotype of CD18 deficiency is probably minor, as mouse models of LFA-1 deficiency recapitulate the human disorder.

Human C3aR, C5aR1 or C5aR2 (or C5L2) deficiencies have not been described. Only *in vitro* studies and KO mice have been reported, with a weak impact in lymphocyte biology.

Collectively, reported CR deficiencies do not show gross lymphocyte dysfunctions, except for CR2 deficiency, which is associated to impaired B lymphocyte development.

1.3.2. CReg deficiencies

CD46 deficiency is associated to atypical hemolytic uremic syndrome (aHUS). However, most severe CD46-deficient patients suffered from common variable immunodeficiency, which could be due to adaptive lymphocyte dysfunctions and recurrent chest infections [31]. In addition, CD46 mutations have been associated to other diseases such as preeclampsia or SLE [57].

Partial CD55 and/or CD59 deficiency are due to acquired somatic mutations in the phosphatidylinositol N-acetylglucosaminyltransferase subunit A gene (*PIGA*), which encodes an enzyme required to synthesize the glycosylphosphatidylinositol (GPI) subunit for membrane GPI-anchored proteins, such as CD55 and CD59, affecting mostly erythrocytes in patients with paroxysmal nocturnal hemoglobinuria (PNH) [58]. However, complete congenital CD55 deficiency has been recently described in a small patient cohort with non-PNH clinical

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Table 2
Human and mouse CReg comparison. Adapted from [49–52]. MAC, membrane attack complex; FDC, follicular dendritic cell.

Protein	Species	Gene	kDa	Function	Expression
CD46	Human	*CD46*	60	C3b/C4b inactivating cofactor	Only nucleated cells
Crry	Mouse	*Cr1l*	65	C3b/C4b inactivating cofactor and C3 convertase decay-accelerating activity	All cell types, including erythrocytes
CD46	Mouse	*Cd46*	60	Involved in sperm acrosome reaction	Testis
CD55	Human	*CD55*	70	C3/C5 convertases decay-accelerating activity	All cell types, including erythrocytes
CD55	Mouse	*Cd55a,b*	70	C3/C5 convertases decay-accelerating activity	All cell types, including erythrocytes
CD59	Human	*CD59*	20	Inhibits MAC (membrane attack complex), preventing host cell lysis	All cell types, including erythrocytes
CD59	Mouse	*Cd59a,b*	20	Inhibits MAC (membrane attack complex), preventing host cell lysis	All cell types, including erythrocytes
CR1	Human	*CR1*	180-280	Binds C3b/iC3b and C3b/C4b-opsonized particles C3b/C4b inactivating cofactor and C3/C5 convertases decay-accelerating activity	T cells, B cells, phagocytes, FDC, erythrocytes, glomerular podocytes
CR1	Mouse	*Cr2*	200	Binds C3b/iC3b and C3b/C4b-opsonized particles C3/C5 convertases decay-accelerating activity	B cells and Folicular Dendritic Cells (FDC)
CR2	Human	*CR2*	145	Binds iC3b/C3dg/C3d-opsonized particles Lowers BCR stimulation threshold	B cells and FDC
CR2	Mouse	*Cr2*	145	Binds iC3b/C3dg/C3d-opsonized particles Lowers BCR stimulation threshold	B cells and FDC

features. They showed complement hyperactivation, angiopathic thrombosis and early-onset protein-losing enteropathy, associated to recurrent infections in some of them [32]. In contrast, complete CD59 deficiency affects mostly red blood cells or neurons, causing chronic hemolysis and early-onset relapsing peripheral demyelinating disease resembling recurrent Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy [33,59].

Therefore, CReg deficiencies cause complement-dependent tissue damage, rather than lymphocyte dysfunctions.

1.3.3. CR or CReg ligand deficiencies

Congenital C3 deficiency can be classified as primary, due to LOF *C3* mutations, or secondary to C3 convertase stabilization (GOF *C3* mutations) or to LOF mutations in convertase regulators such as factor I or factor H. C3-deficient patients are characterized by selective naïve to memory B, but not T cell differentiation impairment [60] and by the development of recurrent pyogenic infections (mainly by *Streptococcus pneumoniae* and *Neisseria meningitidis*) than can be associated with immune complex diseases such as SLE or membranoproliferative glomerulonephritis [61]. Additionally, *C3* mutations or polymorphisms have been linked with higher risk development of age-related macular degeneration [62], aHUS [63], dense deposit disease [64], and poor outcome in kidney [65] or liver [66] transplantation or vaccination [67].

C4 deficiency patients show SLE-like disorders and recurrent infections by encapsulated bacteria [68].

Primary C5 deficiency (which includes MAC deficiency) is mainly associated with severe and recurrent *Neisseria* infections such as meningitis and extragenital gonorrhea [69]. Secondary C5 deficiency is now common due to Eculizumab in PNH and aHUS patients, who develop similar clinical features [70].

Properdin or complement factor P (CFP) deficiency is an X-linked disorder associated with an increased susceptibility to *Neisseria* infections and sepsis [71].

Collectively, CR and CReg deficiencies cause susceptibility to bacterial infections and in the case of C3, impaired B lymphocyte development.

2. Complement cues in innate lymphocytes

2.1. Innate lymphoid cells (ILC)

Recently, interactions between the complement system and ILC have emerged, which may help to understand and thus manipulate their responses, although their CR and CReg expression profile remains, except for NK cells, mostly undetermined (Table 1).

2.1.1. Innate lymphoid cells group 1 (ILC1 and NK cells)

It has been reported that CFP is a ligand for NKp46, a Natural Cytotoxicity Receptor (NCR), mainly expressed by NK cells and some subsets of mucosal ILC1 and ILC3. Patients lacking CFP are more susceptible to *Neisseria meningitidis* infection and CFP protection was dependent on NKp46 and ILC1 in mice (Fig. 1, left). Although CFP does not induce classical NK activation, it does promote their antibacterial activity through Chemokine (C motif) ligand (XCL1) [21]. These data suggest that a) ILC and the alternative complement pathway collaborate against bacterial infection and b) complement-binding receptors in ILC may regulate their functions. Indeed, the NCR NKp46 and NKp30 are physically associated with CD59, which could signal through them upon antibody engagement, and induce enhanced cytolysis when cross-linked (Fig. 1, right). However, human CD59 deficiency does not associate to infections by herpesvirus, the main target of NK cells.

Human NK cells express most CR (Table 1). Interestingly, the main NK cell subsets ($CD56^{dim}$ $CD16^{+}$, the most common and cytolytic, and $CD56^{bright}$ $CD16^{-}$, their likely precursors) express different CR levels, high C3aR vs high CR4, respectively [9]. Indeed, pathogens and inflammation can regulate CR expression levels: human CR3 is induced by lipopolysaccharide (LPS), interleukin (IL)-15, tumour necrosis factor (TNF)-α, Poly (I:C) or serum, whereas CR4 is induced only by LPS or IL-15. C3aR expression is induced by Poly (I:C) and reduced by serum. C5aR1 and C5aR2 levels are reduced by Poly (I:C), whereas C5aR2 only by TNF-α. C5aR1 is only expressed after inflammatory stimuli [73,74]. NK cells also express all tested CReg proteins to avoid complement-mediated membrane damage (Table 1), although significantly less than T cells [8,75], and in some cases at different levels in $CD56^{dim}$ vs $CD56^{bright}$ subsets (lower vs higher CD55, respectively). Cytokines, but not mitogens like phytohaemagglutinin, regulate NK CReg expression levels. For instance, IL-2 reduced CD46 and CD59, but not CD55, despite the fact that the last two are GPI-linked, whereas IL-15 increased all three CReg [75].

2.2. γδ T lymphocytes

Information about γδ T cells and surface CR and CReg expression is still scarce (Table 1), as the putative contribution of complement signals to their functions.

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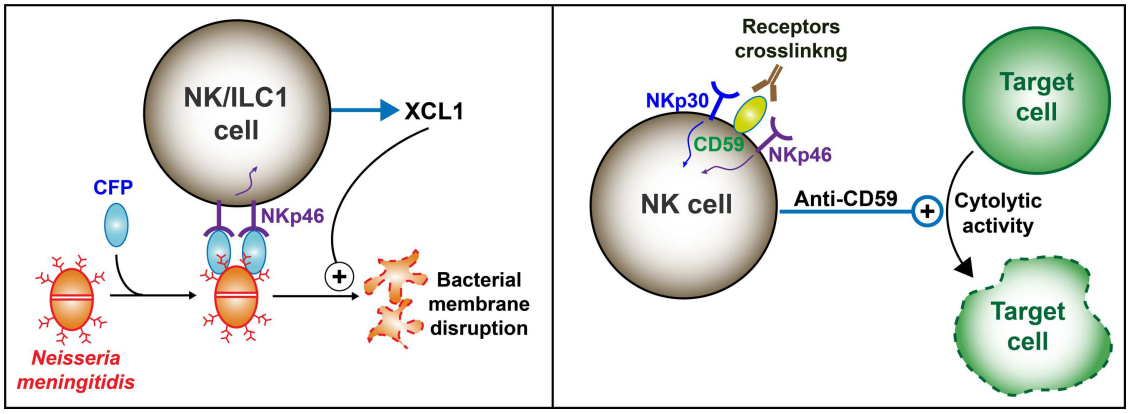

Fig. 1. Innate Lymphoid Cell group 1 regulation by complement cues. Left: CFP promotes antibacterial activity in NK and ILC1 cells. [5,21]. Right: CD59 crosslinking activates NK cell-mediated cytotoxicity [72]. Lines with a + indicate enhanced function.

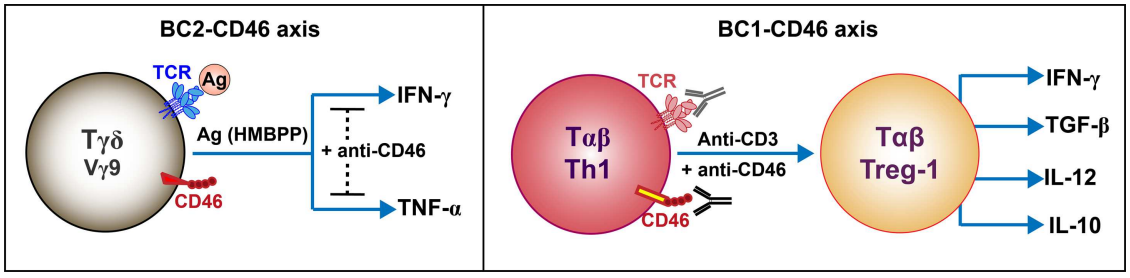

Fig. 2. γδ (left) vs αβ (right) T cell regulation by differential CD46 isoform cues. While CD46/CD3 crosslinking of Th1 cells switched them from IL-2-secreting to IL-10-secreting by signalling through the BC1 CD46 isoform, signalling through the BC2 CD46 isoform of Vγ9Vδ2 γδ T cells after TCR engagement by its antigen (HMBPP, 4-Hydroxy-3-methyl-but-2-enyl pyrophosphate) reduced Th1 cytokines such as IFN-γ and TNF-α, but could not induce IL-10 production [13,78]. Black dashed T lines indicate impaired cytokine production.

It was proposed that during age-related macular degeneration (AMD) pathogenesis, the inadequate control of complement-driven inflammation results in the generation of the anaphylatoxin C5a, which recruits IL-17-producing T cells to the eye via C5aR [76]. The IL-17 released in the eye could generate an increase in vascular endothelial growth factor production, augmenting choroidal neovascularization (CNV), which would finally lead to loss of vision. In murine CNV, γδ rather than αβ T cells secrete the IL-17 detected in damaged eyes, and antibodies or antagonists disrupting the C5/C5a-C5aR axis completely prevented the rise of eye IL-17 and γδ T cells, supporting the hypothesis that C5a contributes to the recruitment of $C5aR^+$ γδ T cells in the eye [76].

CReg proteins such as CD46 have been reported to regulate the major human peripheral blood γδ T cell subset (Vγ9Vδ2), which normally shows a Th1-like cytokine profile. αβ T cells express a variable pattern of CD46 cytoplasmic domain splicing isoforms including BC1, which is involved in their differentiation from interferon gamma (IFN)-γ-secreting Th1 cells into IL-10-secreting Treg type 1 (Treg-1) cells after TCR/CD46 co-engagement (Fig. 2, right). In contrast, Vγ9Vδ2 γδ T cells expressed only the BC2 CD46 isoform, which inhibited its Th1-like cytokine profile but was unable to induce IL-10 secretion after stimulation with their specific phosphoantigen and anti-CD46 (Fig. 2, left). Thus, CD46 seems to use two distinct mechanisms to regulate the production of proinflammatory cytokines in γδ vs αβ T cells [77].

3. Complement cues in adaptive lymphocytes

3.1. αβ T lymphocytes

3.1.1. T cell development

Patients carrying mutations in the central C3 component do not show overt thymus abnormalities, αβ T-cell dependent infections or peripheral αβ T cell subset alterations [60]. Indeed, complement levels are likely lower in the thymus than in peripheral blood [79]. However, the expression of certain CR such as CR2 is developmentally regulated in T cells, from high in early progenitors to low in mature thymocytes [80]. In neonates and children, CR2 is highly expressed in naïve $CD4^+$ T cells just emerged from the thymus, decreasing with age [81], thus it has been proposed as a marker of thymus function.

3.1.2. Th and Treg lymphocytes

The use of agonist or antagonist monoclonal antibodies against CR or CReg expressed on T cells has yielded rich insights on their role in Th or Treg regulation, although the physiological relevance of this approach has not been always validated using their natural ligands, and congenital human deficiencies seldom support the conclusions.

The anaphylatoxins C3a and C5a have been shown to be strong αβ T cell modulators. Indeed, αβ T cells from C3aR1 and C5aR1 double KO mice showed strong iTreg cytokine responses [82] (Fig. 3 top). Indeed, in allogeneic responses, genetic deficiency or pharmacological blockade of C3aR/C5aR signalling augments murine and human induced Treg generation, limiting the clinical expression of graft-versus-host disease [83]. However, many of the reported results may be indirect, due to other cell types responding to complement cues, e.g. signalling through C5aR and several toll-like receptors (TLR) to drive Th17 differentiation [84]. Later it was confirmed in a mouse model that macrophages are central for such C5a-dependent Th17 differentiation of self-reactive T cells that mediate autoimmune arthritis [85].

CD55, like CD46, protects T cells from complement lysis, but upon crosslinking it induced intracellular phosphorylation activation events and thus may act as a TCR co-receptor [87]. This was explored in mouse [86] and human [32] T cells lacking CD55 (Fig. 3, bottom). TCR engagement by antigen or antibodies increased Th1

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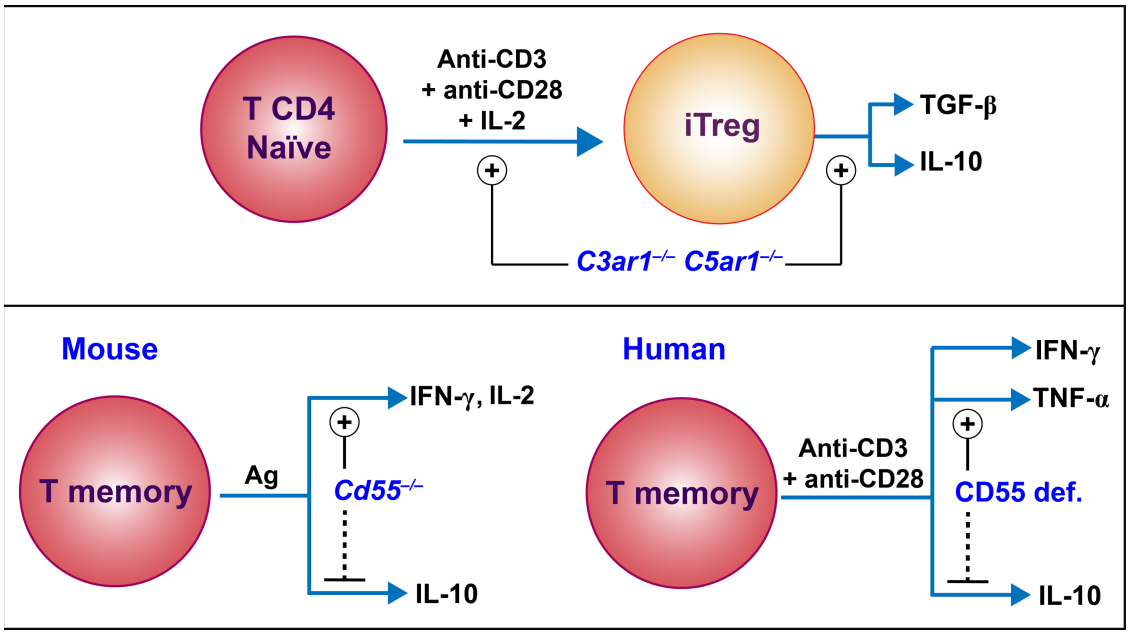

Fig. 3. αβ T cell regulation by complement cues. Top: CR-dependent signals as deduced from studies in C3aR1 + C5aR1 double KO mice. [82]. Bottom: CReg-dependent signals as deduced from studies in CD55 deficient mammals [32,86]. Black dashed T lines indicate impaired cytokine production; black solid lines with a + indicate enhanced differentiation or cytokine production.

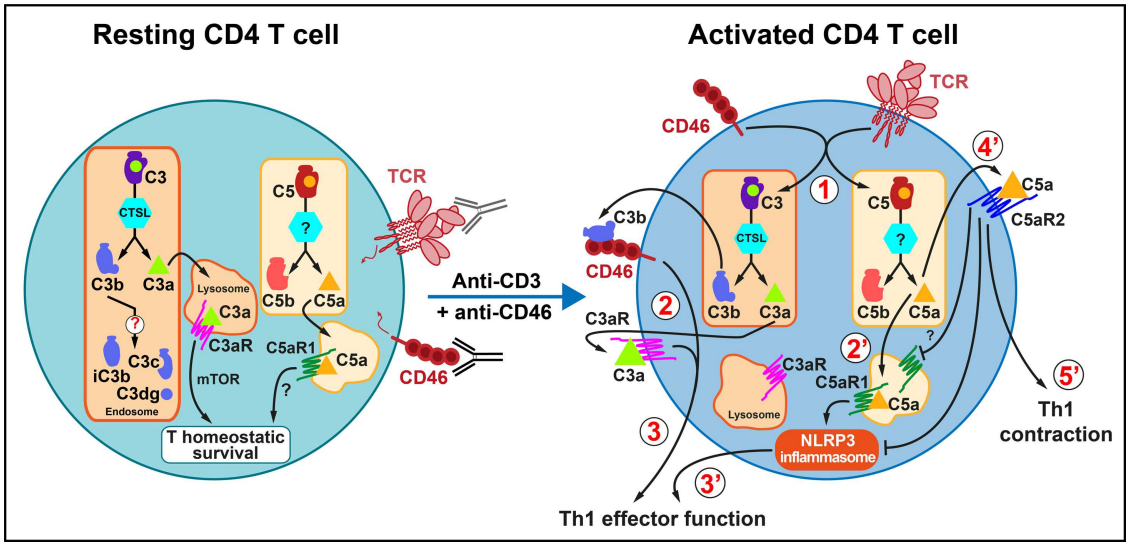

Fig. 4. Intracellular complement signalling in T cells. Left. Resting CD4+ T cells contain intracellular C3 and C5 stores, which undergo proteolytic cleavage by CTSL and an undefined protease, respectively. "Tonic" lysosomal C3a/C3aR engagement sustains T cell homeostatic survival; the mechanism for C5a is likely similar but yet undefined. Right. After CD46+TCR-activation (1), intracellular C3a and C3b translocate to the cell membrane (2), where their engagement to C3aR and CD46, respectively, promotes Th1 effector function (3). In parallel (2′), intracellular C5a binding to C5aR1 induces NLRP3 inflammasome assembly, which promotes Th1 effector functions (3′). A Th1 contraction response (5′) may ensue by extracellular C5a binding to C5aR2 (4′) in the cell membrane [6,7].

cytokines such as IFN-γ and IL-2 in mice or TNF-α (but not IFN-γ) in humans, and decreased Treg cytokines such as IL-10 in both species. Therefore, CD55 signalling likely impacts effector T cell differentiation.

Recently, intracellular C3 (iC3) and C5 activation mechanisms were reported that might in part explain some of these findings. Indeed, iC3 activation by cathepsin-L (CTSL) was shown to be crucial for T cell survival and for T cell differentiation after TCR and CD46 activation (Fig. 4). Secreted intracellular C3a and C3b promote T cell survival through their surface receptors (C3aR and CD46, respectively) (Fig. 4, left). On the other hand, CD4+ T cells from C3-deficient patients or C3 KO mice are unable to induce a normal Th1 response, probably because they cannot generate T-cell derived C3a and C3b [88,89]. This supports an autocrine loop of C3 fragments binding CD46 and C3aR for Th1 responses to occur. In addition, the co-engagement of TCR with CD46 induces the production of Th1 cytokines such as IFN-γ [78] (Fig. 4, right). Lending support to this notion, inhibiting the protease CTSL impairs IFN-γ after TCR/CD46 co-triggering [6], and CD46-deficient patients and patients with hypomorphic mutations in the gene encoding Jagged1 (a physiological ligand for CD46), showed impaired Th1 responses [90,91]. However, our recent data on congenital C3-deficient patients do not support gross Th subset derangements [60], and C3 or CD46 deficient patients do not resemble interferonopathies [92].

In turn, TCR and CD46 signalling generates iC5a that binds to intracellular C5aR1, leading to nucleotide-binding domain, leucine-

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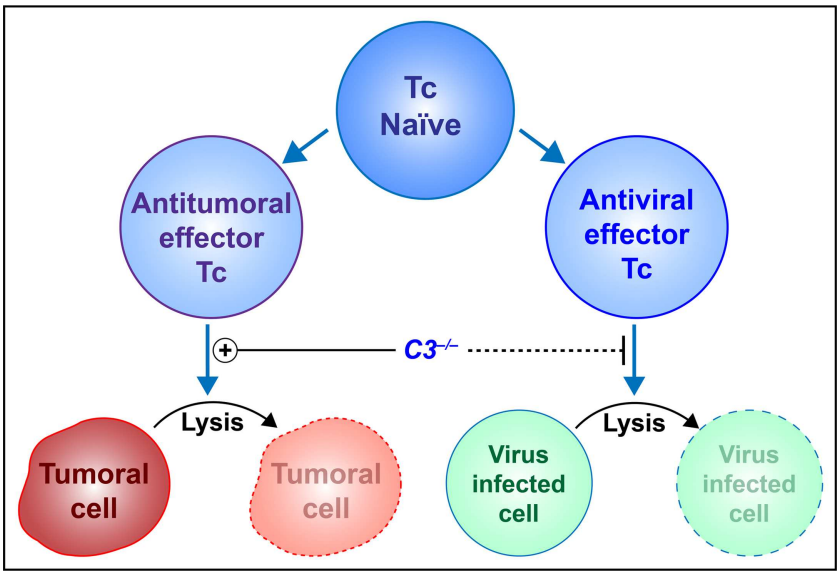

Fig. 5. Tc cell regulation by complement cues. Antitumoral (left) [97] and antiviral (right) [94–96] Tc activities are antagonistically dependent on C3. Black dashed T line indicates impaired lysis; black solid line with a+ indicates enhanced lysis.

rich repeat family, pyrin domain containing 3 (NLRP3) assembly and Th1 induction, whereas secreted intracellular C5a binds to surface C5aR2, negatively regulating this mechanism [7]. Again, C5-deficient patients do not show obvious T cell-dependent diseases.

In this context, other groups have reported that TCR/CD46 co-engagement in $CD4^+$ T cells switches Th1 into Treg differentiation (Fig. 2) [13], thus inhibiting *Mycobacterium*-specific αβ and γδ T cells [93].

3.1.3. Tc lymphocytes

Although less studied than Th cells, complement has also been involved in Tc ($CD8^+$) cell activation and differentiation, but the mechanisms remain unclear. For instance, C3 KO mice, but not CR1/CR2 KO mice, showed poor Tc responses and high susceptibility to infection with influenza virus [94], as well as poor expansion of lymphocytic choriomeningitis virus -specific effector Tc cells in an epitope-dependent fashion [95]. Subsequent studies indicated that C5a also plays a role in the generation of Tc cell responses, because a C5aR antagonist prevented the generation of a proper response in influenza-infected mice (Fig. 5, right) [96].

In contrast, C3 KO mice tumour-infiltrating Tc lymphocytes improve resistance to tumor development in a T-cell- and IL10-dependent manner (Fig. 5, left) [97]. The authors conclude that C3aR (and C5aR) may be a novel class of immune checkpoints that could be targeted for tumour immunotherapy.

Together, these results suggest that C3aR may enhance or inhibit Tc effector activity depending on the pathological context.

3.2. B lymphocytes

B lymphocyte regulation by complement is directly linked to its opsonizing, rather than inflammatory, function [98], mainly through CR2 (Table 1). CR2 is expressed mainly in mature B lymphocytes as part of the B-cell co-receptor complex, which includes CD19, CD81 and CD225. Upon engagement, this complex lowers the BCR activation threshold more than 1,000-fold [99] and enhances antigen processing and presentation to T cells [100]. Interestingly, anergic (i.e., self-tolerant) B cells also lower their BCR activation threshold when co-triggered by C3d(g)-opsonized self-antigens, which may give rise to autoimmune responses in mice [101]. This was the case in collagen-induced arthritis, which could be ameliorated by C3 depletion [102], and in the mouse model for multiple sclerosis [103].

Most of these studies approaching the role of complement in B cell differentiation and function were based on mouse models [109], but human CR2 deficiency (see above) also showed suboptimal BCR costimulation, impaired naïve to memory B cell differentiation and hypogammaglobulinemia (Fig. 6) [27,30]. Unexpectedly, antibody responses to protein or polysaccharide vaccination were normal or moderately impaired, respectively. Lack of CR2 ligands as observed in human C3 deficiency, whether primary or secondary mutations [60,104] caused similar features (except hypogammaglobulinemia), indicating that CR2-mediated signals are critical for normal B cell differentiation, but not for specific antibody responses in humans (Fig. 6).

C4-binding protein (C4BP) functions as a complement regulator that acts as a factor I cofactor or accelerates the decay of the classical and the lectin pathways C3/C5 convertases. It has also been reported to bind the costimulator protein CD40 on B cells [110], although more recent work failed to confirm the C4BP/CD40 interaction [111]. Interestingly, CD46/CD40 crosslinking inhibited CD40-mediated induction of surface CD23 and IL-4-dependent IgE isotype switching, suggesting that CD46 can reduce CD40 signalling [112].

Taken together, these findings support a strong impact of complement in B cell ontogeny and function, often associated to B cell-related diseases when complement is dysregulated.

4. Conclusions and future directions

In addition to their traditional role as microbe and immune complex identification and elimination, complement proteins, receptors and regulators have specific roles in the ontogeny and function of different cell types, including both innate and adaptive lymphocytes. Signals through complement-binding surface molecules such as CR or CReg improve lymphocyte responses, adapting them to environmental changes or inflammatory states, as shown for CFP and NKp46 in mouse ILC1. In addition, lymphocytes show differential subset-specific CR and CReg expression patterns and regulate their surface expression levels after activation, lending further support to their role in immunity. Unravelling the underlying mechanisms that drive these processes will help to understand

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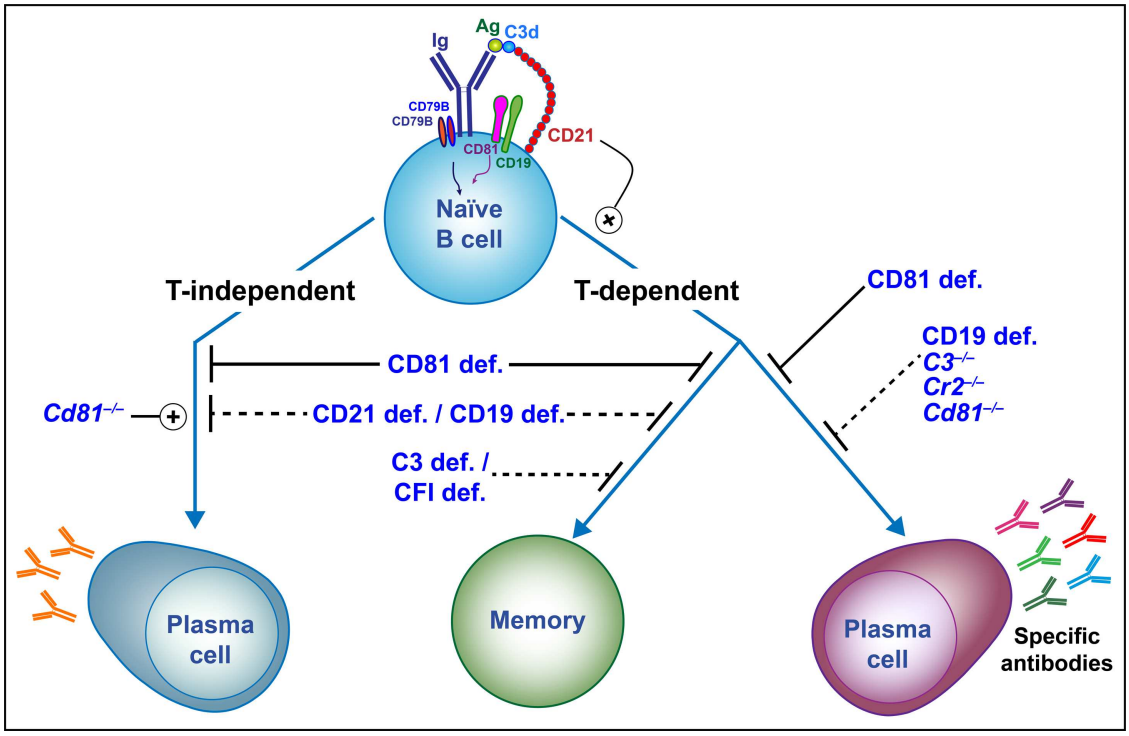

Fig. 6. B cell regulation by complement cues. [27,30,60,89,99,104–108]. Black solid/dashed T lines indicate blocked/impaired differentiation pathways; black solid line with a + indicates enhanced differentiation pathway. Human PID are identified by def., mouse KO by −/−.

better the immune mechanisms triggering lymphocyte development and homeostasis.

Although truly physiological studies are scarce, CR such as anaphylatoxin receptors C3aR and C5aR or CR2, and CReg such as CD46 and CD55 can enhance or inhibit certain Th, Treg and Tc responses. In contrast, several studies clearly support that B lymphocytes are regulated by CR, as shown for memory B cell differentiation, which is impaired when CR2 or its C3-derived ligands are absent.

While complement studies are re-emerging in the last years due to these new roles in lymphocyte biology, further work is warranted to define their specific roles in each lymphocyte subset. To that end, mouse models are useful but insufficient for non-homologous human CR or CReg. In those cases, careful studies in human PID and cell lines thereof are required to fully understand the role of extracellular and intracellular complement (the complosome) in lymphocyte physiopathology and the functional connection between complement and others processes in a broader range of cells and activities.

Conflict of interest

All authors declare that they have no relevant conflicts of interest.

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