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Molecular Immunology 89 (2017) 2–9

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Review

Intracellular complement – the complosome – in immune cell regulation

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ABSTRACT

The complement system was defined over a century ago based on its ability to "complement" the antibody-mediated and cell-mediated immune responses against pathogens. Today our understanding of this ancient part of innate immunity has changed substantially and we know now that complement plays an undisputed pivotal role in the regulation of both innate and adaptive immunity. The complement system consists of over 50 blood-circulating, cell-surface expressed and intracellular proteins. It is key in the recognition and elimination of invading pathogens, also in the removal of self-derived danger such as apoptotic cells, and it supports innate immune responses and the initiation of the general inflammatory reactions. The long prevailing classic view of complement was that of a serum-operative danger sensor and first line of defence system, however, recent experimental and clinical evidences have demonstrated that "local" tissue and surprisingly intracellular complement (the complosome) activation impacts on normal cell physiology. This review will focus on novel aspects of intracellular complement activation and its unexpected roles in basic cell processes such as metabolism. We also discuss what the existence of the complosome potentially means for how the host handles intracellular pathogens such as viruses.

1. Systemic complement activation

The complement effector molecules, circulating in serum and interstitial fluids, exist largely in precursor states that are activated rapidly in a proteolytic and cascade-like fashion following recognition of pathogen-associated molecular patterns (PAMPs) and/or noxious self-derived danger-associated molecular patterns (DAMPs). Complement can be activated systemically in the blood via three main routes: the classical pathway (initiated by the C1q molecule in complex with the proteases C1r and C1s) recognizes uncoated or immunoglobulin-coated antigens and the lectin pathway is triggered by the recognition of microbial carbohydrates through mannose binding lectin (MBL), collectins or ficolins followed by activation of the mannose-binding lectin-associated serine proteases (MASPs). MASPs and C1r/s then cleave C4 and C2 to generate the classical/lectin pathway C3 convertase C4bC2a. The third activation pathway, the alternative complement pathway (which is also called the amplification pathway as it perpetuates complement activation initiated by the classical and/or lectin pathways), is characterised by tonic low-level C3 hydrolysis to C3(H2O), which exposes binding sites for Factor B (FB), which is then cleaved by Factor D (FD) to generate the alternative pathway C3 convertase C3bBb. Both C3 convertases – C4bC2a and C3bBb catalyse the proteolysis of C3 into C3a and C3b and the subsequent cleavage of C5, either by the classical/lectin pathway C5 convertase C4bC2aC3b, or the alternative C5 convertase C3bBbC3b, into C5a and C5b (all reviewed in more detail in (Walport, 2001; Ricklin et al., 2010; Kolev et al., 2013).

C5b binds to the surface of targets – for example bacteria – and together with C6, C7, C8 and C9 forms the membrane attack complex (MAC) which ultimately leads to the direct lysis of the pathogen or target cell. The anaphylatoxins C3a, a ligand of the receptor C3aR, and C5a, a ligand for the receptors C5aR1 and C5aR2, are potent chemoattractants which recruit monocyte, granulocyte and mast cells to the site of infection. Apart from cell migration, the anaphylatoxins also induce enhanced smooth muscle cell contraction and vasodilatation, degranulation of neutrophils and mast cells and cytokines secretion by a broad range of immune cells (reviewed in (Heeger and Kemper, 2011)). Since C3b, C4b and C5b bind in a non-discriminatory fashion to pathogens and host cells alike, several soluble and cell-bound regulators control complement activation to prevent unwanted host tissue damage. Examples of complement regulators are factors that accelerate the decay of convertases, such as surface-bound CD55 or fluid-phase Factor H (FH), the transmembrane glycoprotein CD46, which prevents

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http://dx.doi.org/10.1016/j.molimm.2017.05.012
Received 6 May 2017; Received in revised form 14 May 2017; Accepted 19 May 2017
Available online 07 June 2017
0161-5890/

complement deposition by functioning as cofactor for the inactivation of C3b and C4b by Factor I (FI), and CD59 which blocks the MAC assembly (Morgan et al., 2005; Schmidt et al., 2016).

2. Local complement activation and modulation of immune responses

While the main source of serum-circulating complement components is the liver, complement proteins, receptors and regulators are also produced locally and expressed by non-immune cell populations (including epithelial cells, fibroblasts, adipocytes and astrocytes) as well as by many immune cells, including monocytes, macrophages, dendritic cells, granulocytes, natural killer cells, and B- and T-lymphocytes (Heeger and Kemper, 2011; Kolev et al., 2014; Kolev and Kemper, 2017). The presence of complement receptors on such a broad range of somatic cells endows them with the ability to respond to either paracrine- and/or autocrine-derived complement products in a specific fashion. Although initially, such cell responses were thought to be driven by serum-derived complement activation products, work particularly over the last decade has demonstrated that immune cell-produced 'local' complement activation fragments are critical drivers of T cell activation (Kolev et al., 2014; Freeley et al., 2016). For example, anaphylatoxins C3a and C5a generated by the antigen presenting cell (APC) during the cognate APC/T cell interaction (and that then signal back to the APC and T cell) control T lymphocyte expansion and differentiation as demonstrated by *in vivo* disease models of infection and transplantation (Lalli et al., 2008; Strainic et al., 2008). Furthermore, C3 deposition induced locally on apoptotic cells was shown to facilitate their endocytosis by myeloid cells and to then act as chaperone for lysosomal degradation and subsequent antigen presentation to T cells (Baudino et al., 2014). Mouse studies revealed that C5a generated by the T cell and/or APC (via secretion of C3 and C5, Factors B and D and subsequent local activation of the alternative pathway in the extracellular space) binds to the C5aR1 expressed by $CD4^+$ T cells in an autocrine/paracrine fashion and inhibits cell apoptosis − thus enhancing T cell expansion (Lalli et al., 2008). The activation of the C3aR and C5aR1 via such immune cell-derived C3a and C5a generation was also shown to initiate the activation of the phosphatidylinositol 3-kinase (P13K), Akt (also known as protein kinase B, PKB), mechanistic target of rapamycin (mTOR) and MAP kinases in both APCs and T lymphocytes, which results in pro-inflammatory Th1 and Th17 response *in vitro* and *in vivo* (Strainic et al., 2008; Sarma and Ward 2012). Conversely, absence of C3aR and C5aR1 signalling on these cells types is associated with activation of TGF-β1 signaling and default induction of $FOXP3^+$ induced T regulatory cells (Le Friec et al., 2013). Locally generated anaphylatoxins also modulate Th2 immunity positively with the C3a/C3aR interaction driving Th2 induction (Drouin et al., 2002) and the C5a/C5aR1 interaction inhibiting Th2 induction (Köhl et al., 2006) as demonstrated in mouse models of allergic asthma.

Particularly work on the effects of complement on human T cell responses has demonstrated that the activity of the T cell-derived C3 activation fragments C3a and C3b is critical to normal T helper 1 (Th1) biology. In human $CD4^+$ T cells, autocrine CD46 signaling together with T cell receptor (TCR) activation was initially shown to induce proliferation and acts as a potent costimulator during human T cell activation (Astier et al., 2000; Zaffran et al., 2001). Later studies revealed that signals mediated by autocrine activation of the C3aR and CD46 (which binds C3b) by T cell-derived C3a and C3b are required for the secretion of interferon (IFN)-γ and successful induction of T helper 1 (Th1) effector responses (Cardone et al., 2010; Le Friec et al., 2012). The critical importance of CD46 mediated signals in Th1 induction is further exemplified by the fact that patients deficient for C3 or CD46 are unable to mount Th1 responses *in vitro* and *in vivo* and suffer from recurrent infections early in life (Cardone et al., 2010; Liszewski et al., 2013; Kolev et al., 2015). Mechanistically, autocrine CD46 engagement by C3b is crucial in up-regulating the expression of CD25 (the interleukin (IL)-2 receptor α-chain) and CD132 (the IL-2 receptor common γ-chain), therefore enhancing the ability of T cells respond to IL-2 which is a requirement for normal T cell proliferation and Th1 induction (Cardone et al., 2010; Le Friec et al., 2012). Interestingly, the complement CD46-induced signals also control Th1 contraction: The CD46 and IL-2R crosstalk that occurs upon increases in IL-2 concentration in the microenvironment through the expansion of the ongoing Th1 response induces the co-expression of immunosuppressive IL-10 in Th1 cells and moves the effector response towards a (self)regulatory T cell phenotype, with the cells finally 'collapsing' into an IL-10 single producing T cell denoting successful Th1 contraction (Cardone et al., 2010). We proposed that this CD46-driven molecular switch regulates the natural 'life-cycle' of Th1 cells with the purpose of keeping immune responses under tight control and preventing the local overproduction of IFN-γ which could lead to tissue pathologies (Cope et al., 2011). This notion is supported by the observation that dysregulation in CD46-driven IL-10 production is associated with hyperactive Th1 response in T cells from patients with rheumatoid arthritis and multiple sclerosis (Astier et al., 2006; Ni Choileain and Astier 2011; Liszewski et al., 2013). Auto- and paracrine complement activation also intersects with other molecular pathways such as the Notch pathway to modulate T cell effector function. In $CD4^+$ T cells, CD46 binds the Notch ligand Jagged1 with high affinity and via this sequesters Jagged1 from an interaction with Notch1 that would normally induce T cell activation (Le Friec et al., 2012). Upon TCR and autocrine CD46 engagement, the downregulation of CD46 on the cell surface occurring upon its activation (Le Friec et al., 2012), allows Jagged1 to bind and activate the Notch1 receptor which then also contributes to successful IFN-γ production. In accordance with these observations, patients that suffer from Alagille Syndrome and that have a mutated Jagged1 protein with altered binding affinity to CD46 show impaired Th1 (but not Th2) responses and suffer from recurrent ear and respiratory infections (Le Friec et al., 2012).

In addition, there are studies suggesting that other complement receptors and/or regulators also contribute to normal human T ecll responses. For example, CR1 (also known as CD35) and CD59 which are both expressed on $CD4^+$ T lymphocytes can negatively affect their effector responses in terms of proliferation and secretion of cytokines such as IFN-γ and IL-2 (Longhi et al., 2005; Wagner et al., 2006) and C1q has been shown to reduce T cell proliferation (Clarke et al., 2015) albeit with the receptor mediating C1q binding to T cells remaining to be identified conclusively. Of note, it is not clear yet whether the engagement of these other complement receptors/regulators on T cells also occurs in an autocrine fashion or not.

3. Intracellular complement activation: the 'C3 and C5 complosome'

Just when the idea that local complement production is important to normal immune cell activity became more main stream and generally accepted at least among complementologists, it was discovered that complement activation is not confined to the extracellular space as always thought but occurs intracellularly (Liszewski et al., 2013; Arbore et al., 2016). Specifically, human $CD4^+$ T cells contain intracellular stores of C3, intracellular C3aR (located on lysosomes) and cathepsin L (CTSL). CTSL continuously cleaves intracellular C3 into bioactive C3a and C3b in resting T cells and the engagement of lysosomal C3aR by intracellular C3a sustains T cell survival via low-level mTOR induction (Liszewski et al., 2013). Upon TCR activation, this whole intracellular complement C3 system translocates rapidly to the cell surface were C3a and C3b signal via their receptors C3aR and CD46 respectively in autocrine fashion, triggering IFN-γ production and Th1 induction (Liszewski et al., 2013). Thus, while the intracellular C3 activation system dictates T cell survival as T cells in which intracellular C3aR expression is reduced do not survive, the engagement of the C3aR and CD46 on the cell surface are needed for Th1 induction. This means in

essence that the location of complement activation and subsequent receptor engagement (intra- versus extracellular) defines the functional outcome of complement activation. Furthermore, and equally important, dysregulation of intracellular C3 activation contributes to disease: T cells from patients with juvenile idiopathic arthritis (JIA) have increased intracellular C3 processing resulting in exaggerated Th1 responses and the hyperactive intracellular C3 activation observed in these patients can be normalised *in vitro* by treatment with a cell-permeable CTSL inhibitor, which also decreases the hyperactive IFN-γ production of the patients' T cells. Finally, intracellular C3 activation has been observed not only in $CD4^+$ T cells but also in monocytes, B cells, fibroblasts, epithelial and endothelial cells and is therefore likely of broad physiological significance (Liszewski et al., 2013; Satyam et al., 2017).

Since these early − and so far limited − studies indicate that the amounts of intracellular C3 (activation) can hold the key to modulating T cell effector activity, it is now important to understand how *C3* gene expression and protein generation is regulated. Interestingly, it was recently demonstrated that at least part of the intracellular C3 is transported from the extracellular milieu (serum/blood) into T and B cells (Elvington et al., 2017). This observation was in agreement with earlier report demonstrating that C3 can be internalized in Ca_{2+} dependent manner via the lipoprotein-receptor-related protein/α2-macroglobulin receptor in mouse fibroblasts (Meilinger et al., 1999). The internalized C3 form, however, was surprisingly not the intact C3 molecule but rather its hydrolyzed form termed C3(H_2O). C3(H_2O) uptake was rapid, with most of C3(H_2O) being returned to the extracellular space within 24 h, and this process was coined by the group as 'recycling pathway for extracellular-derived C3'. The intracellular C3(H_2O) was found to be also cleaved by intracellular CTSL into C3b and C3a, confirming earlier reports on intracellular C3 activation, and actually led to an increase in IL-6 production by human $CD4^+$ T cells (Elvington et al., 2017). Elvington and colleagues also observed parallel *de novo C3* mRNA synthesis in $CD4^+$ T cells in agreement with our recent data suggesting that in C3 'poor' environments (such as in tissues) T cells initiate *de novo* synthesis of C3 mRNA in a Lymphocyte function associated antigen (LFA) 1-dependent manner (Kolev et al., 2016).

Not much surprising, after the discovery of the intracellular C3 system, it has been demonstrated that T cells also harbour an intracellular C5 system, which is also required for normal T cell activation (Arbore et al., 2016). We recently reported that human T cells possess intracellular stores of C5 (similar to C3), which is cleaved by a yet unknown protease to generate C5a. Upon T cell activation, intracellular C5a binds to C5aR1 (expressed exclusively intracellularly on a not yet defined subcellular compartment) which results in increased reactive oxygen species (ROS) production and subsequent activation of the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome similar to the C5aR1-driven NLRP3 activation that was already demonstrated in myeloid cells (Samstad et al., 2014). The intrinsic NLRP3 inflammasome activation in T cells leads to autocrine IL-1β secretion, which sustains specifically IFN-γ and production (Th1 response). $CD4^+$ T cells also express surface and intracellular C5aR2, which is also engaged in autocrine fashion by both secreted C5a and the des-Arginated form of C5a, C5a-desArg (Arbore et al., 2016). C5aR2 negatively regulates the C5aR1-driven NLRP3 inflammasome activity, leading to decrease in IFN-γ production, switching to IL-10 secretion and contraction of Th1 responses (Arbore et al., 2016). These findings underpin our current understanding that autocrine C3 and C5 activity is crucial in the regulation of IFN-γ secretion (Liszewski et al., 2013; Kolev et al., 2014; Arbore et al., 2016) and indicate that both the C3 and the C5 'systems' and their cross-talk with another innate danger sensor, the inflammasome, are indeed needed for optimal Th1 immunity (summarized in Fig. 1). This crosstalk between intracellular complement and the inflammasome regulating T cell responses may also involve the APC as the C3aR controls ATP efflux and subsequent toll-like receptors-induced inflammasome activation and IL-1β secretion also in macrophages (Asgari et al., 2013). In addition, the C5aR1 induces NLRP3 inflammasome and IL-1 β secretion in monocytes upon C5a binding, while in macrophages, C5a-mediated signals suppress NLRP3 inflammasome assembly (Haggadone et al., 2016).

Based on the finding that T and other cells seem to contain a wide array of complement components, receptors and regulators (we actually suggest that most cells contain a full-fledged complement system as observed in serum) and somewhat in analogy to the inflammasome, Peter Garred coined the suitable term 'complosome' for the intracellular complement system.

Since the level of C5 activation in T cells also regulates the magnitude of Th1 induction, it will likely be important to understand the mechanism of intracellular C5 activation. This may be mediated a specific protease, however, we have unpublished data suggesting that an intracellular C5 convertase can activate C5 in T cell and human monocytes (Niyonzyma, Kemper and Espevik, unpublished data) − supporting the idea of the existance of a complete intracellular complement system. Further, the specific subcellular location of intracellular C5 is not known and the regulation of *C5* gene expression or its potential uptake from serum (similar to C3(H_2O)) remains to be explored. It is also not clear whether T cell-expressed C5aR2 inhibits inflammasome activation via direct activation of an inhibitory pathway or indirectly via inhibition of C5aR1 activation. The latter possibility may be the more plausible, as in myeloid cells it has already been shown that C5aR2 can form heteromers with the C5aR1 and then activate β-arrestin to inhibit C5aR1-driven extracellular signal regulated kinase 1 and 2 (ERK1/2) signaling (Croker et al., 2014).

4. Complosome-mediated regulation of nutrient and oxygen metabolism

The discovery of the complosome is a relatively recent event and its functional implications are not understood yet. What is, however, surprisingly clear from the few studies published is that this systems impacts heavily on the cell metabolic machinery. In particular, CD46 signalling modulates key metabolic events in human $CD4^+$ T lymphocytes, including glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) (Kolev et al., 2015). CD46 is a membrane glycoprotein expressed on all nucleated cells (Seya et al., 1988) and expressed on most cells in four isoforms with two distinct cytoplasmic tails, termed CYT-1 and CYT-2, originating from the alternative splicing of a single gene (Wang et al., 2000). Both tails transduce intracellular signals in a broad range of cells (Ni Choileain et al., 2011). Resting T cells have higher expression of CD46-CYT-2. Upon TCR stimulation which triggers the autocrine engagement of CD46 by C3b, CD46-CYT-1 is upregulated, cleaved by γ-secretase and translocates to the nucleus where it drives the expression of the glucose transporter 1 (GLUT1, *SLC2A1*) and the large neutral amino acids transporter 1 (LAT1, *SLC7A5*). Increased expression of these channels promote the influx of glucose and amino acids (AA) into the cell. CD46-CYT1 signaling also mediates the expression of the late endosomal/lysosomal adaptor, MAPK and MTOR activator 5 (LAMTOR5), which is part of the amino acid sensing Ragulator complex (Bar-Peled et al., 2012). Together, increased nutrient influx and increased LAMTOR5 expression promote the docking of mechanistic target of rapamycin complex 1 (mTORC1) on the lysosomal surface and its activation. mTOR activation is crucial for the induction of the high levels of glycolysis, specifically needed for IFN-γ secretion and Th1 induction (Bar-Peled et al., 2012; Chang et al., 2013; Kolev et al., 2015). This model aligns well with the findings by King and colleagues demonstrating that CD46 drives *GLUT1* expression in activated human $CD4^+$ T cells throughout down-regulation of the inhibitory miR-150 (King et al., 2016). The critical role for CD46 in the metabolic reprogramming of $CD4^+$ T lymphocytes is underpinned by the observation that T cells from CD46-deficient patients have defective glycolysis, OXPHOS and thus Th1 induction (Kolev et al., 2015). CD46-

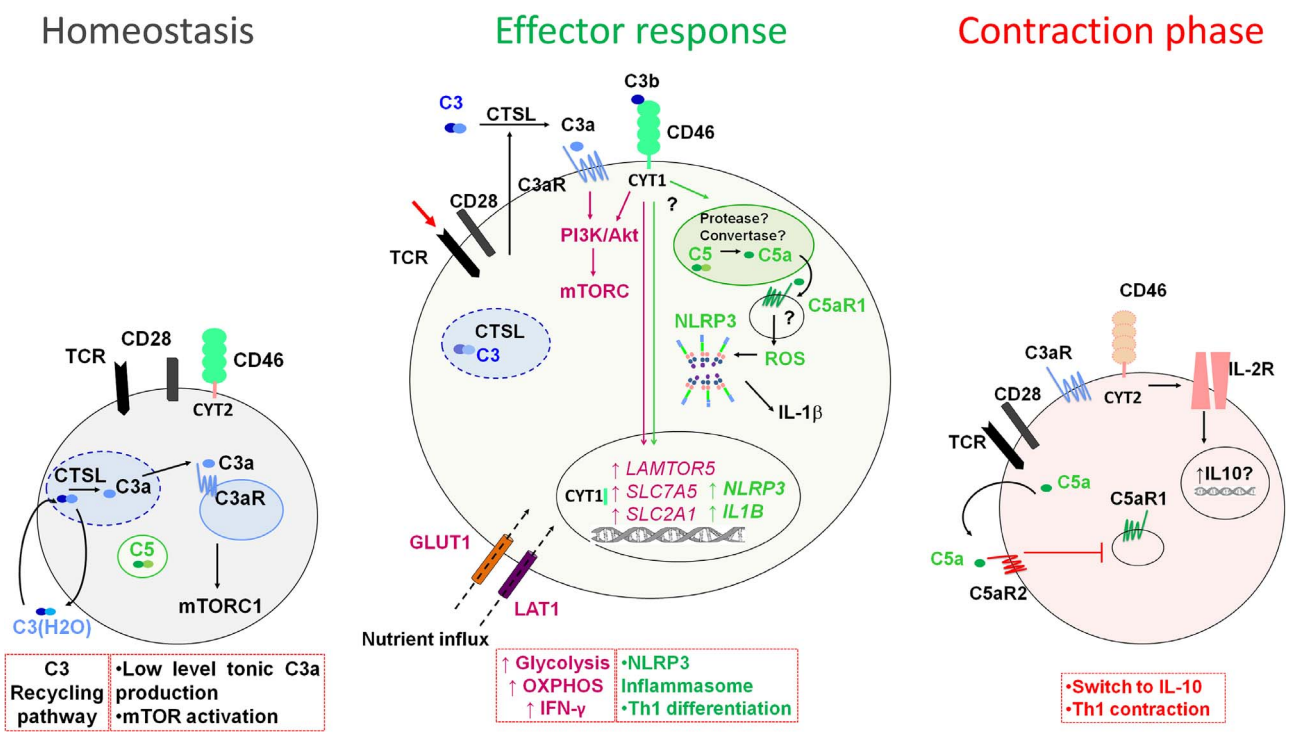

Fig. 1. The complosome in T cell regulation. In the resting state (homeostasis), T lymphocytes have intracellular stores of C3, C5 and cathepsin L (CTSL). C3 can be expressed by T cells or taken up from serum (recycling pathway). Small amounts of C3(H_2O) are constantly cleaved by CTSL into C3a and C3b. Intracellular C3a engages intracellular C3aR to induce low level mTOR activation to sustain cell survival. T cell receptor (TCR) stimulation (effector response) induces the translocation of C3 and C3 activation fragments and CTSL to the cell surface where C3a and C3b fragments signal in autocrine activation though C3aR and CD46, respectively. Upon CD46 activation, predominant CD46-CYT-2 expression switches to increased CD46-CYT-1 expression. CYT-1 is then cleaved by γ-secretase (not shown) to allow for CYT-1 nuclear translocation which drives expression of *LAMTOR5*, the glucose transporter GLUT1 (*SLC7A5*) and the amino acid transporter LAT1 (*SLC2A1*). The activation of the C3 complosome cumulates in mTORC activation, nutrient influx, and augmented glycolysis and oxidative phosphorylation (in violet). Furthermore, CD46 stimulation induces gene expression of *NLRP3* and *IL1 B* to prime the NLRP3 inflammasome. CD46 also induces intracellular C5 activation and C5a generation via yet unknown mechanisms. Intracllular C5a then engages the intracellular C5aR1 to amplify ROS production which triggers the assembly of the NLRP3 inflammasome and subsequent IL-1β production for optimal Th1 induction (in green). During the contraction phase of Th1 response, CD46-CYT-2 tail isoform expression becomes dominant again and, in conjunction with IL-2R signalling, induces IL-10 co-production in Th1 cells and the transition into a (self)regulatory Th1 contraction phase. The switch to IL-10 is accompanied by C5a secretion to the cell surface which engages surface expressed C5aR2 that blocks C5aR1 signaling and therefore negatively controls Th1 responses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mediated signals also trigger the switch from high glycolytic activity to steady-state glycolysis in CD4 + T cells during IL-10 co-production and Th1 contraction; this change from high to low glycolysis level is mediated by the CD46-CYT-2 isoform, which becomes again the predominant CD46 isoform in contracting T lymphocytes (Kolev et al., 2015). The mechanism regulating the expression/splicing of CD46 isoforms has not yet been defined however it is known that CYT-2 is expressed predominantly in memory $CD4^+$ T cells (Hansen et al., 2016). While mice express a complement regulator that can inactivate mouse C3b and C4b, termed Crry (Ruseva et al., 2009), a fully functional murine homologue of human CD46 in terms of its T cell function has so far not been discovered. Mice transgenic for human CD46 turned out to be no suitable models to validate CD46 function *in vivo* – likely because the mouse intracellular signalling machinery does not 'work well' with the human CD46 protein (Kemper et al., 2001).

As mentioned above, intracellular C5 also plays a key role on the initiation of oxygen metabolism during T cell activation and has been shown to regulate ROS production in neutrophils and other cells (Lee et al., 2008; Kalbitz et al., 2016), further solidifying the growing the functional connection between the complosome and cell metabolism.

5. Role of complement in cell proliferation and survival

Since normal cell metabolic activity is a defining feature of life, it is not surprising that complement and the complosome are also intimately intertwined with cell survival. Local complement signals promote cell cycle progression and cell proliferation. In T lymphocytes, CD46 activation supports directly proliferation via transmission of intracellular pathways (Astier et al., 2000; Zaffran et al., 2001) and also renders cells responsive to exogenous growth factors via augmented expression of growth factor receptors such as the IL-2R (Cope et al., 2011). In myeloid cells, activation of the complement C3 activation fragment iC3b receptors CR3 and CR4 favour the transition from the cell cycle progression G1 to S phases (Luo et al., 2005). Similarly, C5aR1 signaling after C5a engagement triggered the transition to G2 and M phases, resulting in increased DNA synthesis and cell division, also in the microvascular endothelial cell line HMEC-1 (Kurihara et al., 2010) and deposition of sublytic amounts of MAC on oligodendrocytes induces c-Jun activation and proliferation (Fishelson et al., 2001).

Complement mediated signaling can also impact on cell survival through the inhibition of apoptosis. For example, expression of the anti-apoptotic molecule B-cell lymphoma 2 (Bcl-2) was induced in human $CD4^+$ T lymphocytes by CD46 (Kolev et al., 2015), while C5aR1 activation induced Bcl-2 in activated mouse $CD4^+$ T cells (Lalli et al., 2008). Furthermore sublitic MAC deposition was shown to decrease apoptosis in oligodendrocytes via the upregulation of Bcl-2 that led to inhibition of caspase-3 (Soane et al., 1999) or caspase-8 (Cudrici et al., 2006).

The observations discussed above suggest that complement components C3 and C5 are potentially at the basis of normal cell physiology. If true, it is conceivable that total complement C3 and C5 deficiencies are incompatible with life and should therefore be absent in humans. Interestingly, accumulating data from our and other groups support such notion: Serum C3 (and C5) deficient patients succumb to recurrent infections, however their $CD4^+$ T cells, for example, survive and proliferate normally, which seems in contrast with the new

important role of the complosome in cell metabolism (Liszewski et al., 2013; Arbore et al., 2016). However, we were able to demonstrate that T cells from all C3-deficient patients assessed so far contained *C3* mRNA and could generate intracellular C3a that sustained their survival (Liszewski et al., 2013) − the lack of secretion of C3 or its activation fragments however precluded Th1 normal induction (Katz et al., 1994; Singer et al., 1994). Similarly, immune cells from C5-deficient patients could not secrete C5/activation fragments but were still able to generate intracellular C5a fragments and to activate intracellular C5aR1 (Lappegard, Niyonzima and Kemper, unpublished). Thus, we have as of yet to identify an individual with complete absence of intracellular C3 or C5.

6. The complosome in non-immune cells

While the role of complosome in T cells and monocytes is now being explored in depth, there is emerging evidence that the complosome also exists and also plays a critical role in non-immune cells. For example, a recent study from Satyam and colleagues associated intracellular C3 activation in intestinal mucosal cells with local ischemia/reperfusion injury: *in vitro* studies using the CaCo2 cell line revealed that *C3* mRNA expression was induced by hypoxia and that the resulting C3 protein was cleaved by both cathepsin B (CTSB) and cathepsin L (CTSL) into to C3a and C3b (Satyam et al., 2017). The authors further suggested that subsequent formation of the MAC was responsible for the local ischemic injury, however, they did not clarify the exact location of MAC deposition. Intriguingly, recent work found that intracellular inhibition of CTSL and CTSB blocked severe acute respiratory syndrome and ebola peudotype virus infection in neuronal/adrenal/epithelial-like 293T cells (Shah et al., 2010) − and it may now be interesting to define whether this involves indeed changes in complosome activation in these cells.

The notion that serum complement components such as C3(H_2O) (Elvington et al., 2017) can be transported into the cell as discussed in the previous chapter has also been subject to investigation in cells with non-immune function. In a study from 2016, Martin and colleagues showed that FH can be actively internalized by apoptotic Jurkat T cells and the retinal pigmented epithelial cell line − ARPE-19 (Martin et al., 2016). In this study, factor H was shown to bind to the surface of apoptotic bodies and of nucleosomes, facilitating their phagocytosis and enhancing C3 cleavage by cathepsin L within phagocytes. This process leads to iC3b deposition and subsequent clearance of the internalized apoptotic debris. Increased C3 (and C5) activation in ARPE-19 cells upon treatment with amiloyd-β was also observed in another study and is associated with increased mitochondrial ROS production (Wu et al., 2017). C1q was also shown to unexpectedly play role in the eye during the development of age-related macular degeneration (AMD) (Doyle et al., 2012) by binding to drusen deposits and supporting the NLRP3 inflammasome activation in monocytes which resulted in secretion of proinflammatory IL-1β. Although, the authors showed that ARPE-19 cells also express the NLRP3 inflammasome and secrete IL-1β, the source of C1q was not defined and it is clear that more investigations are required in regards to an intra-epithelial complosome (Luo et al., 2011).

Interestingly the complement regulator C1 inhibitor was found to colocalize intracellularly in cardiomyoblasts and endothelial cells with the activation fragments C4d and C3d in a rat model of myocardial infarction (Emmens et al., 2016). Furthermore, the complement regulators FH and FI are also present in the cytoplasm of endothelial cells and the authors observed that these proteins are not secreted upon treatment with histamine, which usually induces the 'spillage' of innate effector molecules (Turner et al., 2015). These data could indicate a possible function for these retained proteins in the regulation of the intracellular complosome − an idea that has so far not been investigated (Liszewski et al., 2013; Arbore et al., 2016; Elvington et al., 2017).

Finally, the complosome may also contribute to neuronal fitness as Jung and colleagues showed that mesenchymal stem cells (MSC) induced down-regulation of intracellular C3 expression in neurons to promote their survival under hypoxic conditions (Jung et al., 2016).

7. C1q and the C1q-TNF superfamily in metabolism

We include here a specific small section on C1q because this molecule now emerges as a complement component being also particularly involved in single cell metabolism (often via changing mitochondrial activity) aside fom C3 and C5. For example Intracellular C1q which can be recognised by the mitochondrially expressed receptor gC1qR (Dedio et al., 1998), was shown to drive mitochondrial ROS production and subsequent neuronal death during hypoxia mediated damage (Ten et al., 2010). The C1q-TNF family (also known as C1q-TNF-related protein (CTRP) family) comprises at least 15 proteins with many roles in both immunity and metabolism. These molecules are structurally related to both C1q and TNF and form hybrid proteins and were recently reviewed extensively (Schäffler and Buechler, 2012). Adiponectin is best characterised member of this C1q/TNF family and is exclusively produced by adipocytes. It was shown to enhance insulin sensitivity and thus to control whole body energy metabolism (Basu et al., 2007). Another member of C1q-TNF-CTRP family, CTRP3, negatively regulates lipid metabolism by downregulating PPAR-γ and C/EBPα during adipocyte differentiation (Nishimoto et al., 2017). CTRP3 was also shown to protect mesenchymal stem from ischemia-induced apoptosis via activation of PI3 K/Akt pathway (Hou et al., 2014). In coelomocytes, miR-31 induced downregulation of CRTP9 expession which resulted in altered the lipid metabolism balance and eventually led to apoptosis in these cells (Shao et al., 2017). CTRF3 mediates OXPHOS-supported protein expression and mitochondrial ROS production in smooth muscle cells (Feng et al., 2016) and exogenous C-TRF3 supplementation inhibited apoptosis of mesenchymal stem cells through activation of the PI3K-AKT-mTOR axis (Hou et al., 2014). Importantly, using C1q-TNF-related protein 3 siRNA knockdown technique, the authors showed that intracellular and/or autocrine C1q synthesis rather than systemic production was important for its function. CRTP9 along with CRTP1, CRTP12 and CRTP13 are also all associated with type 2 diabetes and insulin resistance (Afrookhteh et al., 2017; Bai et al., 2017). As most studies on these chimeric molecules have so far focused on the C1q portion, it will be important to also define the TNF domain contributions and to possibly dissect the exact 'combined' functions of C1-TNF hybrid proteins versus those of 'stand alone' TNF and C1q − for example, in most cases, it has not been defined whether the CRTPs work through activation of local complement and/or engagement of specific receptors (Kolev and Kemper 2017). Furthermore, an investigation into whether C1q defects not only prevent normal clearance of apoptotic cells but may also provide additional pathophysiological mechanisms (based on dysregulation of cell metabolism) in systemic lupus erythematosus (SLE) may be warranted.

8. Interaction between intracellular pathogens and the complosome

Because of its sentinel function and the fact that serum complement-deficient individuals suffer from recurrent severe infections, it is undisputable that complement is critical to the protection against pathogens. However, the discovery of the complosome now suggests that we should take a second look at the relationship between complement and pathogens − and possibly particularly how pathogens (ab)use complement activation fragments to gain not only cell entry but to also impact subsequently on basic cellular functions for their advantage. For example, complement components mediate the recognition and binding of viral particles to B lymphocytes during chronic hepatitis C virus infection (HCV) via a complex involving C3d-tagged HCV with CD19 and CD81, leading ultimately to re-arrangement of the distribution of B cell

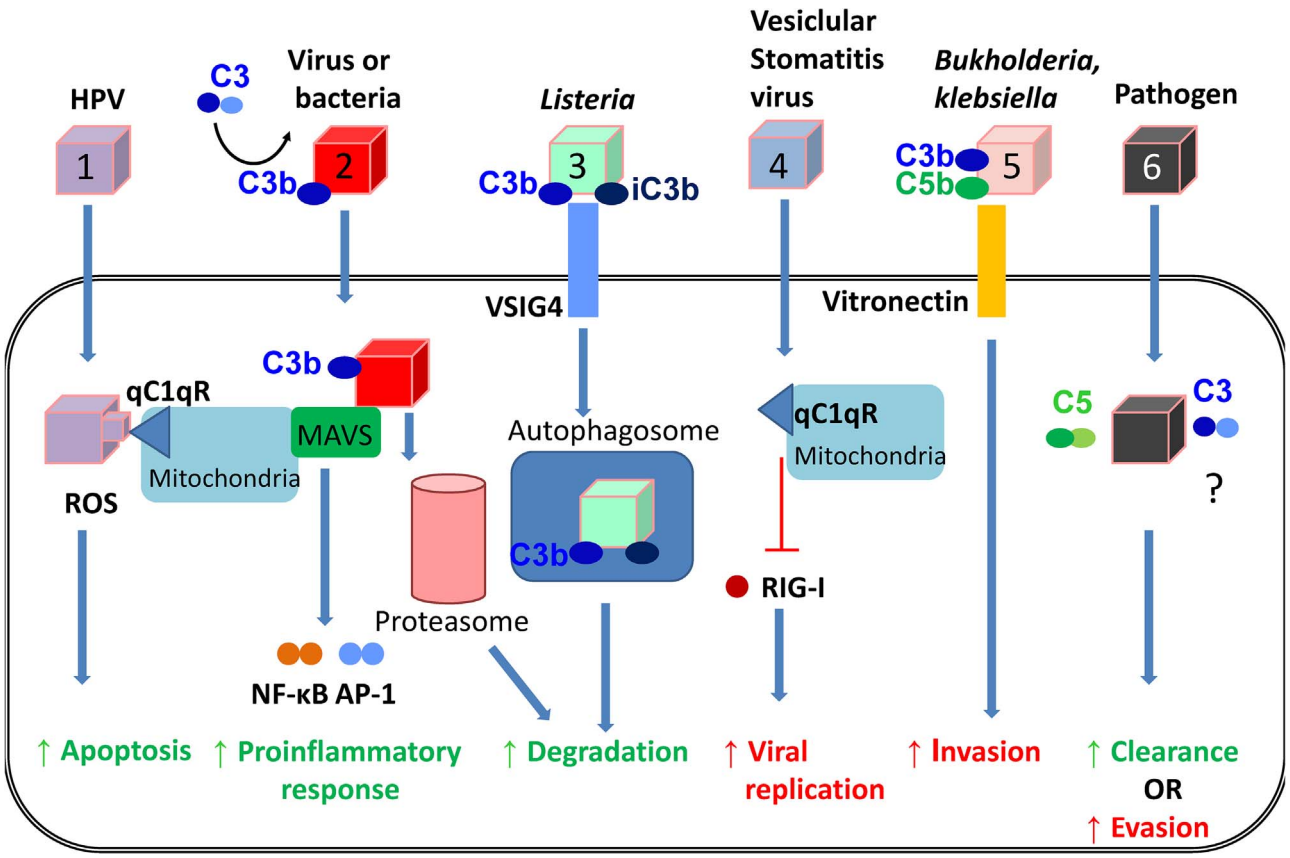

Fig. 2. Suggestions on the potential impact of complosome-derived and/or pathogen-shunted intracellular complement on key cell processes during the host/pathogen interaction. Pathogens trigger an array of responses when interacting with complement during cell infection processes − some of which are beneficial for the microbe and some of which support host protection. For example, infection of human papillomavirus (HPV) triggers globular C1q receptor signaling (gC1qR) which leads to mitochondrial dysfunction and apoptosis (1). Opsonized bacteria trigger mitochondrial antiviral signaling which increases the expression of AP-1- and NF-κB −controlled genes and proinflammatory cytokine responses. C3-opsonized viruses, on the other hand, are targeted for degradation via the proteosome (2). Opsonized *Listeria* is also targeted in an intracellulr complement-dependent fashion for degradation after cell entry through v-set immunoglobulin domain containing 4 (VSIG4)-driven autophagosome formation (3). Supporting viral and bacterial propagation, gC1R signaling on mitochondria was also shown to block retinoic acid-inducible gene I (RIG-I) activation in a process that promoted the replication of vesicular stomatitis virus (4), while opsonized *Klebsiella* and other species use vitronection to gain entry in non-phagocytic cells (5). Although in most of these processes, complement fragments were 'dragged' into the cell by microbes, we propose that there will also be (subsequent) interactions of invading intracellular pathogens with components the complosome, for example C3 and C5 activation fragments (6). In line with the 'scheme' observed for the role of serum-derived complement, we further predict that in some cases the complosome will mediate clearance pf the pathogen while in other cases, it will be utilized by the pathogen to promote its survival.

receptors. This results in reduced B cell activation, proliferation and anti-viral responses (Wang et al., 2016). Importantly, patient-derived HCV binding to B cells can be prevented *in vitro* through blockage of the complement receptors CR1 and CR2. Further investigations are now warranted to elucidate the signaling pathways involved in complement-mediated HCV binding in chronic extrahepatic HCV infection as they may lead to novel anti-viral therapies (Wang et al., 2016). Further, some pathogens such as *Bukholderia pseudomallei* and *Klebsiella pneumonia* were shown to 'highjack' C3 opsonization to gain entry into nonphagocytic and non-immune cells (Tan et al., 2017). In this instance C3 aided the invasion in a vitronectin-dependent manner. Additionally, C5aR1 was shown to associate as heterodimer with the C−C chemokine receptor 5 (CCR5), in a process that can facilitate the entry of the human immunodeficiency virus (HIV) in the host cells (Hüttenrauch et al., 2005). Also, qC1qR was shown to downmodulate RIG-I signaling pathway in PI3K independent fashion promoting vesicular stomatits virus replication during infection of BHK21 hamster kidney cells (Xu et al., 2009). The notion of qC1qR being used by viruses to down-modulate immune responses is supported by studies from Yao and colleagues who showed that HCV core protein interacted intracellularly with qC1qR to suppress ERK/MEK driven T cell proliferation and IL-2 production during HCV infection (Yao et al., 2001).

However, intracellular complement of course also aids in the protection against pathogens: v-set immunoglobulin domain containing 4 (VSIG4) is a transmembrane protein expressed in macrophages and dendritic cells that recognizes C3b and iC3b. It was recently shown to induce efficient killing of C3-opsonized intracellular *Listeria* via formation of autophagosomes (Kim et al., 2016). This notion was further confirmed in various non-immune cell lines where C3-opsonised viruses or bacteria are processed intracellularly and targeted for degradation. In an elegant study by Tam and colleagues, the authors showed that intracellular presence of C3-opsonized pathogens activate NF-κB and AP-1 through induction of the adaptor mitochondrial antiviral signaling (MAVS) (Tam et al., 2014). These transcription factors then mediate a strong proinflammatory cytokine (IL-6, IL-1β, IFN-β) response (Tam et al., 2014). This puts intracellular C3 right at the heart of a major intracellular pathogen sensing machinery and aligns with an earlier study in which C3 induced strong anti-adenoviral response in the livers of infected mice through an NF-κB dependent mechanism (Appledorn et al., 2008).

Also in neutrophils, C3 increased the killing of intracellular *B. Pseudomallei* in and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH-oxidase) dependent manner (Woodman et al., 2012). Another example of complement proteins mediating anti-pathogenic intracellular response in neutrophils is provoded by Li and colleagues. The group observed that MBL-mediated phagocytosis of *Candida albicans* induced dectin-1 expression which in turn triggered ROS production (Li et al., 2012). The globular C1q receptor (qC1qR) was shown to

mediate apoptosis of C33a and SiHa cervical carcinoma cell lines during infection with Human papillomavirus (HPV-16) (Chen et al., 2014). The mechanism proposed by the authors suggested that qC1R induced mitochondrial dysfunction due to excessive ROS production which eventually resulted in apoptosis of HPV-infected cells. Finally, FH was shown to bind to *Mycobacterium bovis* BCG (an intracellular pathogen infecting macrophage and causing tuberculosis) and to inhibit bacterial uptake by the THP-1 macrophage cell line. FH-treated *M. Bovis* induced elevated levels of proinflammatory cytokine secretion particularly in the early stages of infection (Abdul-Aziz et al., 2016).

The findings presented above (summarized in Fig. 2) are likely just scratching the surface of the intricate and undoubtly very complex relationship between the complosome and pathogens. And as already clear now there are complosome activities that can either promote pathogen survival or pathogen clearance − just as has been observed for many decades for serum-circulating complement function (Fig. 2).

9. Concluding remarks and future perspectives

Recent studies have highlighted the emerging important functional connection between autocrine and/or intracellular C3 and C5 activities and the cellular metabolism axis. This new connection involves − at minimum in T cells and monocytes − the activation of NLRP3 inflammasome and has emerged as fundamental to the induction of human Th1 responses. With this 'new angle' of complement activity, it will be of significant interest to now investigate the complex interactions between the complosome and intracellular pathogens in a broad range of cells.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization, M.K., G.A. and C.K; Writing − Original draft, G.A., M.K. and C.K.

Funding

Work in the Kemper laboratory is supported by the MRC Centre grant MR/J006742/1, an EU-funded Innovative Medicines Initiative BTCURE (C.K.), a Wellcome Trust Investigator Award (C.K.), and the King's Bioscience Institute at King's College London (G.A.), the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London, and by the Division of Intramural Research, National Heart, Lung, and Blood Institute, NIH and the intramural research program of NIAID, NIH.

Acknowledgements

The authors would like to acknowledge Prof Peter Garred for coining the term complosome.

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