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Production of complement components by cells of the immune system

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Summary

The complement system is an important part of the innate immune defence. It contributes not only to local inflammation, removal and killing of pathogens, but it also assists in shaping of the adaptive immune response. Besides a role in inflammation, complement is also involved in physiological processes such as waste disposal and developmental programmes. The complement system comprises several soluble and membrane-bound proteins. The bulk of the soluble proteins is produced mainly by the liver. While several complement proteins are produced by a wide variety of cell types, other complement proteins are produced by only a few related cell types. As these data suggest that local production by specific cell types may have specific functions, more detailed studies have been employed recently analysing the local and even intracellular role of these complement proteins. Here we review the current knowledge about extrahepatic production and/or secretion of complement components. More specifically, we address what is known about complement synthesis by cells of the human immune system.

Keywords: cell activation, complement, human

Introduction

The complement system is an ancient cascade of proteins which was first described in the 19th century [1]. The complement system has been described to have many different functions, but especially three main functions have been well documented: opsonisation, chemotaxis and lysis.

The complement system is part of the innate immune defence, and functions as a cascade of proteases that activate each other in an enzymatic fashion. Next to a set of soluble proteins, complement also comprises several membrane-bound complement regulators and receptors. The complement cascade can be activated via three different pathways: the classical pathway (CP), the lectin pathway (LP) and the alternative pathway (AP). These pathways are activated via different recognition molecules. The recognition molecule for the CP is C1q, which upon binding to ligands such as surface-bound immunoglobulin (Ig)M, hexameric IgG or pentraxins, such as C-reactive protein and pentraxin-3, trigger CP activation [2]. Several recognition molecules have been described for the LP, including mannose-binding lectin (MBL), ficolins-1, 2 and 3 and collectins (CL-10, CL-11) [3]. The AP is activated spontaneously via a tick-over activation mechanism, but a role for properdin (FP) has also been proposed [4]. Activation of each of these pathways results in the formation of C3 convertases, C4b2a by the CP and the LP and/or C3bBb via the AP. The C3 convertase cleaves C3 into C3a and C3b, where C3a serves as a chemoattractant and C3b serves as an opsonin. C3b becomes bound covalently to its target via its thioester, which binds to amine and carbohydrate groups on the activating surface. When a threshold of activation is reached and another C3b binds to the C3-convertase, the C5-convertase is formed. The C5-convertase will cleave C5 and this initiates the terminal pathway, resulting in the generation of C5a and a multimeric complex called the membrane attack complex (MAC) C5b-C9, which eventually can cause lysis of cells [5] (Fig. 1).

Apart from these traditional activities of the complement system in attacking invading pathogens, it has become clear that its effector functions extend to instruction of the adaptive immune system and to several physiological processes. A large part of these effects are translated into cellular effector functions via a set of complement receptors (CR) specific for proteolytically cleaved

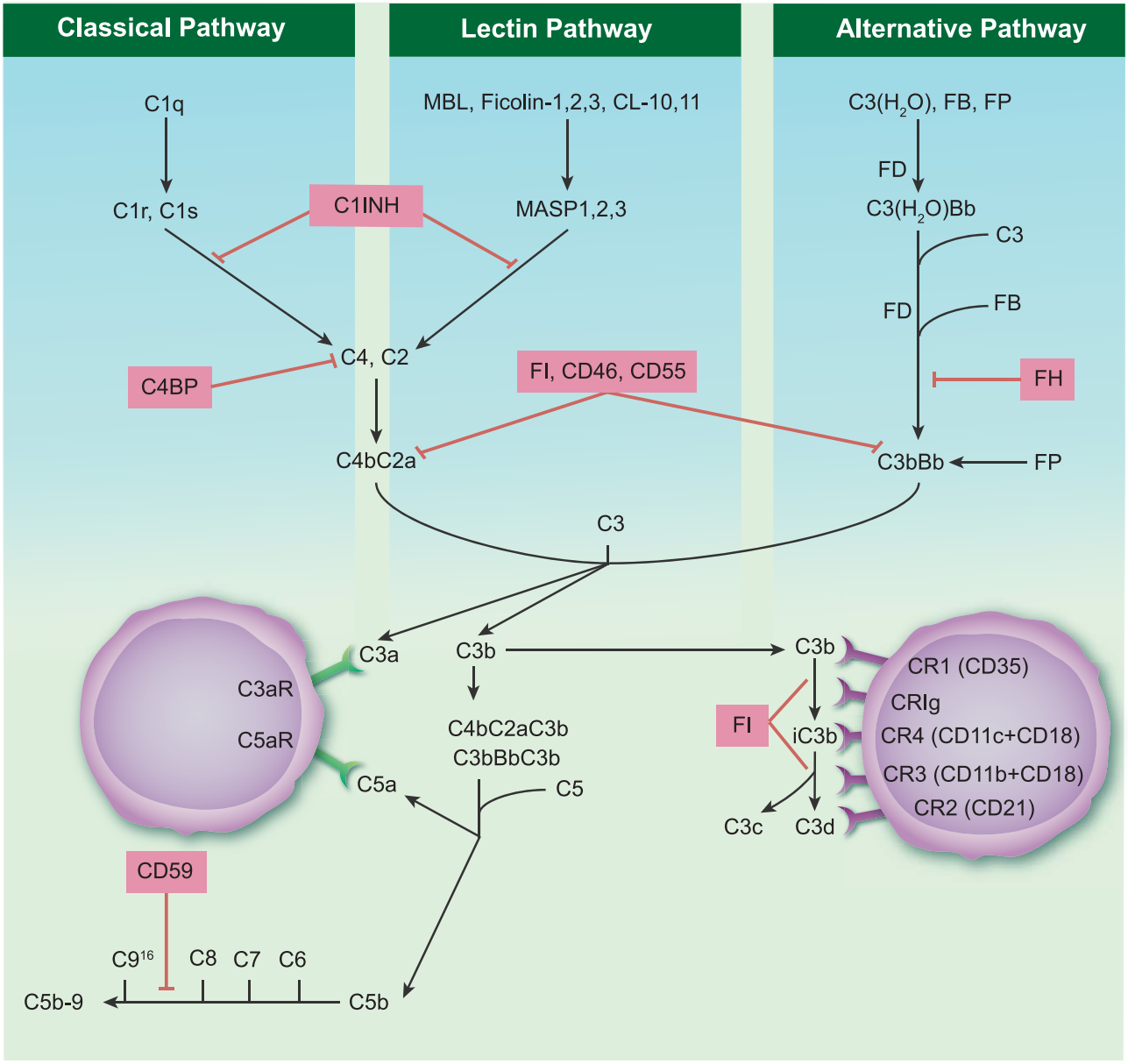

Fig. 1. Schematic representation of the complement system. The complement system can be activated via three different pathways: the classical pathway (CP), the lectin pathway (LP) and the alternative pathway (AP). These pathways have their own sequential manner in forming a C3 convertase: C4b2a or C3bBb. These C3 convertases cleave the central component C3 generating two activation fragments, C3a and C3b. The C3a is able to bind its anaphylatoxin receptor the C3aR, whereas C3b can opsonize a target membrane. C3b and its further degradation products, iC3b, C3c and C3d/C3dg are able to bind various complement receptors (CRs). Additionally, C3b can bind to the former C3 convertase which then results in formation of the C5 convertase: C4bC2aC3b or C3bBbC3b. The C5 convertase cleaves C5 in two activation fragments C5a and C5b. C5a can bind to its anaphylatoxin receptors C5aR1 and C5aR2, whereas C5b marks the start of the formation of the membrane attack complex (MAC). In a sequential manner C5b, C6, C7, C8 and up to 16 molecules of C9 bind together to form a MAC. Various inhibitors of this system are marked in pink boxes. MBL = mannose binding lectin; MASP = MBL-associated serine protease; FB = factor B; FP = factor P; FD = factor D; FH = factor H; C1INH = C1 inhibitor; FI = factor I (FI), C4BP = C4b-binding protein; CR = complement receptor.

complement fragments. CR1 (CD35) is both a complement receptor for C3b, iC3b and C4b and a complement inhibitor, by competing with factor B (FB) for C3b binding and by functioning as a co-factor for factor I (FI) [6]. CR2 (CD21) binds iC3b, and especially C3d/C3dg, CR3 (MAC-1, CD11b/CD18) binds iC3b and C3d/C3dg, whereas CR4 (gp150/95, CD11c/CD18) binds only iC3b [7–12]. Another complement receptor, complement receptor of the immunoglobulin superfamily (CRIg), binds to C3b and iC3b and also to soluble C3c [13,14].

Several receptors have also been described for C1q; however, the relative contributions of these receptors and their functions is not yet resolved [15–18]. Next to receptors for the complement opsonins, a set of receptors can also be triggered by the anaphylatoxins, C3a and C5a. One receptor is known for C3a, the C3aR, and for C5a two receptors are identified; C5aR1 (CD88) and C5aR2 (Fig. 1). The different cellular expression profiles of these receptors are outlined below.

Next to activators, the complement system comprises both fluid phase and membrane-bound regulators to keep complement activation in check. C1-inhibitor (C1INH) is a circulating complement regulatory protein which can inactivate C1r, C1s, MBL-associated serine protease (MASP)-1 and MASP-2, thereby preventing/limiting complement activation via both the CP and the LP. C4b-binding protein (C4BP) acts as an inhibitor by accelerating the decay of the C3 convertase and is a co-factor for FI-mediated cleavage of C4b and C3b. FH serves as a co-factor for FI-mediated cleavage of C3b/iC3b in a similar manner. Next to a role as a co-factor, FH also functions as a decay accelerator. Besides the full-length FH, a truncated splice variant FH-like 1 exists, and other complement FH-related proteins have been found, of which the functions are just recently being explored [19]. For the membrane-bound regulators of complement, CD46 or membrane co-factor protein (MCP) serves as a co-factor for FI; additionally, CD46 can bind the C3 activation fragments. CD55, a decay accelerating factor (DAF), accelerates the decay of C3 convertases. Finally, CD59 or protectin inhibits the binding of C9 to the C5b-8 complex, thereby preventing the last step needed for MAC formation [20]. These-membrane bound regulators, CD46, CD55 and CD59, are expressed on all circulating cells, including all the cell types addressed in this review [21]. It is conceivable that the expression of abundant membrane-bound complement inhibitors is necessary to protect these immune cells from the high levels of complement in circulation or in the local environment where they reside.

Complement has been considered mainly in the systemic compartment, and serum levels of most components of the complement system, including C3, C4 and MBL, are produced by hepatocytes [22,23]. Other tissues also contain cells capable of complement production; for example, endothelial and epithelial cells are also able to secrete various complement components [24], thereby contributing to local processes (Fig. 2). However, for C1q, FP and factor D (FD) it has been shown that the major/only site of production is outside the liver [24–30]. Additionally, there is a growing body of evidence that local secretion of complement proteins plays an important role in regulating physiological processes even in the absence of further complement activation. C1q also has effector functions that are outside the scope of traditional complement activation. For example, C1q exerts effects during pregnancy (where it is involved in remodelling of the maternal decidua), embryonic development, coagulation processes and neurological synapse function, which has been reviewed by Nayak *et al.* [31]. In the tumour microenvironment, C1q can also serve as a tumour-promoting factor by favouring cell adhesion, migration and proliferation independently of complement activation [32]. Finally, a new dimension has been provided by the observation that there might even be an intracellular role for complement and complement activation. The importance of intracellular processing of C3 by cathepsin-L (CTSL), where the intracellularly produced C3a was involved in the mTOR phosphorylation pathway in $CD4^+$ cells, was first shown by Liszweski *et al.* [33]. Furthermore, Garbore *et al.* described intracellular signalling by the C5aR1 in $CD4^+$ cells which was required for NLRP3 assembly [34].

Altogether, it is clear that it is important to look at complement outside its traditional functions. Complement can have an important role in immune regulation, and immune cells have been identified as an additional source for local complement activation. In this review we focus on the extrahepatic complement production and more specifically complement proteins expressed and/or secreted by various human immune cells and discuss its functional implications. We focus on the proteins for which evidence is available that they are actually produced. Lack of production is interesting, but scientifically difficult to prove, and therefore we refrain from strong statements on the absence of certain complement proteins in specific immune cells.

Polymorphonuclear leucocytes

Polymorphonuclear leucocytes (PMNs) are the most abundant leucocytes in blood and accumulate quickly at sites of infection, and may therefore be important for the production of local inflammatory mediators such as complement proteins. Stimulated PMNs were reported to secrete C3 with an intact thioester and it was speculated that the PMN-derived proteases, which are also released locally, can subsequently activate this newly secreted C3 [35,36]. Neutrophils not only store C3 but also FP, the only complement regulator that enhances complement activation, which can be secreted upon stimulation [30,35,37]. Besides the release of C3 and FP, FB was also demonstrated to be secreted upon activation of neutrophils [38]. Locally released FP, FB and C3 could provide a local platform for further complement activation via the AP. Based on liver and/or bone marrow transplantations, using organs from individuals with differences in the C7 M/N genetic variant, it was found that a substantial part of serum C7 was not derived from the liver [39,40]. PMNs were found to be of importance for the C7 serum levels when comparing the C7 content

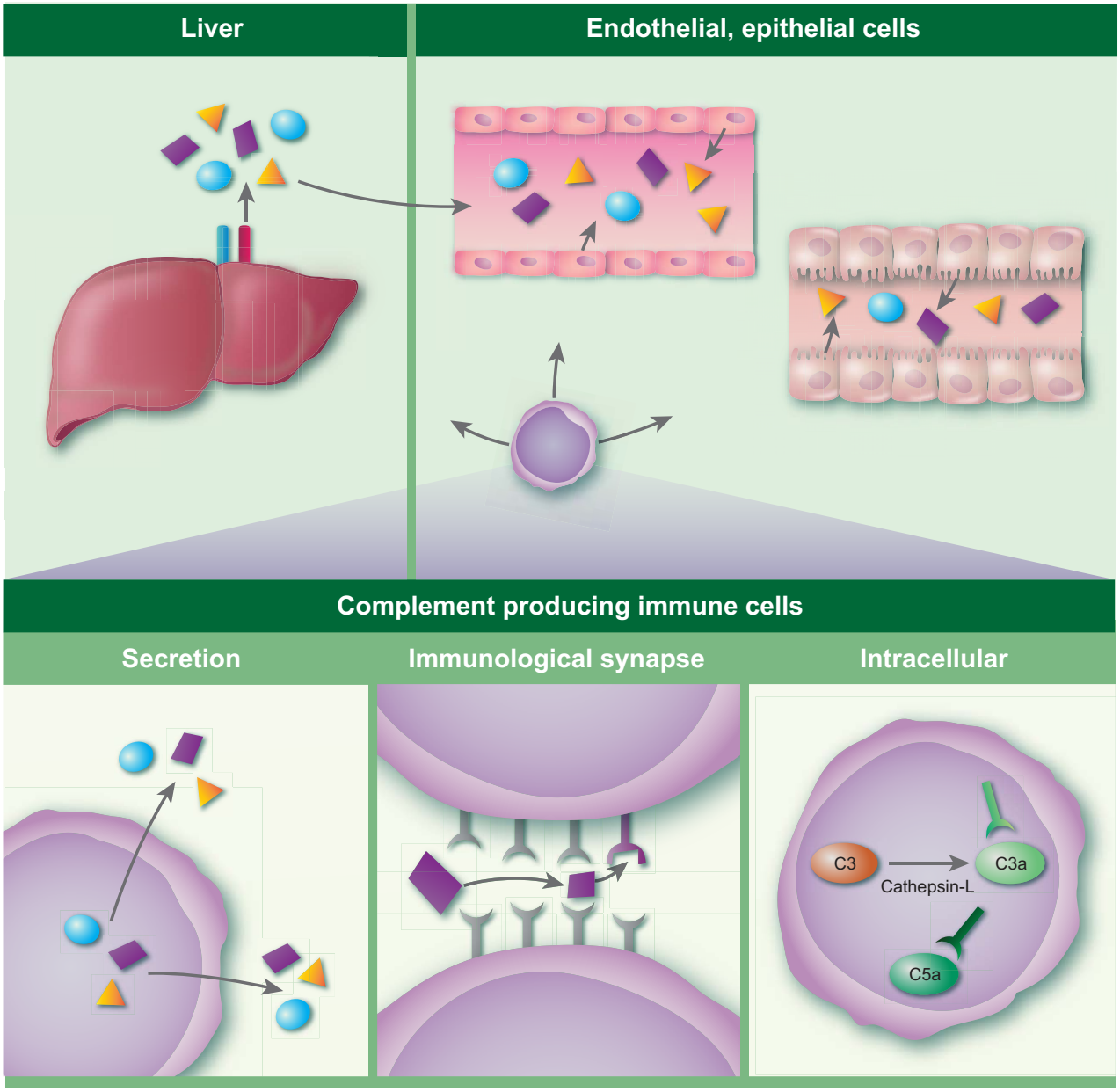

Fig. 2. Production of complement proteins occurs in different tissues and by different cell types. Several sites are depicted in the figure, on the top left by hepatocytes in the liver, on the top right by endothelial and epithelial cells. In this review we focus on the production of complement proteins by immune cells, as illustrated in the bottom panel. Immune cells can secrete complement proteins, respond to complement proteins in the immunological synapse and more recently intracellular functions for complement proteins have been proposed.

between PMN and PBMCs [41]. Furthermore, it was found that C6, next to C7, also belonging to the terminal pathway of complement activation, was also secreted by PMNs [41]. M-ficolin/ficolin-1, which is an activator of the LP pathway, was shown to be localized in secretory granules of neutrophils [42]. PMNs express a wide array of complement receptors on their cell surface, including CR1, CR3, CR4, C3aR and C5aR [43–45]. The production of complement proteins by each of the immune cells is summarized in Table 1.

Mast cells

Mast cells (MC) are known mainly for their role in inflammatory and allergic responses, where they release potent inflammatory mediators upon stimulation through IgE receptors. From mast cells different subsets exist, which are often classified based upon the presence of the serine proteases tryptase and chymase. It was demonstrated that different subsets of MC express C5 and C3 [46,47]. Human skin mast cells showed a diffuse cytoplasmic labelling of both C3

Table 1. Summary of complement protein synthesis/secretion by various immune cells

	Classical		Lectin		Alternative		Terminal	
PMN			Ficolin-1	(42)	C3, FB, FP	(30, 35–38)	C6, C7	(41)
Mast cell	C1q	(52)			C3	(46, 47)	C5	(46, 47)
Monocyte	C1q, C1r, C1s, C4, C2	(26, 28, 57–59)			C3, FB, FD, FP	(24, 59–64)	C5, C6, C7, C8, C9	(24, 65)
Macrophage	C1q, C1r, C1s, C4, C2	(72–77, 79)			C3, FB, FD, FP	(73, 74, 77–79)	C5	(73, 74)
Dendritic cell	C1q, C1r, C1s, C4, C2	(25, 85, 88)			C3, FB, FD, FP	(86-88)	C5, C7, C8, C9	(86-88)
Natural killer cell								
B lymphocyte							C5	(99)
T lymphocyte					C3, FB, FD, FP	(101–105)	C5	(102)

	Regulators soluble		Regulators membrane-bound		Receptors	
PMN			CD46, CD55, CD59	(21)	CR1, CR3, CR4, C3aR, C5aR1	(43–45)
Mast cell			CD46, CD55, CD59	(50)	CR1, CR4, C3aR, C5aR1	(47, 49–51, 53, 54)
Monocyte	C1INH, C4BP, FH, FI	(59, 62, 67)	CD46, CD55, CD59	(21)	CR1, CR3, CR4, C3aR, C5aR1	(45, 68–70)
Macrophage	C1INH, FH, FI	(73, 74, 77)	CD46, CD55, CD59	(80, 81)	CR1, CR3, CR4, CRIg, C3aR, C5aR1, C5aR2	(14, 44, 70, 82–84)
Dendritic cell	C4BP, FH, FI	(86–88)	CD46, CD55, CD59	(80, 88, 89)	CR1, CR3, CR4, CRIg, C3aR, C5aR1	(87, 88, 90)
Natural killer cell			CD46, CD55, CD59	(21)	CR3, CR4, C3aR, C5aR1, C5aR2	(91, 92)
B lymphocyte			CD46, CD55, CD59	(21)	CR1, CR2, CR4, C5aR1	(93–96, 99)
T lymphocyte			CD46, CD55, CD59	(21)	CR1, C3aR, C5aR1	(100, 109)

PMN = polymorphonuclear; FB = factor B; FP = factor P; FD = factor D; FH = factor H; C1INH = C1 inhibitor; FI = factor I; C4BP = C4b-binding protein; CR = complement receptor. We have only indicated the proteins for which evidence is available that they are actually produced. Lack of production is scientifically difficult to prove, and therefore we have not included lack of production in the table.

and C5. The basal secretion of C3 by MCs can be up-regulated with various cytokines [tumour necrosis factor (TNF)-α with interleukin (IL)-4 or IL-13] [46]. Laufer *et al.* investigated Crohn's disease and with *in-situ* hybridization found C4 mRNA but not C3 mRNA in mast cells in both normal and diseased intestines [48]. Both tryptase and chymase are able to cleave C3, and as a consequence the locally secreted C3 can be activated by the MC enzymes and give rise to C3a. C3a is a powerful anaphylatoxin, which can bind to the C3aR present on surrounding cells or exert an autocrine effect on MCs. In this setting, the MC-derived C3 has a role in the periphery which is independent from the conventional complement pathways [47,49]. Besides the C3aR, skin MC also express C5aR1, whereas MC from lung, uterus or tonsils do not express C5aR [50,51]. Furthermore, Schaarenburg *et al.* showed recently that functionally active C1q is produced by MCs generated *in vitro* from $CD34^+$ progenitor cells. Additionally, skin MCs were stained for C1q and the MCs were positive for C1q both in normal and in diseased conditions [52]. Human mast cells express CR1 and CR4 [50,53,54], and murine data suggest that mouse mast cells also express CR2 and CR3 [55,56].

Monocytes

Monocytes are the circulating precursors of tissue macrophages and subsets of dendritic cells (DCs). Monocytes produce a broad range of complement components belonging to several complement pathways, and this has been studied extensively. The whole C1 complex can be assembled locally, as C1q, C1r and C1s are secreted. Additionally, C2 and C4, which are also part of the CP, have been shown to be secreted by monocytes [26,28,57–59]. Monocytes also secrete various AP components as C3, FB, FD and FP [24,59–64]. Moreover, the terminal pathway components C5, C6, C7, C8 and C9 are secreted, which are able to assemble as MAC [24,65]. For the recognition molecules of the LP there is less evidence of local production by monocytes; however, it was shown that monocytes have intracellular M-ficolin and in synovial fluid of RA patients there was a correlation between M-ficolin and the total number of blood monocytes [42,66]. Several control proteins are also secreted by cultured monocytes, such as FH, FI, C4BP and C1INH [59,62,67]. Monocytes express receptors for both C3a and C5a: C3aR and C5aR1, respectively [45,68,69]. Besides the receptors for these anaphylatoxins, monocytes can also respond to C3b and iC3b via CR1, CR3 and CR4 [70]. Taken together, monocytes can produce practically the full array of complement proteins. The complement system and monocytes (and the derived macrophages and DCs) are integrated on several levels, making them significant partners that interact with each other to bridge the innate and adaptive immune response.

Macrophages

Macrophages are tissue-resident phagocytes that have differentiated from monocyte precursors. The complement system and macrophages have close interactions; as part of the traditional functions of the complement system to attract cells by chemotaxis and opsonize pathogenic surface by tagging the surface with C3b, macrophages are capable to respond to the chemotaxis and of clearing pathogens or apoptotic and necrotic cells by phagocytosis [71]. Early research has focused upon guinea pig and murine macrophages, where a wide variety of complement components are found to be expressed and/or secreted. However, in these original papers a clear distinction is not always made between monocytes and macrophages, but a wide variety of complement syntheses has been described. For human macrophages, the CP proteins C1, C1q, C1s, C2 and C4 are found for the AP C3, FB, FD and for the terminal pathway C5. Regulators are also secreted, such as FH, FI, FP and C1INH [72–76]. With human mononuclear phagocytes from synovial fluid of RA patients, it was demonstrated that these cells were able to synthesize C2, FH, FI, FD, FP and FB, which were functionally active in a haemolytic assay. C3, C4 and C5 were also detected, but appeared to be inactive [77]. For human macrophages, it has been described that they are able to secrete C2, C3 and FB. For C3 it was shown that the biosynthesis was increased by stimulating the macrophages with acetylated low-density lipoprotein, oxidized low-density lipoprotein, IgA or IgG immune complexes [78,79]. Macrophages cultured from isolated peripheral blood monocytes express complement regulators as CD46, CD55 and CD59 [80,81]. A wide array of complement receptors has been detected on the surface of macrophages, the anaphylatoxin receptors C3aR, C5aR1 and C5aR2 [44,82,83] and the CR1, CR3 and CR4 [70]. The opsonin receptor CRIg is expressed on various tissue resident macrophages such as Küppfer cells [14,84]. To what extent different macrophage subsets, proinflammatory *versus* anti-inflammatory, differ in their capacity to produce and secrete specific complement proteins remains to be established firmly.

Dendritic Cells

DCs are antigen-presenting cells (APC) which function at the interface of innate and adaptive immunity. DCs are present in various tissues, where they reside as immature DCs with a high phagocytic capacity. Once they receive maturation signals they migrate to the draining lymph node and gain the ability to activate T cells. Most research concerning complement production by DCs is performed *in vitro*. DCs are generated from isolated monocytes from the blood and are then cultured towards DC phenotype (moDC). In their immature state DCs are able to produce functionally active C1q; however, upon stimulation [TNF-

α, lipopolysaccharide (LPS) or CD40L], which results in the maturation of these DCs, they lose their ability to produce C1q [25]. However, there are conflicting data regarding whether the C1q production remains intact after maturation of moDCs [85]. DCs present in human tissue stain positive for C1q [25,85]. DCs are also able to synthesize C3, FI, FB, C4BP, C7 and C8 [86,87]. Moreover, it was shown that moDCs expressed C1q, C1s, C1r, C2, C3, C4, C5, C8, C9, FB, FD, FI, FH and FP at the mRNA level, and protein expression was confirmed for all except FI by using flow cytometry, Western blot and/or enzyme-linked immunosorbent assay (ELISA) [88]. moDCs have been shown to produce various functional complement components, and they additionally express complement regulators CD46, CD55 and CD59 [80,88]. Importantly, transient down-regulation of CD55 during APC–T cell interaction has been identified as an important mechanism to allow local complement activation [89]. Other membrane-bound proteins found on the moDCs are several complement receptors, namely CR1, CR3, CR4, CRIg, C3aR and C5aR1 [87,88]. Differences in CR expression have been observed depending on the maturation state of the DC. Immature DCs have low expression of CR1 which disappears upon maturation, whereas CR2 is not found on either immature or mature DCs [90]. Follicular DCs (FDCs) express high levels of CR2. However, although these cells play an important role in the adaptive immune response, particularly by presenting intact antigens to B cells, these cells are not derived from monocytes and are not 'conventional' DCs.

Natural killer (NK) cells

NK cells are cytotoxic innate immune cells that respond mainly to virally infected cells and tumour cells. Regarding the NK cell–complement interaction, it is known that there is extensive cross-talk via several complement receptors and complement fragments. NK cells express several complement receptors as C3aR, C5aR, C5aR2, CR3 and CR4. The expression of these receptors was based on both gene expression and protein expression as analysed by flow cytometry. C5aR1 and C5aR2 protein expression has been reported so far only in $CD56^{+}CD3^{-}$ cells upon permeabilization [91,92]. Therefore, NK cells can act upon complement factors such as C3a, C5a and C3b and its further degradation products iC3b and C3d. However, to our knowledge it has not been studied whether complement factors such as C3 or C5 can be generated and secreted by the NK cell itself.

B cells

The B cells produce antibodies as part of the adaptive immune response. The secreted IgG and IgM antibodies have, upon binding to their target, the capacity to activate the classical pathway by binding C1q [2]. While it is still unclear how many complement proteins are produced by B cells, it is well known that C3-activation products interact via CRs on B cells. Opsonization of an antigen by (i)C3b/C3d results, via CR2, in stimulation of the B cells, which results subsequently in a lowered threshold to produce antibodies [5,93,94]. Besides the well-studied CR2 and C3d interaction, B cells also express CR1 and CR4 which recognize C3b and its degradation product iC3b [95,96]. Synthesis of the separate complement components by B cells has been less well studied. Several B cell lines are positive for C5 when analysing cell lysates and for some B cell lines secreted C5 was also detectable in culture supernatant [97]. Raji cells are able to synthesize FH and FI [98]. Tonsillar B cells were shown to express C5aR1 in part of the memory and naive B cells while germinal B cells were found to be negative [99]. Additionally, both mRNA and protein C5 expression was found in naive, memory and germinal centre B cells [99].

T cells

T cells are an important subset of lymphocytes which are required for proper functioning of the adaptive immune response. Complement has been considered more recently to be involved in both the homeostasis and the effector functions of the T cell. In cognate T cell and APC interactions the locally produced C3a and C5a are able to bind to their respective receptor on the T cell membrane, which subsequently stimulates the effector functions and maintains the viability of the T cell [100]. The T cell itself can produce complement components upon activation via T cell receptor (TCR) and CD28, which results in induced protein expression of C3, C5, FB and FD [101–104]. Moreover, FP from the AP is expressed by various T cell lines and T cells from peripheral blood [105]. Furthermore, it was demonstrated that T helper type 1 (Th1) induction, and not Th2, depended upon T cell-produced C3 cleavage fragments, as was shown by using T cells from $C3^{-/-}$ donors and the earlier observation that not serum-derived C3 but T cell-derived C3 was needed for CD46 activation [106,107]. In T cells, CD46 is not solely a co-factor for complement regulation; it also functions as a co-stimulatory molecule for CD3 and is able to induce proliferation to levels that are comparable to CD28 stimulation [108]. Next to CD46, CR1 is also expressed by T cells [109]. $CD4^{+}$ cells not only secrete C3 but also seem to contain intracellular C3 and C3a, where the C3 is cleaved by CTSL in a tonic manner. This intracellular C3a is subsequently able to bind the intracellular C3aR and signals via mTOR [33]. Besides intracellular C3aR, a role was assigned more recently to intracellular C5aR1 cells in $CD4^{+}$ cells by Arbore *et al.* [34].

Intracellular complement activation

The paradigm that complement solely affects the extracellular space has been challenged quite recently. It was demonstrated by Liszewski *et al.* that $CD4^+$ T cell have intracellular stores of C3 and C3a, but also that C3a is generated intracellularly by CTSL. Subsequently, the newly generated C3a is able to bind to the intracellular C3aR, where it is linked towards a survival mechanism mediated by mTOR [33]. It is suggested that the intracellular C3 phenomenon that was observed is not exclusive to the $CD4^+$ T cells, but C3/C3a stores were also found in both other immune cells and non-immune cells. Furthermore, it was reported recently that FH can be internalized by apoptotic cells (Jurkat T cells), where it did not become degraded but instead could bind directly to CTSL. The FH was then able to function intracellularly as a co-factor for CTSL-mediated cleavage of C3. Therefore, the authors hypothesized that this could be a consequence of FH binding to both CTSL and C3, hence bringing them into proximity with each other [110]. Besides a role for intracellular C3 and C3aR, it was reported that there is also a role for intracellular C5 and C5aR1 in human T cells. It was hypothesized that the NLRP3 inflammasome in T cells receives signals via intracellular engagement of C5aR1, which increases the expression of *IL1B* and induces the production of reactive oxygen species (ROS), thereby activating the inflammasome [34]. It therefore appears that more complement components are involved in intracellular processes. This new concept for intracellular complement has been referred to by Kolev *et al.* as the 'Complosome' [111]. These newly discovered functions for complement components open up exiting new opportunities to endeavour.

Discussion

The complement system has long been thought to be a system that solely attacks invading pathogens. We now know that the complement system comprises more functions than the conventional chemotaxis, opsonization and lysis. It interacts on many levels with various cell types, and various complement proteins exert functions that are independent from activation of the complement cascade. For example, the hierarchical association of deficiencies of the classical pathway with the risk to develop systemic lupus erythematosus (SLE) is striking. C1q deficiency provides the largest risk, while in C1r/s deficiency the risk is somewhat lower. In C4 and C2 deficiency the risk is even less, and C3 deficiency is not a very strong risk factor for SLE [112,113]. If all effects of C1q could be mediated via activation of the CP, then all deficiencies should have the same risk. Clearly, different proteins have different functions that are partially independent from their role in the complement pathways.

The bulk of the complement proteins that are present in serum are produced and secreted by the liver, in particular by hepatocytes. However, serum does not reach all sites in the body where complement activation is needed. Therefore, there are also cells that produce complement proteins locally at those serum-restricted sites. Local complement production and activation play a role in the initiation phase of the immune response. This activation impacts upon the permeability of the local vasculature that subsequently will allow more systemic plasma proteins to leave the vessel and contribute to, or even take over, the initial local response. In this review, we have now addressed the local production of complement by the different cells of the immune system (Table 1).

From several cell types, such as the monocytes, macrophages and the DC, their complement secretion is well studied and these cells seem to possess the capacity to produce locally all proteins needed to form fully functioning complement pathways. Conversely, for other cell types the repertoire of complement proteins that is produced is less well documented. Secretion of the recognition molecules of the LP by immune cells is hardly addressed. The same holds true for the NK cells, where the focus seems to have been on expression of complement receptors. Other innate immune cells such as eosinophils and basophils have also not been studied elaborately regarding complement secretion.

Local complement production not only adds to the total pool of complement proteins that circulates, but influences other local processes via paracrine or autocrine interactions. An important example is the production, targeted secretion and local activation of complement in the T cell–DC synapse [89]. Another exciting example is the production and intracellular activation of C3 and C5 as recently reported to be operational in human T cells [33,34].

Taken together, it seems that various immune cells have the capacity to form fully functioning complement pathways in their own environment. This is especially of importance for sites where the access to serum complement is initially restricted. Because of the existence of additional C3/C5 cleaving enzymes, local secretion of C3 and C5 and the expression of the anaphylatoxin receptors, various cells are capable of creating an environment that is needed for autocrine stimulation with complement proteins which acts independently of the traditional complement cascade.

Now that complement targeting therapies are becoming available for use in the clinic it will be interesting to see how such drugs impact upon systemic *versus* local complement activation. These drugs, often applied intravenously, will target mainly the circulating pool of complement. While animal models using complement-deficient mice may have indicated an essential role for complement in pathogenesis, it may now emerge that the intracellular/autocrine/paracrine complement activation is not targetable easily by complement drugs that are administered

intravenously. Exciting work lies ahead, where the relative importance of locally produced complement *versus* systemically delivered complement will be unravelled further.

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Disclosure

The authors declare no conflicts of interest for this paper.

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