Molecular Immunology 84 (2017) 17–25

Contents lists available at ScienceDirect

Molecular Immunology

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

Complement in the fundamental processes of the cell

Owen A. Hawksworth[a,b], Liam G. Coulthard[c,d], Trent M. Woodruff[a,*]

[a] School of Biomedical Sciences, University of Queensland, St. Lucia, Australia
[b] Australian Institute of Bioengineering and Nanotechnology, University of Queensland, St. Lucia, Australia
[c] School of Medicine, University of Queensland, Herston, Australia
[d] Royal Brisbane and Women's Hospital, Herston, Australia

ARTICLE INFO

Article history:
Received 2 August 2016
Accepted 18 November 2016
Available online 25 November 2016

Keywords:
Complement
Development
Homeostasis
Migration
Survival
Regeneration
Pruning

ABSTRACT

Once regarded solely as an activator of innate immunity, it is now clear that the complement system acts in an assortment of cells and tissues, with immunity only one facet of a diverse array of functions under the influence of the complement proteins. Throughout development, complement activity has now been demonstrated from early sperm-egg interactions in fertilisation, to regulation of epiboly and organogenesis, and later in refinement of cerebral synapses. Complement has also been shown to regulate homeostasis of adult tissues, controlling cell processes such as migration, survival, repair, and regeneration. Given the continuing emergence of such novel actions of complement, the existing research likely represents only a fraction of the myriad of functions of this complex family of proteins. This review is focussed on outlining the current knowledge of complement family members in the regulation of cell processes in non-immune systems. It is hoped this will spur research directed towards revealing more about the role of complement in these fundamental cell processes.

1. Introduction

The complement system has long been regarded as the effector arm of innate immunity. After initial activation of complement, a multitude of split products are able to facilitate the recruitment of immune cells to sites of inflammation and pathogen clearance via opsonisation or direct destruction. It is now well established that these actions represent only one part of a diverse array of complement functions, with emerging research demonstrating the versatility of this phylogenetically conserved family throughout numerous cell systems and developmental stages.

Traditionally, complement activation has been thought to occur through three pathways; the C1 antibody-antigen complex of the classical pathway, spontaneous C3 hydrolysis of the alternative pathway, or recognition of damaged or pathogenic surfaces by mannose-binding lectin (MBL) through the lectin pathway. Pathway activation initiates a cascade resulting in the cleavage of complement factor 3 (C3) and complement factor 5 (C5) to their active fragments (C3a, C3b, C5a, C5b). These cleavage fragments represent the foundation of the complement-initiated cellular immune response (for a comprehensive review, see (Merle et al., 2015a, 2015b)). Both C3a and C5a are capable of signalling through their respective G-protein coupled receptors, C3aR1 and C5aR1, to regulate the activation of immune cells and their recruitment to sites of tissue injury and inflammation. C5a can also interact with a second C5a receptor, C5aR2, which despite lacking G-protein coupling, can alter the response of a cell to C5a (Croker et al., 2016). C3b acts as a powerful opsonin, tagging foreign pathogens and cells for destruction, whilst C5b can combine with further downstream complement factors, C6, C7, & C9, to form the membrane attack complex (MAC) capable of disrupting bacterial cell membranes. In the absence of complement cascade activation, C3 and C5 can also be cleaved by a variety of predominantly cell and blood-derived serine proteases (Amara et al., 2010; Huber-Lang et al., 2006; Perl et al., 2012). This 'extrinsic' pathway provides a mechanism by which complement can be locally activated in the absence of inflammation, to control a number of immune and non-immune cell processes.

It is now evident that the activation of the innate immune response represents only one arm of the diverse array of physiological functions that receive contribution from the complement proteins. Throughout development, complement activity has been demonstrated from early sperm-egg interactions in fertilisation, to regulation of epiboly and organogenesis, and later in refinement of cerebral synapses. Complement has also been shown to regulate homeostasis of adult tissues, controlling cell processes such

* Corresponding author at: Laboratory for Neuroinflammation, School of Biomedical Sciences, The University of Queensland, St. Lucia, Brisbane, QLD 4072, Australia.
E-mail address: t.woodruff@uq.edu.au (T.M. Woodruff).

http://dx.doi.org/10.1016/j.molimm.2016.11.010
0161-5890/

as migration, survival, repair, and regeneration. Given the continuing emergence of novel actions of complement, the existing research likely represents only a fraction of the full role of this complex family of proteins. This review is focussed on outlining the current knowledge on both divergent and conserved actions of complement family members in the regulation of cell processes in non-immune systems.

2. Complement in basic cell processes

2.1. Migration

The coordinated migration of cells is a core process in multicellular organisms, facilitating actions such as embryogenesis, wound healing, and the immune response. The complement system has been demonstrated to have a broad role in the control of cell migration, extending to, and beyond, immunity. Through selective expression and activation, complement factors control a number of migratory processes in the organisation of the developing embryo and in recruitment of adult stem cell pools. The ability of complement to control cell migration also represents a significant arm of the complement-mediated immune response. Activation of the complement cascade results in the cleavage of complement factor 5 (C5) to the active fragment, C5a; a potent mobiliser of immune cell migration capable of recruiting monocytes and neutrophils to sites of inflammation (Marder et al., 1985; Boneschansker et al., 2014). The action of C5a in recruiting leukocytes is pivotal in the mounting of host defences against pathogens, however, aberrant activity can also play a role in disease pathology. Complement control of cell migration can also have anti-inflammatory actions, moderating the extent of the immune response. This is demonstrated in a model of intestinal ischemia-reperfusion injury, where C3a/C3aR signalling attenuates neutrophil mobilisation into the circulation, leading to reduced neutrophil recruitment and tissue damage (Wu et al., 2013). Interestingly, this same impaired mobilisation response leads to increased tumour growth in cancer models (Nabizadeh et al., 2016).

In the non-immune context, both C3a and C5a have both been demonstrated to induce actin polymerisation and chemotaxis of mesenchymal stem cells (MSCs) through C3aR1- and C5aR1-dependent phosphorylation of ERK (Schraufstatter et al., 2009). The mobilisation of MSC pools to sites of tissue injury is an important step in repair and regeneration, as such is it proposed that increased C3a and C5a concentrations during inflammation can serve a dual function in both facilitating acute immune responses, as well as mobilising cell pools such as MSCs for subsequent tissue repair. A similar function has also been observed in cardiac progenitor cells (CPCs). Here C3a and C5a, through activation of ERK, PKC, and NFkB pathways, induced transition of CPCs from an endothelial to a mesenchymal state, promoting migration of the cells to sites of repair (Lara-Astiaso et al., 2012). In addition, anaphylatoxin signalling increased proliferation of the CPC pool and induced their maturation towards myofibroblasts, required for repair following cardiac injury.

This action on progenitor cells is not a global phenomenon. Both C3a and C5a also contribute to the mobilisation of bone marrow hematopoietic stem cells (HPSCs). However, in HPSCs C5a and C3a demonstrate opposing actions via separate mechanisms. Through indirect activation of granulocytes, C5a, produced via thrombin cleavage of C5, promotes the release of pro-mobilisation factors that facilitate egress of HPSCs from their bone marrow (BM) niche (Lee et al., 2009). C3a opposes this action, promoting retention of BM HPSCs. C3 and C3aR1 deficient mice show decreased mobilisation of HPSCs in response to G-CSF (Ratajczak et al., 2004). Interestingly, this is not a direct effect, instead C3aR1 signalling sensitises HPSCs to BM stromal cell released SDF-1 (Ratajczak et al., 2004; Wysoczynski et al., 2009). This effect has also been reported in HPSC derivatives including myeloid, erythroid, and megakaryocytic progenitors (Reca et al., 2003). However, other reports have suggested that C3aR1 is not expressed on human HPSCs, with the action of C3a occurring independently of C3aR1 (Honczarenko et al., 2005). Interestingly, this mechanism extends to neural progenitor cells (NPCs) in the adult brain. C3a alone had no observed effect on mouse whole brain-derived NPCs, however it was shown that the presence of C3a increased SDF-1 induced ERK phosphorylation, resulting in chemotaxis and proliferation of NPCs (Shinjyo et al., 2009). The underpinning function of this response was again suggested to lie in complement mobilisation of regenerative/repair responses following injury such as ischemic stroke.

The ability of complement factors to regulate cell migration across a number of systems may also have pathogenic consequences, with aberrant complement expression linked to the migratory properties of a number of cancer cells. Increased C5aR1 levels have been reported in squamous cell carcinomas, adenocarcinomas, and transitional cell carcinoma across a number of tissues. C5aR1 expression was associated with increased cell migration and invasiveness in bile, colon, and renal cancers (Nitta et al., 2013; Maeda et al., 2015). In addition, both C3a and C5a anaphylatoxins are capable of driving chemotaxis and adhesion of leukemic cells, primarily through p38 MAPK dependent downregulation of heme oxygenase 1 (Abdelbaset-Ismail et al., 2016). As well as being directly chemotactic, C5aR1 has also been shown to promote epithelial to mesenchymal transition in hepatocellular carcinoma, increasing cell motility and invasiveness (Hu et al., 2016).

2.2. Adhesion

Adhesion is a well-known facet of complement action in the immune context. Multiple arms of complement are involved in the adhesion and extravasation of leukocytes from the circulation to damaged tissues. However, given the scope of this review, we restrict our focus to the non-immune context.

CD46 is a membrane protein that acts traditionally as an inhibitor of complement activation, through the inactivating cleavage of C3b and C4b. However, at the point of conception, expression of CD46 is restricted to the inner acrosomal membrane (IAM) of sperm (Riley et al., 2002a). This unique localisation has been postulated to facilitate the adherence of spermatozoa to the oocyte, permitting penetration and fertilisation (Riley-Vargas et al., 2005; Taylor et al., 1994; Anderson et al., 1993). Interestingly, studies in new world monkeys have suggested that the mechanism of action for CD46 is not through traditional C3b binding, but through an alternative binding domain CCP1 which is selectively expressed in the testes of these animals (Riley et al., 2002b). In support of this, CCP1 blocking antibodies reduced human spermatozoa-egg binding, whereas an antibody against the C3b binding site of CD46 had no effect (Taylor et al., 1994).

C1q, an initiator of the classical complement cascade, has also been linked with adhesive processes outside of immunity. Following fertilisation, the developing embryo must implant into the maternal endometrium. Invasive cytotrophoblasts (CTBs) migrate into the maternal decidua to establish maternofoetal connections required for nutrient exchange and foetal growth. C1q has been demonstrated to facilitate this process, with C1q released by invading CTBs mediating gC1qR and B1 integrin dependent CTB adhesion and decidual migration (Agostinis et al., 2010). Loss of this process in C1q-deficient mice results in embryonic growth restriction with increased foetal resorptions and increased foetal weight after 15 days of pregnancy.