



## REVIEW

# Mast cells and complement system: Ancient interactions between components of innate immunity

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**Abstract**

The emergence and evolution of the complement system and mast cells (MCs) can be traced back to sea urchins and the ascidian *Styela plicata*, respectively. Acting as a cascade of enzymatic reactions, complement is activated through the classical (CP), the alternative (AP), and the lectin pathway (LP) based on the recognized molecules. The system's main biological functions include lysis, opsonization, and recruitment of phagocytes. MCs, beyond their classic role as master cells of allergic reactions, play a role in other settings, as well. Thus, MCs are considered as extrahepatic producers of complement proteins. They express various complement receptors, including those for C3a and C5a. C3a and C5a not only activate the C3aR and C5aR expressing MCs but also act as chemoattractants for MCs derived from different anatomic sites, such as from the bone marrow, human umbilical cord blood, or skin in vitro. Cross talk between MCs and complement is facilitated by the production of complement proteins by MCs and their activation by the MC tryptase. The coordinated activity between MCs and the complement system plays a key role, for example, in a number of allergic, cutaneous, and vascular diseases. At a molecular level, MCs and complement system interactions are based on the production of several complement zymogens by MCs and their activation by MC-released proteases. Additionally, at a cellular level, MCs act as potent effector cells of complement activation by expressing receptors for C3a and C5a through which their chemoattraction and activation are mediated by anaphylatoxins in a paracrine and autocrine fashion.

**KEYWORDS**

C3aR, C5aR, inflammation, innate immunity, urticaria

## 1 | INTRODUCTION

The ability of the complement system to fight infections was revealed soon after its discovery.<sup>1</sup> Through time, more functions and activation

mechanisms mediated by soluble and cell surface components of this system were discovered.<sup>1</sup> Subsequently, regulatory molecules involved in homeostasis and protection of self cells were introduced one by one.<sup>1</sup> Tracing the evolutionary emergence of complement has

**Abbreviations:** AP, Alternative pathway; BMDC, Bone marrow-derived mast cells; C4BP, C4b-binding protein; CCP, Complement control protein; CRIg, Complement receptor of the immunoglobulin superfamily; DAF, Decay-accelerating factor; FDC, Follicular dendritic cell; FP, Properdin; GPCR, G-protein-coupled receptor; iDC, Immature dendritic cells; LP, Lectin pathway; MASP, Mannose-binding lectin-associated serine protease; MBL, Mannose-binding lectin; MC, Mast cell; MCRPs, Membrane-bound complement regulatory proteins; PCA, Passive cutaneous anaphylaxis; RBC, Red blood cell; SCR, Short consensus repeat.

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revealed that the system was first formed in sea urchins in the shape of a primary system similar to contemporary alternative pathway.<sup>2</sup> Moreover, several complement components belonging to the alternative and lectin pathways have been traced in jawless fish.<sup>3</sup> Close homologs of complement C3 have been found even in mosquitoes, where they are part of a primitive system combining host defense and coagulation systems.<sup>4</sup> The complement system is based on the recognition molecules that are activated via the classical pathway (CP) (C1q as the recognition molecule), the alternative pathway (AP) (also called the amplification pathway), and the lectin pathway (LP). In the LP, the recognition molecules are the mannose-binding lectin (MBL) and ficolins (Ficolins 1, 2, and 3).<sup>5,6</sup> Interaction between complement receptors expressed by immune cells with their ligands mediates diverse functions, such as metabolic activation, antibody production, antigen-uptake, phagocytosis of pathogens, and clearance of immune complexes<sup>7</sup> (Figure 1). The receptors for the anaphylatoxins C3a and C5a have an entirely distinct set of activities in generating inflammation (see below). Although the liver is the main producer of complement proteins, including C3 and C5, the extrahepatic production of these proteins by a variety of cells, mainly macrophages, dendritic cells (DCs), fibroblasts, epithelial cells, endothelial cells, keratinocytes, and MCs, has also been well documented.<sup>8</sup> These cells produce complement proteins of the classical pathway (including C1q, C1r, C1s, C4, and C2) and alternative pathway (C3, FB, FD, P, and FH). To defend themselves against complement attack, express membrane-bound complement regulators such as CD46, CD55, and CD59.<sup>5</sup> Activation of the complement cascade occurs at the site of inflammation, where typically also MCs accumulate. The chemoattractant nature of C3a and C5a for MCs explains their accumulation at these sites. MCs amplify this cross talk by producing complement proteins and activating them via their released tryptase.<sup>9,10</sup> Chymase after being released from MCs degrades C3 that results in generation of C3a that exerts biological functions on MCs mainly chemoattraction and activation.<sup>10</sup> Interestingly, *in vitro* exposure of recombinant human chymase to C3a may result in degradation of anaphylatoxin, therefore inactivation of C3a suggesting that MC-released chymase may even have a role in regulation of C3a biofunction on MCs.<sup>10</sup> It also has been reported to act on other products of C3 degradation such as vessel wall C3c.<sup>10</sup> The expression of complement receptors by MCs links them to the pathogenesis of both allergic disorders and nonallergic inflammatory reactions with potentially hazardous consequences. MCs in various locations can have different functional properties. For instance, the majority of MCs residing in the lungs are of the connective tissue subtype without C3aR expression, while MCs with C3aR expression infiltrate the mucosal layer of the bronchial tree.<sup>11</sup>

## 2 | COMPLEMENT SYSTEM AT A GLANCE

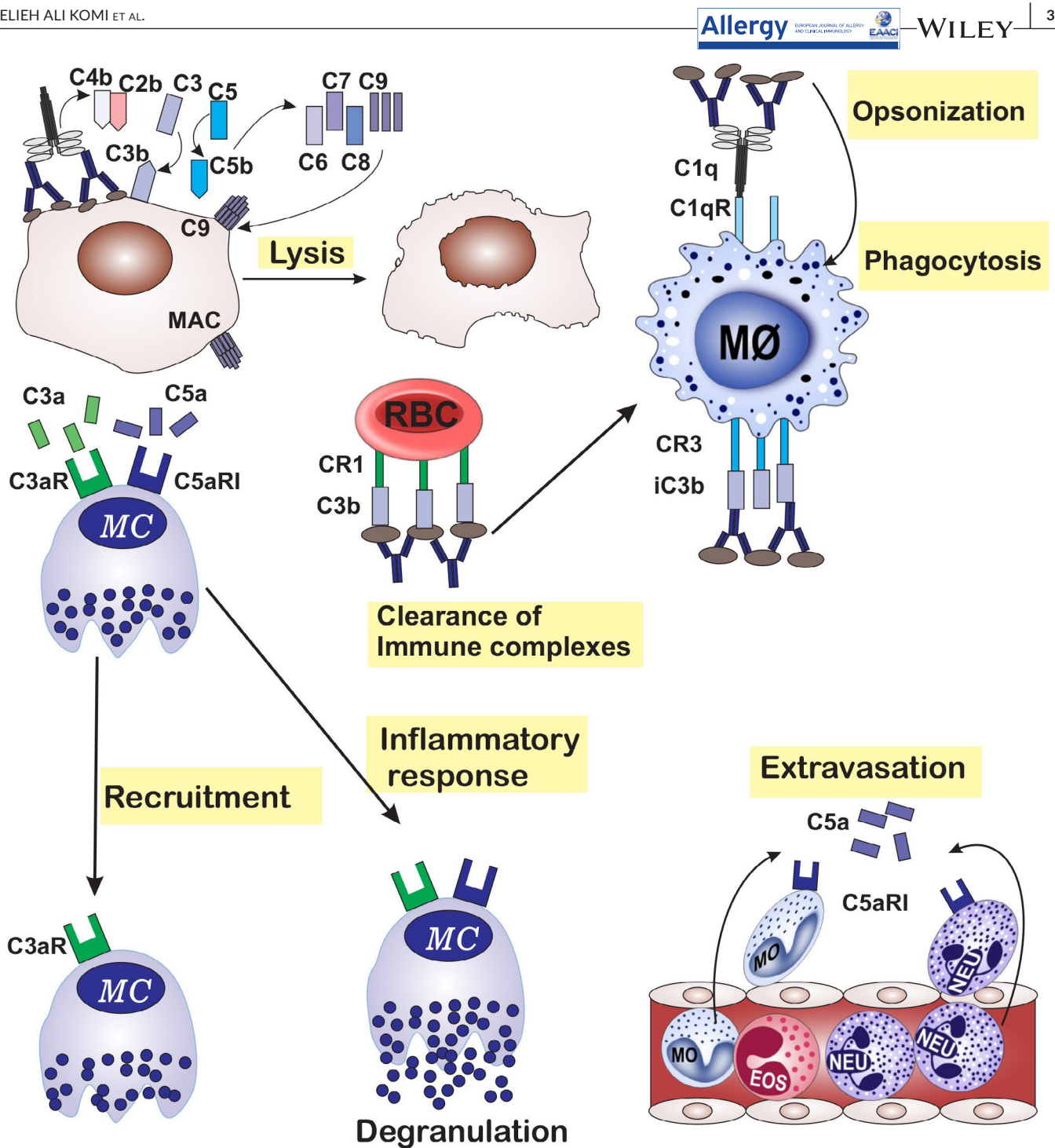
### 2.1 | Pathways and mechanisms of action

The first recognition molecule of the classical pathway, C1q, is a polymer of 6 subcomponents with globular heads and collagenous

tails. Each subcomponent contains 3 polypeptide chains (A, B, and C) to create a 462 kDa assemblage of 18 polypeptide chains usually presented as a “bundle of tulips”-like structure.<sup>12</sup> C1q binds to apoptotic cells and necrotic cell components to make them easier targets for phagocytes.<sup>13</sup> Upon binding of C1q to the Fc region of IgM or IgG antibodies complexed with antigen, C1r and C1s in the C1 protein complex are activated. C1s cleaves C4 into components C4a and C4b, and C2 into C2a and C2b. Binding C4b and C2b then forms C4bC2b, which acts as the classical pathway C3 convertase.<sup>14</sup> Due to historical reasons, C2b used to be called C2a, but in analogy with the alternative pathway convertase C3bBb and the other small cleavage fragments (C3a, C4a, and C5a) the nomenclature has changed so that the small released fragment will be called C2a and the convertase bound component C2b.<sup>15</sup> Upon activation of the complement system, the different pathways generate C3 convertases, C4bC2b through the CP and the LP, and C3bBb through the AP.<sup>5</sup> The functions of the C3 convertases are to cleave C3 into two components C3a and C3b.<sup>5</sup> C3a and C3b are formed once the  $\alpha$ -chain of C3 is cleaved by one of the two convertases.<sup>16</sup> C3a acts as a chemoattractant, while C3b promotes complement activation and acts itself as an opsonin and as a ligand for the complement receptor 1 (CR1, CD35).<sup>5</sup> Further degradation of C3b results in the formation of products including iC3b, C3c, and C3dg/C3d.<sup>5</sup> The C3 convertases can also cleave C5. For this, binding of C5 to an additional nearby C3b molecule is needed.<sup>5</sup> After being produced C5b binds to C6 and further to C7. The C5b-7 complexes may bind to the surface of attacking microbes that have a membrane (eg, gram-negative bacteria), where the complexes can incorporate. Binding of C8 and C9 from the fluid phase leads to the formation of the membrane attack complex (MAC), which can lyse and destroy the microbe or another target cells.<sup>6</sup> C3a and C5a can attract leukocytes including MCs, granulocytes, and monocytes to the site of infection.<sup>6</sup> These complement components are able to promote the contraction of bronchial smooth muscle cells, vasodilatation of small vessels within the tissue in which they are generated, and boost the degranulation of neutrophils and MCs and the release of cytokines from many different types of cells.<sup>6,17</sup> A key common feature of complement and MCs is their rapid activation (within minutes) (Figure 2A).

### 2.2 | Regulatory molecules of the complement system

Membrane-bound complement regulatory proteins, mainly CD35, CD46, CD55, and CD59, are responsible for protecting our cells from the potentially destructive activity of the complement system. CD46 (membrane cofactor protein, MCP) is expressed by all cells except red blood cells (RBCs). It acts as a cofactor for factor I (C3b/C4b inactivator) in cleaving and inactivating C4b and C3b.<sup>14</sup> CD55 (decay-accelerating factor, DAF) degrades the C3 convertases by displacing C2b or Bb away from them.<sup>14</sup> CD59 (protectin) prevents MAC attack by binding to C8 and C9 to inhibit the insertion



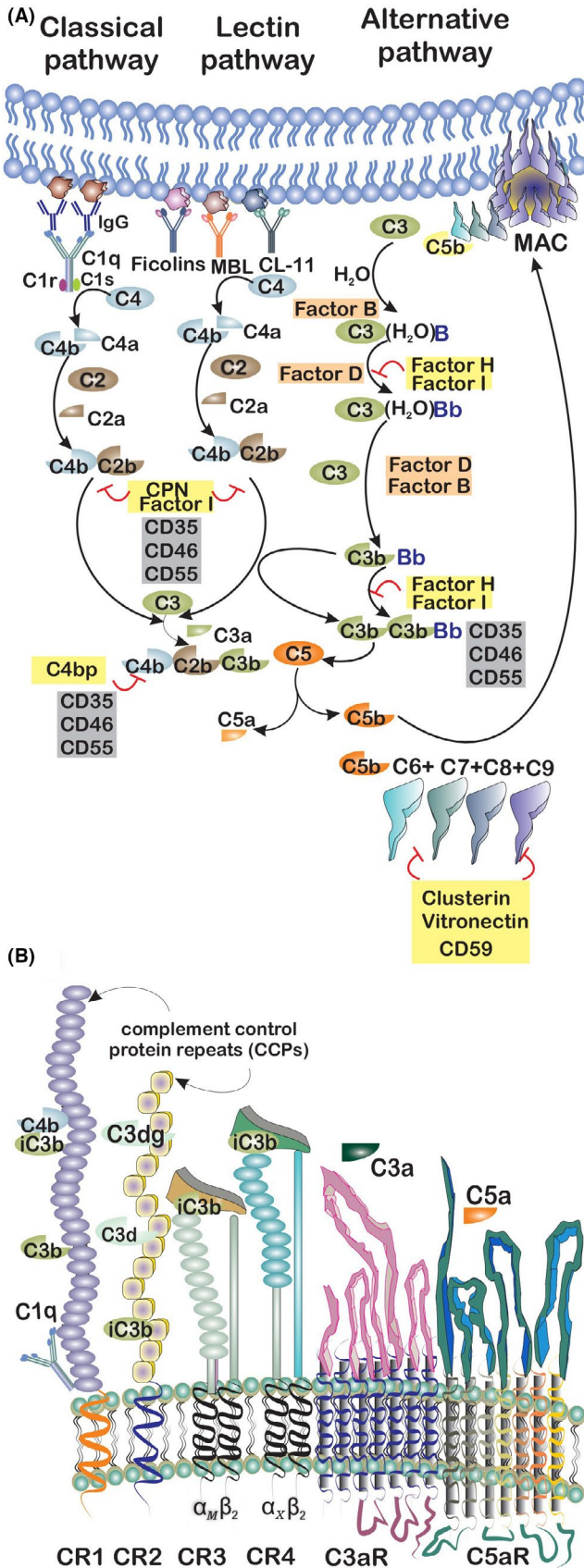
**FIGURE 1** An outline of the main biological functions of the complement system

of the C9 component into the membrane located C5b-8 and C5b-9 complexes.<sup>14</sup> CD55 and CD59 play a crucial role in preventing complement-mediated lysis of RBCs and thrombosis. This is well exemplified by the disease paroxysmal nocturnal hemoglobinuria (PNH), in which the deficiency of CD55 and, more importantly, CD59 predisposes blood cells to complement-mediated lysis.<sup>18-20</sup> Factor H (FH) is a soluble protein capable of binding to C3b and self-glycosaminoglycan and sialic acid markers to inhibit complement activation and to protect host cells. This is achieved by decay-accelerating activity for the C3bBb convertase and by cofactor activity for factor

I to degrade C3b to iC3b.<sup>21</sup> The expression of FH by podocytes in kidneys has also been associated with removal of immune complexes from subendothelial and subepithelial regions.<sup>22</sup> C1-INH acts as the inhibitor of the kinin-kallikrein system. Individuals with malfunction of C1-INH may experience angioedema attacks. C1-INH functionally suppresses autoactivation of factor XII and inhibits the conversion of prekallikrein to kallikrein.<sup>23</sup> C1-INH is capable of inhibiting activation of C1r and C1s, and the cleavage of two important components of complement system C2 and C4.<sup>24</sup> Moreover, C1-INH has a regulatory role in the coagulation system through inhibition of factor XI.<sup>23</sup>

One of the soluble complement inhibitor molecules which acts at the level of C3 convertases is C4b-binding protein (C4BP).<sup>25</sup> It is a cofactor in factor I-mediated cleavage of complement component

**FIGURE 2** A, Illustration of the enzymatic cascades of activation of classical, lectin, and alternative pathways. Regulatory molecules are also depicted. Note that the description of C2a has recently been changed to C2b. B, Schematic structures of the main complement receptors



C4b-C4c + C4d. Moreover, it facilitates the dissociation of C2b from the classical pathway C3 convertase.<sup>26</sup> Interestingly, some pathogenic microbes including *Neisseria gonorrhoeae* evade the complement system through binding C4BP.<sup>25</sup> Vitronectin, in addition to having a role in the biological processes like cell migration and tissue repair, regulates the formation of MAC.<sup>27</sup> Carboxypeptidases have been reported to have modulatory effects on anaphylatoxins. For instance, carboxypeptidase N (CPN) is a potent inactivator of C3a and C5a.<sup>28</sup> Early studies showed that both C3a and C5a act as histamine liberators when exposed to MCs, and that they can release up to 25%-30% of the total histamine content from MCs. Treatment of these anaphylatoxins with pancreatic carboxypeptidase B was reported to hamper their histamine-releasing capacity.<sup>29</sup>

### 3 | STRUCTURE AND FUNCTION OF COMPLEMENT RECEPTORS

Many of the biological functions of the complement proteins are mediated by a variety of cell surface-expressed receptors. Similar to other members of the regulators of complement activation (RCA) family, CR1 consists of domains, called complement control protein (CCP) or short consensus repeats (SCR).<sup>30</sup> Structurally, the receptor is composed of 30 SCRs, each of which consists of ~60 amino acids.<sup>31</sup> CR2 is strongly expressed on the surface of follicular dendritic cells (FDCs) and B cells. It contains 15 or 16 SCRs, of which SCR1 and SCR2 mediate the CR2 interaction with the ligands.<sup>32</sup> Structurally, CR3 and CR4 are heterodimers of CD11b/CD18 and CD11c/CD18, respectively, and belong to the family of  $\beta_2$  (CD18) integrins.<sup>33</sup> Moreover, C3aR, C5aR1, and C5aR2 belong to G-protein-coupled receptors (GPCRs).<sup>34</sup> C5aR1, also known as CD88, has a helix-bundle structure consisting of 74 amino acids. C5aR2 has a glycosylation site in the N-terminal domain, and also contains intracellular phosphorylation sites and a PKC phosphorylation motif.<sup>35</sup> Complement receptor of the immunoglobulin superfamily (CRIg) is capable of binding to the  $\beta$ -chain of C3b to inhibit the AP C3 and C5 convertases. The N-terminal domain of this receptor belongs to the IgV family of Ig-like domains.<sup>36</sup> These receptors are expressed by immune cells including the MCs. The anaphylatoxin C3a binds to C3aR, while C5a binds to C5aR1 and C5aR2 (Figure 2B). C5aR1 represents the main C5a receptor and is therefore later in the text referred to as C5aR. Upon C3a binding to the C3aR expressing human LAD2 mast cell line and CD34<sup>+</sup> cell-derived primary MCs, a 50% internalization of C3aR has been shown to occur.<sup>37</sup> One important feature of MCs residing in the skin is their ability to express both C3aR and C5aR, while MCs residing in lungs, uterus, or tonsils have not been described to express C5aR.<sup>5</sup> The roles of some of

these receptors are far beyond of just those of traditional receptors. The complement receptors can participate in the assembly of more complex structures with diverse functions. For example, CR3 is expressed also by peritoneal MCs and helps them to migrate to the site of inflammation. Studies have shown that Mac-1<sup>-/-</sup> mice have reduced numbers of residing MCs in some tissues, which is associated with a higher rate of mortality in septic peritonitis in these mice.<sup>38</sup> The main complement receptors and their identified ligands, functions, and structures are summarized in Table 1.

#### 4 | BIOLOGY OF MAST CELLS AT CELLULAR AND MOLECULAR LEVELS

Like the complement system, MCs are ancient components of the innate immune system with an evolutionary history dating back to nearly 500 million years ago. They were first traced in the hemolymph of the ascidian *Styela plicata*.<sup>39</sup> MCs are densely granulated innate immune cells developing from CD34<sup>+</sup>/CD117<sup>+</sup> pluripotent MC progenitors (MCPs).<sup>40</sup> After being released from the bone marrow into the circulation, the MCPs migrate to target tissues through an intricate trafficking system based on integrin/ligand and chemokine/chemokine receptor interactions, which is controlled in a tissue-specific manner.<sup>41</sup> Under the influence of stem cell factor (SCF), MCPs differentiate into mature MCs.<sup>42-44</sup> Other growth factors involved

in the maturation and differentiation of MCs include IL-3, IL-4, IL-9, IL-10, TGF- $\beta$ , IL-33, and CXCL12.<sup>45-49</sup> Upon cross-linking of Fc $\epsilon$ RI on MC surface with allergen-specific IgE, a cascade of signaling molecules is triggered. This results in MC activation with ensuing degranulation and secretion of mediators.<sup>50</sup> The mediators have been categorized into three groups: (a) preformed mediators, (b) de novo synthesized mediators, and (c) cytokines.<sup>51-54</sup> According to the granule contents and staining properties, two subtypes of MCs have been identified in humans: (a) MC<sub>T</sub> express tryptase and are found in the mucosal surfaces of lungs and gut and (b) MC<sub>TC</sub>, which produce tryptase, chymase, cathepsin, and carboxypeptidase and are found particularly in the connective tissue compartments of various organs.<sup>45,55,56</sup>

#### 5 | PRODUCTION OF COMPLEMENT PROTEINS BY MCS

In addition to immature dendritic cells (iDCs) and macrophages, also MCs have been reported to produce C1q.<sup>13</sup> The biological activity of C1q released by MC was confirmed by the reconstitution of C1q-depleted serum in hemolytic assays.<sup>13</sup> MCs have been demonstrated to produce also C3, particularly in dermatological diseases.<sup>16</sup> C3 can be found in the cytoplasmic compartment of MCs, but not within the cytoplasmic secretory granules.<sup>8,16</sup> Chymase released

**TABLE 1** Main complement receptors expressed by immune cells and their identified ligands and functions

CR	Complement ligand(s)	Expression, Biofunction, and structure	Ref
CR1 (CD35)	C3b, iC3b C4b, C1q	Catches C3b, C4b, and/or C1q coated structures for transport to the reticuloendothelial system Modulates B-cell functions, potentially binds the Epstein-Barr virus (EBV), the IgE receptor CD23, and IFN $\alpha$ . CD35 facilitates the decay of C3/C5 convertases, thus, acting as an inhibitor of the complement system at the C3 level. Promotes interleukin-1 (IL-1) secretion from antigen-presenting cells (APCs) and enhances differentiation of B cell to plasma cells	5,88 14,88,89 90
CR2 (CD21)	C3d/C3dg iC3b	Expressed by B cells, dendritic cells, BMDC and RBL-2H3 cells, the receptor for the Epstein-Barr virus (EBV)	5,7
CR3 (MAC-1,CD11b/CD18, $\alpha$ M $\beta$ 2)	iC3b	Comprised of CD11b/CD18, member of the leukocyte $\beta$ 2-integrin family. The main opsonophagocytic receptor on neutrophils and monocytes/macrophages, in addition to iC3b the receptor binds C3dg, ICAM-1 and fibrinogen	5,91-93
CR4 (gp150/95, CD11c/CD18, $\alpha$ X $\beta$ 2)	iC3b	Comprised of CD11c/CD18, member of the leukocyte $\beta$ 2-integrin family. Like CR3, acts as a receptor on myeloid cells, like macrophages and neutrophils	90,91,94
C3aR	C3a	Structurally a G-protein-coupled receptor (GPCR), which is mainly expressed on B and T cells, but also on many other cell types. C3aR has intracellular expression in resting T cells and surface expression on activated T cells	88
C5aR1 (CD88)	C5a	A GPCR with an ability to bindC5a and C5a <sup>desArg</sup> . C5a/ C5aR1 interaction is associated with the pathogenesis of inflammatory diseases. Expressed by multiple different cell types	88
C5aR2	C5a	BindsC5a and C5a <sup>desArg</sup> and has been described to have both intracellular and membrane expression. It is a 7-transmembrane receptor but does not seem to engage in "G protein-coupled signaling"	88
CRlg	C3b and iC3b	Expressed by phagocytes. Contributes to phagocytosis, inhibits convertases of the alternative pathway	36

**FIGURE 3** A, A summary diagram of the interactions between the complement system and MCs. MCs express C3aR and C5aR, which react to C3a and C5a, respectively, and become activated. MCs produce complement proteins, including C3, which under the influence of MC-released tryptase is converted to C3a and C3b. Binding of C3a to MC surface-expressed C3aR completes the loop. C3a and C5a have also a role in the migration of MCs. B, Complement components like C5a not only activate MCs but mediate their recruitment into tissues. Blocking the Gi proteins using pertussis toxin hampered the process indicating the involvement of Gi proteins in the migration of MCs toward anaphylatoxins

from MCs may have a role in controlling C3-associated pathology, as it can degrade the  $\alpha$ - and  $\beta$ -chains of C3, as well as isolated C3a.<sup>16</sup> Culturing skin MCs revealed their capacity to produce complement proteins in response to cytokines. For example, treatment of MCs with TNF- $\alpha$  and IL-4 or IL-13 synergistically induces C3 production by MCs.<sup>8</sup> Additionally, MC-derived tryptase and chymase can cleave C3, and generate C3a.<sup>5</sup> The produced C3a in turn acts on C3aR expressed on the MCs in an autocrine manner<sup>5</sup> (Figure 3A). In vitro studies showed that C3a and C4a could be produced by monomeric  $\beta$ -tryptase at acidic pH in the presence of low molecular weight dextran sulfate, whereas C5a could be produced under the influence of monomeric  $\beta$ -tryptase at acidic pH in the presence of high molecular weight dextran sulfate.<sup>57</sup> Since the levels of C3a, C5a, and tryptase are increased in bronchoalveolar lavage fluid (BAL) obtained from asthmatic individuals, the cross talk between the complement system and MCs may have a role in the pathogenesis of asthma.<sup>57</sup>

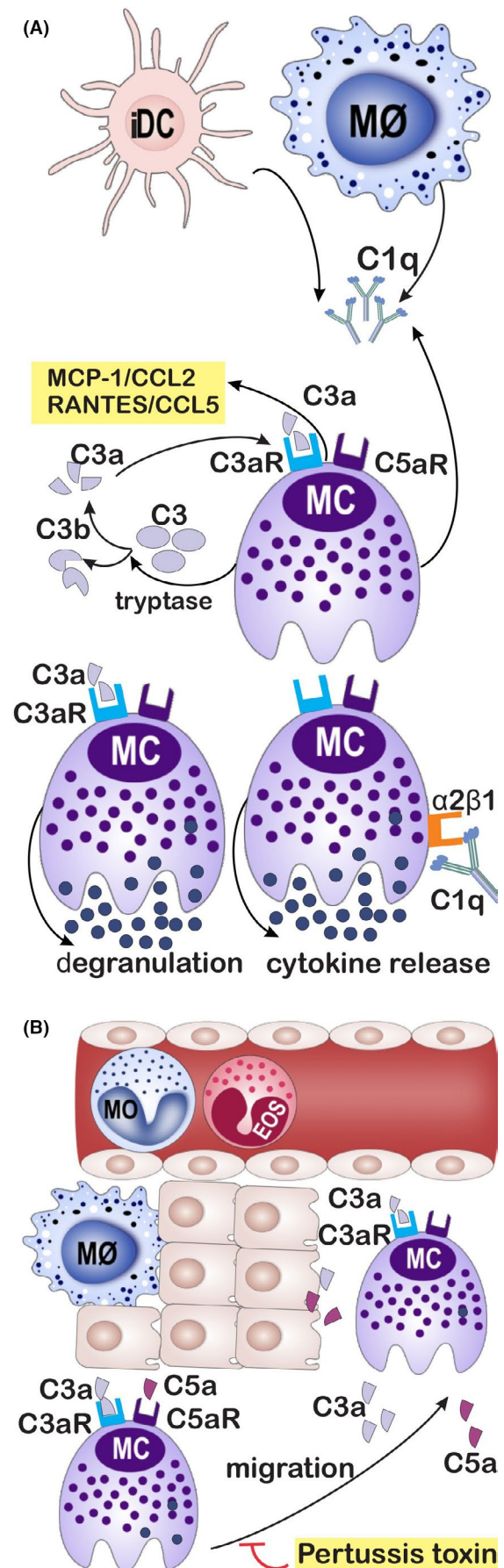
## 6 | COMPLEMENT-MEDIATED REGULATION OF MC ACTIVATION AND FUNCTION

### 6.1 | C1q and MC activation

Considering that C1q possesses collagen-like sequences capable of binding to the  $\alpha 2\beta 1$  integrin and the fact that peritoneal MCs express  $\alpha 2\beta 1$  integrin,<sup>58</sup> Edelson and coworkers investigated the role of C1q in the release of proinflammatory cytokines in *Listeria monocytogenes*- and zymosan-induced peritonitis in mice. In a subsequent work, they concluded that  $\alpha 2\beta 1$  integrin acts as a receptor for multiple collectins and the C1q complement protein on mouse peritoneal MCs, and that this integrin provides a costimulatory function required for MC activation and release of cytokines by the activated MCs.<sup>59</sup>

### 6.2 | C3a influences the activation and migration of MCs

It was recently suggested that adenosine is capable of inhibiting C3a-mediated activation of MCs by acting through the  $G_{\alpha s}$  protein-dependent pathway.<sup>60</sup> Further in vitro studies showed that the



engagement of A2<sub>A</sub>, A2<sub>B</sub>, and A3 adenosine receptors promoted FcεRI- or C3a-mediated degranulation in LAD2 cells.<sup>11</sup> Moreover, C3a induces the production of MCP-1/CCL2 and RANTES/CCL5 by human MCs,<sup>37</sup> and also acts as a chemoattractant for C3aR-expressing MCs.<sup>61</sup> Indeed, MCs have been reported to migrate toward an increasing gradient of C3a and C5a, and pertussis toxin pretreated HMC-1 cells have exhibited a hampered migration toward these anaphylatoxins indicating the involvement of G<sub>i</sub> proteins in the signal transduction pathway.<sup>62</sup> (Figure 3B) In their comprehensive study, Schäfer and coworkers used MC-deficient C57BL/6-Kit<sup>W-sh/W-sh</sup> mice and normal congenic wild-type littermates as controls.<sup>63</sup> Moreover, they studied C57BL/6J C3aR<sup>-/-</sup> and C5aR<sup>-/-</sup> mice and used C57BL/6 wild-type mice as controls. The role of C3a and C5a in inducing a swelling response was studied by injecting an intradermal dose of C3a and C5a into the right ear and vehicle into the left ear as a control. To study the IgE-dependent passive cutaneous anaphylaxis (PCA), DNP-specific IgE was injected into the right ear and vehicle as control into the left ear. Intravenous injection of DNP-conjugated human serum albumin (HSA) after 24 hours was used to challenge the mice. By adoptively transferring into the Kit<sup>W-sh/W-sh</sup> mice BMMCs derived and cultured from WT, C3aR<sup>-/-</sup> and C5aR<sup>-/-</sup> mice showed that the adoptive transfer of WT BMMCs to Kit<sup>W-sh/W-sh</sup> mice improved their response to injection of C3a and C5a.<sup>63</sup> They concluded that skin MC expression of C3aR and C5aR enables these cells to respond to these anaphylatoxins and induce the skin swelling and local inflammation during IgE-dependent PCA in vivo. These findings in MC-engrafted Kit<sup>W-sh/W-sh</sup> mice were interpreted to indicate that the local inflammation induced by the intradermal application of C3a or C5a largely depends on the expression of their respective receptors by mast cells at the site of the reaction.<sup>63</sup> Investigations of endothelial cell infection by the dengue virus have revealed another potential cross talk between the complement system and MCs.<sup>64</sup> The infection led to activation of the alternative pathway (AP), whereby factor B bound to C3b to form the C3 convertase. This led to C3a and C5a production and histamine release by MCs which in turn increased vascular permeability.<sup>64</sup> Another complement-related autocrine activity has been reported among epidermal keratinocytes (KCs), which produce C3 and also express C3aR.<sup>65</sup> Thus, C3 produced by these cells may have been activated by trypsin released from locally residing MCs. The formed C3a then acted on the C3aR expressed by KCs to induce their production of C3 and CCL2. The latter chemokine may then mediate migration of a variety of immune cells including CD4<sup>+</sup> T cells, monocytes, and DCs during cutaneous inflammation.<sup>65</sup>

### 6.3 | C5a influences the activation and migration of MCs

C5a enhances the chemotaxis of HMC-1 and LAD-2 cell lines, possibly via a pertussis toxin-sensitive G protein.<sup>66</sup> Moreover, C5a induces the degranulation of C5aR-expressing MC subtypes.<sup>67</sup> Kordowski and coworkers investigated the role of C5a/

C5aR interaction in a model of induced food allergy in C5aR 1<sup>-/-</sup> mice (63). They reported complete protection from developing anaphylaxis in male C5aR 1<sup>-/-</sup> mice, when compared to BALB/c wild-type mice as a control group. Instead, only partial protection in female C5aR 1<sup>-/-</sup> mice was seen. The male test group showed reduced MC protease-1 and allergen-specific IgE levels. Additionally, in vitro investigations of C5aR1<sup>-/-</sup> BMMCs revealed reduced levels of IL-6 production and hampered IgE-mediated MC degranulation. The authors concluded that the C5aR1/C5a interaction may play a role in the development of food allergy by mediating MC activation, degranulation, and cytokine release.<sup>68</sup> Taken together, the ability of C3a and C5a in inducing degranulation and releasing mediators by MCs is possibly due to activation of signaling pathways involving especially PLCβ-mediated Ca<sup>2+</sup> mobilization, PKC, PI3K, and ERK.<sup>69</sup>

## 7 | DISCUSSION AND CONCLUSIONS

Mast cells and the proteins of complement system both belong to innate immunity and emerged first in marine invertebrates. Under normal circumstances, complement components remain as inactive pro-enzymes. However, when complement activation occurs, the proteases become enzymatically active and form an efficient cascade of mediators, which recognize target cells and bind to cell surface-expressed receptors. Similar to the activated complement components, activated MCs produce a wide variety of mediators, which influence the biology of their target cells. Importantly, the MCs express receptors for activated complement components and thereby allow the components to activate the MCs to release two neutral serine proteases, trypsin, and chymase. These proteases, in turn, can trigger activation of the complement system cascade by converting complement proteins into their active forms. Thus, a potentially self-amplifying loop may ensue. Here, we have discussed some links between the complement system and MCs, which merit further investigations. Although the anaphylatoxins including C3a and C5a and their receptors have been fairly well characterized, clarifying their real biological functions in vivo remains a challenge. The anaphylatoxin C3a, for example, is produced into the extracellular fluid, at the cell surface and even intracellularly. Thereafter, it is rapidly converted by carboxypeptidases to C3a<sup>des-Arg</sup>, which, however, does not bind to the C3aR. Rapid enzymatic conversion of C3a to C3a<sup>des-Arg</sup> (within seconds) and a relatively low capacity of antibodies to discriminate between C3a and C3a<sup>des-Arg</sup> could pose obstacles to research.<sup>70,71</sup> Moreover, not all routinely applied MC lines necessarily have the same profile of complement receptor expression. This should be considered when selecting the cell lines, because, for example, C3a induces degranulation of LAD2 cells but not of RBL-2H3 cells, which actually are derived from basophils and therefore not considered an adequate model for studies on MC mediator release.<sup>72,73</sup>

Interestingly, human MCs obtained from various anatomic sites have different levels of anaphylatoxin receptor expression. For

instance, more than 80% of juvenile foreskin-derived MCs express C5aR, but only 10% of tonsillar or uterine MCs express this receptor.<sup>74</sup> One possible interaction between complement and MCs occurs during envenomation, whereafter anaphylatoxin production and a rise in plasma levels of tryptase have been reported.<sup>75</sup> Unlike C3a and C5a, C4a has been reported to prevent the activation and degranulation of exposed MCs in an autocrine manner. For example, C4a inhibits the release of histamine from recombinant C3a-activated HMC-1 cells, an inhibitory mechanism of C4a that needs to be further investigated.<sup>76</sup> The potential cross talk between the complement system and MCs in the pathogenesis of other diseases also needs further investigation. For instance, in atopic dermatitis, the C5a receptors are overexpressed, and IL-4, IFN- $\gamma$ , histamine, and IgE levels are elevated. In a mouse model, the use of a C5aR antagonist (C5aRA) has been reported to decrease the release and activity of MC mediators.<sup>77</sup> Additionally, investigations on cutaneous leukocytoclastic vasculitis have suggested a possible role for MC<sub>TC</sub> released chymase to activate MC-released C3 to generate C3a.<sup>10</sup> The cardiovascular diseases represent another group of disorders, where there is much suggestive evidence of a contributory pathogenetic role of complement activation. Thus, complement is extensively activated in aortic aneurysms, in the myocardium of ischemic and failing hearts, and also in atherosclerotic lesions, thereby linking an ancient system with a modern life-style disease.<sup>78</sup> Interestingly, a connection between atherosclerotic lesion development and complement-dependent activation of MCs has been suggested both in humans and in experimental animals.<sup>79,80</sup> Thus, C3a and C5a are generated in advanced human atherosclerotic coronary plaques, where most cell types express receptors for both anaphylatoxins, the MCs for C5a only.<sup>81</sup> As already noted, tryptase-dependent generation of C3a and C5a occurs at acidic pH and in the presence of dextran sulfate (53). Since in advanced human atherosclerotic lesions the extracellular matrix is largely composed of sulfated proteoglycans and the pH of the extracellular fluid is acidic, the tissue environment in such lesions may be optimal for human beta-tryptase-dependent generation of anaphylatoxins. Strikingly, in ruptured coronary artery plaques of patients with acute myocardial infarction, the complement system and the MCs are activated, the activated MCs potentially acting as multifunctional effector cells in the rupture process itself.<sup>82,83</sup> Studies in hypercholesterolemic mice have provided experimental evidence to support the atherogenic potential of complement-activated MCs. Thus, for example, in vein segments grafted to an artery in hypercholesterolemic mice, atherosclerotic lesions rapidly develop, and application of C5a to the perivascular layer of the lesions triggers local MC activation.<sup>84,85</sup> Such local C5a-dependent activation of perivascular MCs was found to result in accelerated lesion formation, in the recruitment of newly infiltrating MCs and increased numbers of plaque disruptions with concomitant intraplaque hemorrhages.<sup>84</sup> On the other hand, when the effects of C5a were studied in late-stage advanced graft lesions, the MC stabilizer cromolyn failed to prevent the C5a-induced effects on plaque disruptions, presumably because the numbers of other C5a-responsive immune cells in the vessel wall

were strongly increased.<sup>85</sup> Taken together, therapeutic targeting of the C5a-C5aR axis characterizing the cells in atherosclerotic lesions, MCs among them, could be potentially an attractive adjunct strategy to combat atherosclerotic cardiovascular diseases. Finally, in systemic mastocytosis (SM), in which aberrant and often massive infiltration of MCs into organs is observed,<sup>86</sup> the patients have an altered profile of complement receptor expression. For instance, overexpression of CD11c (CR4), CD35 (CR1), and CD88 (C5aR1) has been documented in BMMC derived from these patients.<sup>87</sup> Interestingly, overexpression of the complement regulators CD55 and CD59 has been reported in patients with SM.<sup>87</sup> Investigations on these patients may reveal further unknown aspects of the interplay between the complement system and MCs. As indicated in this review, both MCs and the complement system have strong biological activities, yet these are carefully controlled. Both systems are involved in a number of human diseases, both acute and chronic, and therefore amenable to therapeutic intervention.

#### CONFLICT OF INTEREST

Daniel Elieh Ali Komi, Farzaneh Shafaghat, Petri T Kovanen, and Seppo Meri declare that they have no conflict of interest.

#### ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

#### INFORMED CONSENT

No informed consent was required to prepare the manuscript.

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