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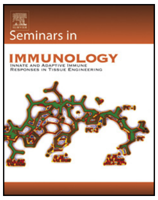

Review

Complement in animal development: Unexpected roles of a highly conserved pathway

Jonathan D. Leslie, Roberto Mayor*

Department of Cell and Developmental Biology, University College London, Gower Street, London WC1E 6BT, United Kingdom

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ABSTRACT

The complement pathway is most famous for its role in immunity, orchestrating an exquisitely refined system for immune surveillance. At its core lies a cascade of proteolytic events that ultimately serve to recognise microbes, infected cells or debris and target them for elimination. Mounting evidence has shown that a number of the proteolytic intermediaries in this cascade have, in themselves, other functions in the body, signalling through receptors to drive events that appear to be unrelated to immune surveillance. It seems, then, that the complement system not only functions as an immunological effector, but also has cell–cell signalling properties that are utilised by a number of non-immunological processes. In this review we examine a number of these processes in the context of animal development, all of which share a requirement for precise control of cell behaviour in time and space. As we will see, the scope of the complement system's function is indeed much greater than we might have imagined only a few years ago.

1. Introduction

The complement system is one of the most ancient immunological systems, with origins in some of the earliest metazoans [1–3]. At its core lies a cascade of activation steps, many of which drive proteolytic cleavages of pro-proteins into activated effectors (Fig. 1). The system is vast and a detailed description of the many components involved can be found in [4]. For the purposes of this review, we will present only the components of the system that are most relevant to the processes described below.

The complement system is activated via three independent pathways that converge on the cleavage of C3 into the fragments C3a and C3b. In the classical pathway, complement activation is triggered by C1, which is composed of C1q, C1r and C1s. Activation of C1q is often initiated by IgM or IgG clusters, and this causes the consecutive activation of C1r and C1s. C1s, in turn, cleaves C4 to generate C4a and C4b and can cleave C4b-bound C2 to produce C4b2b, which drives the activation of C3 (Fig. 1). The lectin pathway is mechanistically similar to the classical pathway: mannose-binding lectins (MBLs) recognise carbohydrates on the surfaces of pathogens, and their associated mannan-binding lectin serine peptidases (MASPs), like C1s, can cleave C4 and C2 to generate the C3 convertase C4b2b as above (Fig. 1). The alternate pathway is involved in surveillance of self versus non-self on all cells, and functionally serves to keep the immune system at an idle speed. It also drives the activation of C3 into C3a and C3b, but a detailed description of the molecules underlying alternative pathway activation is beyond the scope of this review.

Downstream of C3 cleavage C3b production triggers cleavage of C5 into C5a and C5b. C5b in turn recruits C6, C7, C8 and several C9 molecules to generate the membrane attack complex (MAC, or C5b-9_n), which assembles in the plasma membrane of target cells, generating cytolytic pores (Fig. 1). Although osmotic lysis is one result of complement system activity, there are many other processes driven by complement system components. The anaphylatoxins C3a and C5a, which are critical for immune responses and inflammation, signal via their G-protein-coupled receptors C3aR and C5aR, respectively. Both C3a and C5a are strong chemoattractants, directing neutrophil, macrophage and monocyte migration. As we shall see, the interactions between these ligands and their receptors also drive several important developmental processes. Additionally, C3b can be tagged by factor I (fI); iC3b can bind another receptor, CR3, to trigger additional downstream effects. Even the MAC itself can have signalling roles that are different from its function as a lytic pore [5,6], as we will discuss later.

Thus, the complement system includes a vast array of ligands, receptors and regulators that can drive a large number of signalling events. While all of these are involved in immune surveillance, many are also found in other contexts. For example, some members of the complement pathway are important for neuronal elimination during brain development (reviewed in [7]). This observation is not entirely surprising: pruning of synaptic connections is an important

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* Corresponding author. Tel.: +44 20 7679 3323; fax: +44 20 7679 7349.
E-mail address: r.mayor@ucl.ac.uk (R. Mayor).

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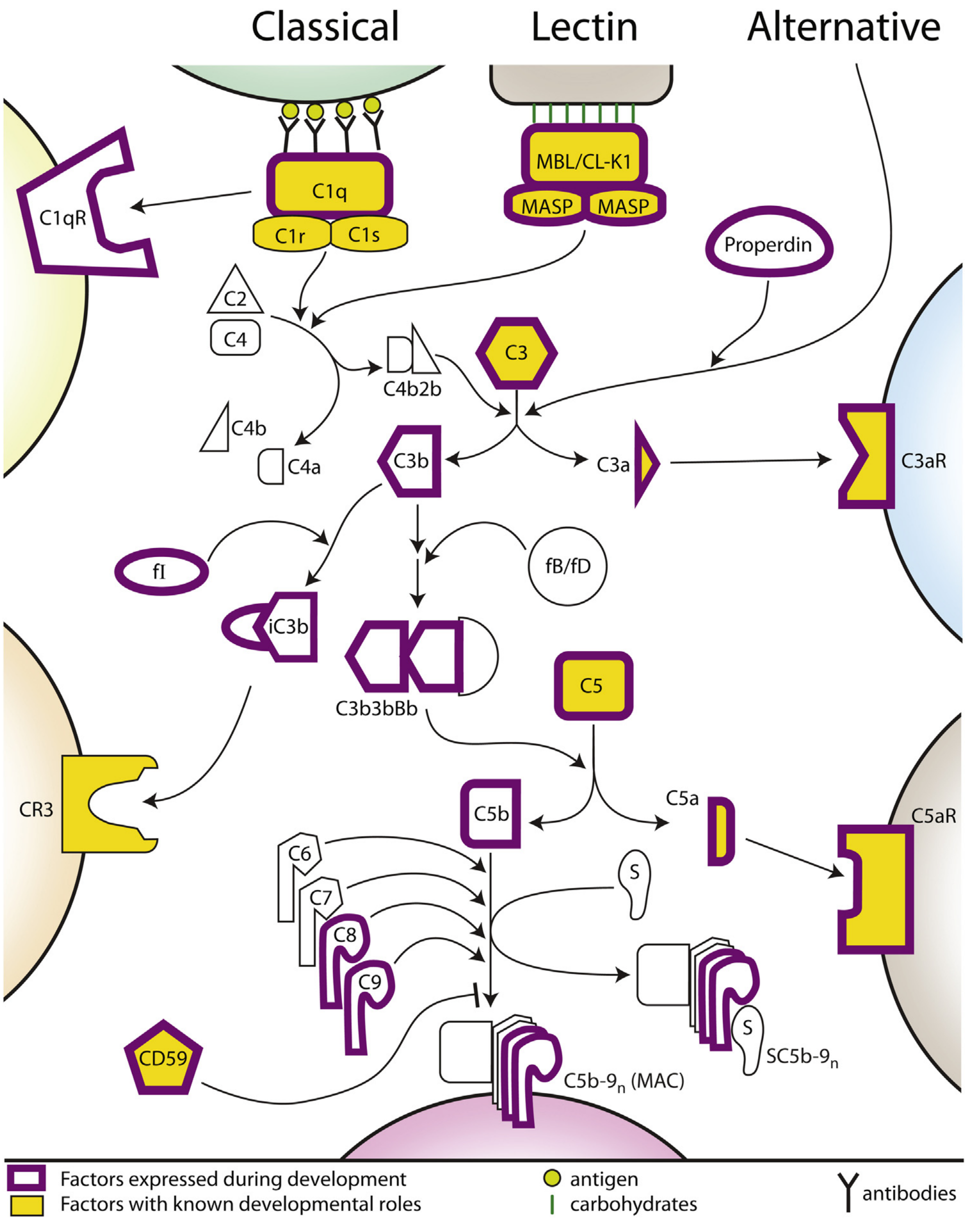

Fig. 1. The complement pathway in development. Simplified representation of the core components of the complement system. Proteins known to be involved in developmental or regenerative processes and discussed herein are highlighted in yellow; those expressed during development or regeneration are outlined in purple. Complement system activation can occur via three separate pathways, the classical, the lectin and the alternative pathways. These converge at the level of C3 cleavage, generating C3a and C3b. C3a can signal via C3aR, while C3b production leads to the cleavage of C5. C3b can also be tagged by factorI (fI) to yield iC3b, which can signal via CR3. C5a can trigger signal transduction via C5aR, and C5b initiates the assembly of the MAC by recruiting C6, C7, C8 and a number of C9 molecules. S-protein/vitronectin (S) can also complex with C5b-9 to form a soluble form of the MAC, called SC5b-9. fB, factor B; fD, factor D.

part of the neuronal development, and elimination of neurons in later stages of development has been well documented [8,9]. Thus, it seems that development and immunology may have evolved to share the same mechanisms for ridding the body of unwanted cells.

Yet the complement system also has other developmental responsibilities that extend well beyond the realm of cell clearance. *Xenopus* embryos express a number of complement components during the early stages of development [10,11]. These early patterns of expression are not limited to amphibians: recent evidence suggests that they may be shared by other vertebrates, such as fish [12], mice [13,14] and humans [14]. These findings have led to surprising findings about how the complement pathway helps to drive morphogenetic movements during development through somewhat unexpected mechanisms [12,15–17].

In this review, we will discuss these observations in more detail and present our current understanding of many of the ways in which the complement pathway contributes to animal development. In many cases, we are only beginning to appreciate the scope this involvement. Yet as we learn more about this complex system, we begin to see a picture of a pathway whose diverse roles in non-immunological processes is indeed remarkable.

2. The complement pathway in development

2.1. Synapse elimination

For years it was believed that the immune system played no role in the central nervous system, neither during development nor in adult life. This concept of “immune privilege” was largely based on the low level of expression of immune system proteins on the surfaces of CNS cells (for example, MHC class I proteins) or