Molecular Immunology 84 (2017) 10–16

Contents lists available at ScienceDirect

Molecular Immunology

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

Complement in basic processes of the cell

Anaïs Jiménez-Reinoso, Ana V. Marin, José R. Regueiro*

Department of Immunology, Complutense University School of Medicine and Hospital 12 de Octubre Health Research Institute, Madrid, Spain

ARTICLE INFO

Article history:
Received 14 August 2016
Accepted 18 November 2016
Available online 3 December 2016

Keywords:
Complement
T lymphocyte
B lymphocyte
Dendritic cell
Complotype

ABSTRACT

The complement system is reemerging in the last few years not only as key element of innate immunity against pathogens, but also as a main regulator of local adaptive responses, affecting dendritic cells as well as T and B lymphocytes. We review data showing that leucocytes are capable of significant autocrine synthesis of complement proteins, and express a large range of complement receptors, which in turn regulate their differentiation and effector functions while cross talking with other innate receptors such as Toll-like receptors. Other unconventional roles of complement proteins are reviewed, including their impact in non-leukocytes and their intracellular cleavage by vesicular proteases, which generate critical cues required for T cell function. Thus, leucocytes are very much aware of complement-derived information, both extracellular and intracellular, to elaborate their responses, offering rich avenues for therapeutic intervention and new hypothesis for conserved major histocompatibility complex complotypes.

1. Introduction

The complement system classically exerts three main activities: host innate defense against infection – through antigen opsonization, driving chemotaxis and leukocyte activation and lysing bacteria and cells –, bridging innate and adaptive immunity – by augmenting antibody responses and enhancing immunologic memory –, and disposing of immune complexes and inflammatory products – through the clearance of tissue immune complexes and apoptotic cells – (Walport, 2001). In the last few years, however, complement has re-emerged as a key regulator of cellular and immunological responses, both innate and adaptive, by providing costimulation and proliferation signals. Such signals act extracellularly through specific cell receptors of classical fragments (Table 1), some still undefined, but also intracellularly after new cleavage schemes and proteases through specific membrane receptors that probe vesicular structures. Some of those vesicles contain pathogens and thus complement has clear defensive roles, but other vesicles are sterile and likely involved rather in leucocyte regulation. The recent success of complement-targeted therapeutics such as anti-C5 for transplant rejection and hemolytic uremic syndrome or anti-factor I for age-related macular degeneration have fueled heightened interest in the complement system among scientists, clinicians and the pharmaceutical industry. As new unconventional roles may suggest new therapies, we summarize unexpected contributions of hepatic and extrahepatic extracellular and intracellular complement soluble proteins, fragments and receptors to physiopathology of a wide range of cells and tissues.

2. Hepatic versus extrahepatic complement

In mammals most complement proteins are of hepatic origin under normal conditions, with some exceptions such as C1q, C7, properdin and factor D (Morgan and Gasque, 1997), which are predominantly produced by myeloid cells, notably monocytes and macrophages (or adipocytes for factor D, also called adipsin). Under inflammatory conditions, however, both hepatic and extrahepatic production are enhanced (Laufer et al., 2001), and extrahepatic sources may become critical for local protection (or damage), particularly for larger proteins such as C1q (400 kD) or for those that are rapidly cleaved such as C3. For instance, C3 from

Abbreviations: AM, adrenomedullin; AMD, age-related macular degeneration; APC, antigen-presenting cells; BCR, B-cell receptor; bm, bone marrow cells; bmDC, bone marrow dendritic cells; cDC, conventional dendritic cells; CLR, calcitonin receptor-like receptor; CR1, complement receptor 1; CR2, complement receptor 2; CR3, complement receptor 3; CR4, complement receptor 4; DC, dendritic cells; eC3, extracellular C3; FDC, follicular dendritic cells; FH, factor H; GM-CSF, granulocyte macrophage colony-stimulating factor; iC3, intracellular C3; iC5, intracellular C5; IFN-γ, interferon-γ; IL-12, interleukin 12; IL-2, interleukin 2; IL-4, interleukin 4; KD, knock-down; KO, knock-out; LPS, lipopolysaccharide; MCP, membrane cofactor protein; MHC, major histocompatibility complex; Mo, monocytes; moDC, monocyte-derived dendritic cells; NLRP3, nucleotide-binding domain leucine-rich repeat family pyrin domain containing 3; pDC, plasmacytoid dendritic cells; RAMP2, receptor activity-modifying protein 2; TCR, T-cell receptor; TLR, Toll-like receptors.

* Corresponding author at: Department of Immunology, Complutense University School of Medicine, 28040 Madrid, Spain.
E-mail addresses: ajreinoso@med.ucm.es (A. Jiménez-Reinoso), anavictoriamarin@ucm.es (A.V. Marin), regueiro@med.ucm.es (J.R. Regueiro).

http://dx.doi.org/10.1016/j.molimm.2016.11.011
0161-5890/

Table 1
Surface complement receptor expression in B or T cells, monocytes, monocyte-derived dendritic cells and follicular dendritic cells.

		Ligand						Cell type				
		C3a	C3b	iC3b	C3dg	C3c	C5a	B	T	Mo	moDC	FDC
Receptor	Alternative names											
CR1	CD35	–	+	+	–	–	–	+	+	+	+	+
CR2	CD21	–	–	+	+	–	–	+	+	–	–	+
CR3	CD11b/CD18; $\alpha_M\beta2$; Mac-1	–	–	+	–	–	–	+	+	+	+	+
CR4	CD11c/CD18; $\alpha_X\beta2$; p150/95	–	–	+	–	–	–	+	+	+	+	+
CRIg	Z93Ig; VSIG4	–	+	+	–	+	–	–	–	+	+	–
C3aR	–	+	–	–	–	–	–	+	+	+	+	+
C5aR1	CD88	–	–	–	–	–	+	–	+	+	+	+
C5L2	C5aR2; GPR77	+	–	–	–	–	+	–	+	+	–	–
MCP	CD46	–	+	–	–	–	–	+	+	+	+	+
DAF	CD55	–	+	–	–	–	–	+	+	+	+	+

Monocytes (Mo), monocyte-derived dendritic cells (moDC) and follicular dendritic cells (FDC). (Arbore et al., 2016; Kremlitzka et al., 2014; Li et al., 2011; Ohno et al., 2000; Qualai et al., 2016; Ricklin et al., 2010; Rubtsov et al., 2011; Török et al., 2015; Zipfel and Skerka, 2009).

bone marrow-derived cells can restore normal lymphoid organ-dependent antibody responses in mice lacking C3 (Fischer et al., 1998). Conversely, the renal contribution to the recipient's plasma C3 pool can increase from the normal 5% to 16% in case of allograft rejection (Tang et al., 1999), and can shorten graft survival time almost ten-fold (Pratt et al., 2002). In other species such as fish the hepatic/extrahepatic complement ratio is reversed (Zhang and Cui, 2014), suggesting that locally synthesized complement may have been the rule rather than the exception earlier in evolution. While most of these studies addressed extracellular complement, they now become relevant in light of the new intracellular roles ascribed to several complement proteins (see below).

3. Extracellular complement

3.1. Complement polymorphisms and tissue damage

The C3 Fast/Slow polymorphism (p.G102R) came to stage because of a report of improved long-term survival of $C3F^+$ kidneys transplanted into $C3S^+$ recipients (Brown et al., 2006), although it could not be reproduced in a larger study (Varagunam et al., 2009). More recently, C4 polymorphism has been shown to influence renal allograft outcome (Bay et al., 2013). Nevertheless, the C3F allele was reported as detrimental in several disorders where extracellular complement is likely involved in tissue damage, such as several nephropathies, age-related macular degeneration (AMD), or systemic vasculitis, but also in other diseases where the conventional role of complement is more controversial (Table 2). Our contribution to this controversy was the unexpected finding of a strong and apparently primary association of chronic renal failure and C3F in a small sample of Spanish patients (Regueiro and Arnaiz-Villena, 1984). Such associations suggested some sort of functional C3 variation associated with the C3 genotype, which has recently been shown biochemically to be caused by a lower affinity of factor H for C3F as compared to C3S (Harris et al., 2012). Studying the combination of interacting common risk vs protection variants for factor H, factor B and C3 in AMD has defined functional complotypes that clearly increase disease susceptibility by drastically facilitating complement activation and thus inflammation. The unconventional roles have not been explored under this new light. In this regard, the reported association of C3 gene variants with asthma and Th2-dependent responses suggests a potential unconventional pathogenic mechanism involving T cells (Barnes et al., 2006), perhaps including complotypes.

The complotype concept was first coined to define combinations of complement alleles within the major histocompatibility complex, MHC (C2, C4 and factor B), and indeed C2/factor B MHC complotypes have been reported in connection with AMD protection (Sun et al., 2012). The conserved linkage of three complement genes within the MHC (class III genes) is still a matter of debate, as classical MHC molecules (class I and class II) are critical for T cell selection and function, seemingly unrelated to the conventional role of complement. It is thus tempting to speculate that the unconventional role of complement in T cells (see 4.1) may explain the conserved mapping of complement genes within ancestral MHC haplotypes (Candore et al., 2002) to ensure balanced protection from pathogens and inflammation.

3.2. Regulation of dendritic cells

The classical role of complement components in dendritic cells (DC) includes inducing migration toward inflamed tissues via the C3a or C5a receptors, or facilitating detection and internalization of opsonized pathogens or immune complexes using complement receptor 3 or 4 (CR3 or CR4, see Table 1). Beyond such roles, several complement components have been shown to impact the differentiation, maturation, cytokine production, Th1/Th2 promotion, and phagocytic capacity of antigen-presenting cells (APC), including DC.

Due to the scarcity of blood DC, the best-studied *in vitro* model for human APC is that of monocyte-derived dendritic cells (moDC) (Fig. 1). The procedure to generate human moDC begins with isolation of monocytes (Mo) from peripheral blood mononuclear cells either by sorting as $CD14^+$ cells or by adherence to plastic microtiter plates at 37 °C. Isolated Mo are subsequently cultured for 5 to 7 days with granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin 4 (IL-4) to yield immature moDC, which may be fully matured by adding pro-inflammatory mediators such as lipopolysaccharide (LPS) for 24 to 48 h (Castiello et al., 2011). Immature moDC are characterized by low to moderate surface expression of antigen presenting molecules such as MHC-II and CD1a and of T cell activating co-receptors such as CD80 and CD86. Mature moDC express high levels of MHC-II, CD80 and CD86, but not CD1a (Merad et al., 2013). moDC are distinct from conventional or plasmacytoid DC (cDC and pDC, respectively) (Qu et al., 2014), but their easy availability and handling have made them the standard in the field. In mice, by contrast, APC are modelled by a similar strategy but starting with bone marrow cells (bm) cultured in the presence of GM-CSF and isolated as $CD11c^+$ cells, which are then termed bmDC. Most of the findings that follow, however, should be confirmed in primary cDC and pDC in both species.

Human Mo and moDC express a wide range of surface complement receptors (Table 1) capable of binding both hepatic and extrahepatic (including autologous) soluble complement proteins. Indeed, both cell types produce autologous complement soluble proteins belonging to all three activation pathways, including C1q,