Molecular Immunology xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Molecular Immunology

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

Review

Complement in therapy and disease
Regulating the complement system with antibody-based therapeutics☆

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ARTICLE INFO

Article history:
Received 16 December 2014
Received in revised form 26 January 2015
Accepted 27 January 2015
Available online xxx

Keywords:
Complement
Immunology
Antibody
Therapy
Antibody engineering
Cancer

ABSTRACT

Complement is recognized as a key player in a wide range of normal as well as disease-related immune, developmental and homeostatic processes. Knowledge of complement components, structures, interactions, and cross-talk with other biological systems continues to grow and this leads to novel treatments for cancer, infectious, autoimmune- or age-related diseases as well as for preventing transplantation rejection. Antibodies are superbly suited to be developed into therapeutics with appropriate complement stimulatory or inhibitory activity. Here we review the design, development and future of antibody-based drugs that enhance or dampen the complement system.

1. The complement cascade: a fine interplay of molecular interactions regulates functional outcome

The complement system is an evolutionarily well-conserved system of which the current complexity in jawed vertebrates emerged 600 million years ago, while some components of the most primitive complement system date 1.6 billion years back (Nonaka and Kimura, 2006). Complement was identified in the late 1800s as a heat-labile, bactericidal component in serum (Bordet, 1895; Ehrlich, 1899). This activity of innate immunity was further unraveled in the following century. One by one, essential components were identified, purified, and assigned a place in the cascade from pathogen recognition to response amplification and pathogen inactivation (Fig. 1A) (Hadding and Mueller-Eberhard, 1969; Mueller-Eberhard and Biro, 1963; Nilsson, 1967; Nilsson and Mueller-Eberhard, 1965; Pillemer and Ecker, 1941). Nowadays, three activation pathways of complement, initiated through distinct ligand–receptor interactions, are well-defined: the classical pathway, the lectin pathway, and the alternative pathway (Fig. 1A). The pathways converge at an amplification stage characterized by the formation of C3 and C5 convertases, and cooperate closely to form opsonins, anaphylatoxins, chemoattractants, and membrane attack complexes (MACs). Complement is heavily regulated by both soluble and cell-surface expressed proteins, by which it is constantly activated and quenched to maintain a delicate balance. However, it can be amplified rapidly when an immediate immune reaction against a pathogenic challenge is required. Approximately 50 soluble and cell surface-attached components are currently known to comprise the major proteolytic components, cofactors, and regulators of the entire complement cascade (Gros et al., 2008; Holers, 2014; Kemper et al., 2014; Meyer et al., 2014; Ricklin et al., 2010) (Fig. 1B).

Antibodies can deploy the complement cascade as a potent effector mechanism. IgG or IgM antibodies activate the classical pathway of complement through binding of C1q *via* their Fc region. C1q consists of six collagen-like arms, each containing an N-terminal triple helix and a C-terminal immunoglobulin-binding globular head domain (Reid and Porter, 1976) with an overall shape of a bunch of tulips (Fig. 2). The affinity of a single C1q globular head for immunoglobulin Fc is low (Feinstein, 1986; Hughes-Jones and Gardner, 1979), such that physiological binding and activation

☆ This article belongs to Special Issue on Therapeutic Antibodies.

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http://dx.doi.org/10.1016/j.molimm.2015.01.028

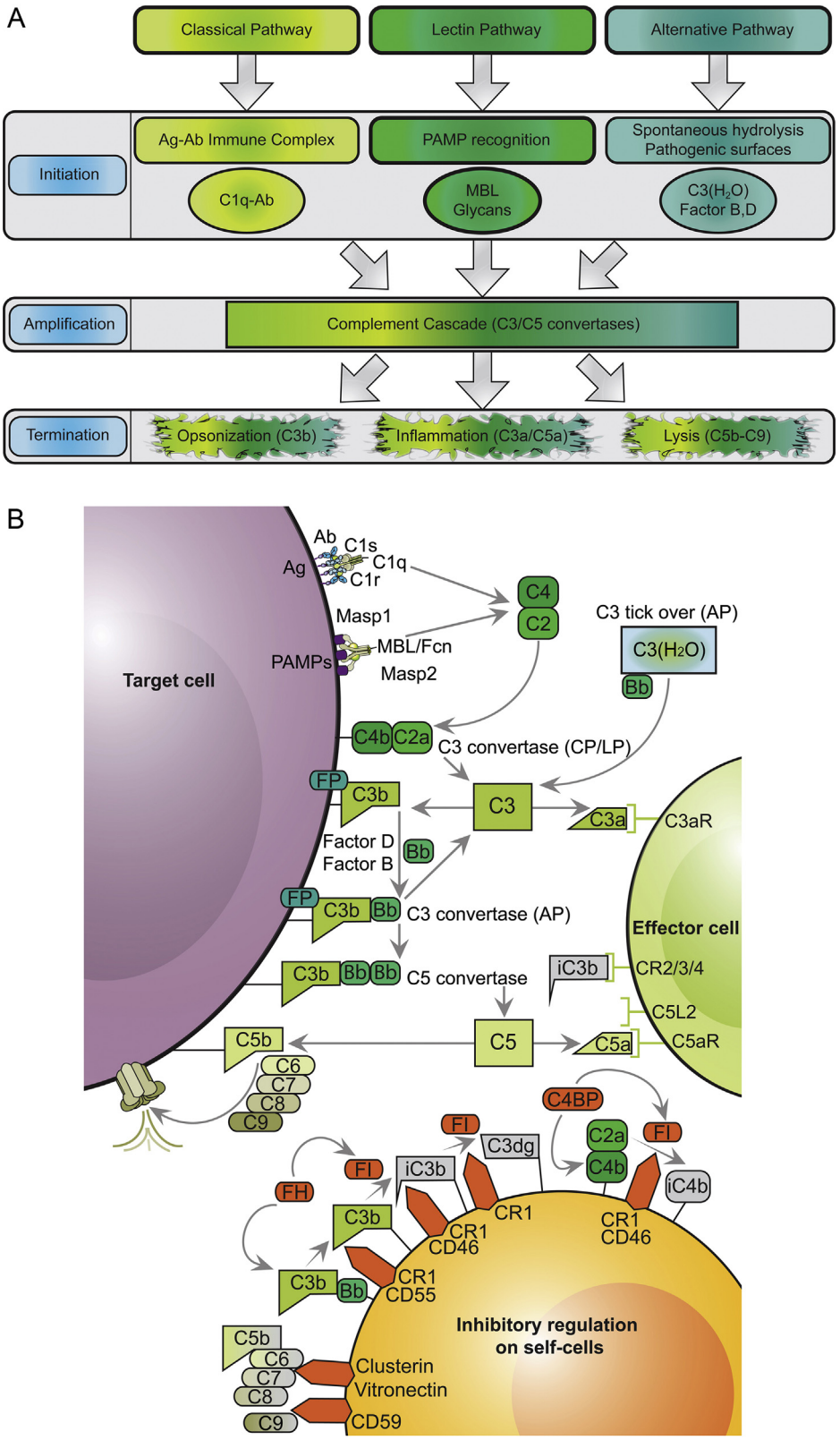

Fig. 1. A simplified (A) and more detailed (B) overview of the complement system. Activation can be achieved *via* the classical pathway, the lectin pathway, or the alternative pathway. Initiation of the classical pathway occurs when C1 (C1q in complex with the serine proteases C1r and C1s) interacts with the Fc region of IgG or IgM antibodies attached to antigenic surfaces. In the lectin pathway, mannose-binding lectin (MBL) and ficolins assemble with MBL-associated serine proteases (MASPs). The alternative pathway is induced by C3 hydrolysis, either spontaneously at low rate or enhanced by interaction of C3 with pathogen's cell surfaces. All three pathways lead to the formation of C3 and C5 convertases, which rapidly amplify the complement response. The outcome of complement activation is three-pronged: (1) opsonization of the target surface by C3b, (2) a boost in inflammation through the generation of anaphylatoxins C3a and C5a and subsequent recruitment of effector cells and (3) formation of the terminal membrane attack complex (MAC), which is responsible for target cell lysis. In addition to the processes described above, several complement regulatory proteins (indicated in orange) are able to inhibit complement by inactivation of C3b and C3 convertases, or by preventing successful formation of the MAC.

Please cite this article in press as: Melis, J.P.M., et al., Complement in therapy and disease. Regulating the complement system with antibody-based therapeutics. Mol. Immunol. (2015), http://dx.doi.org/10.1016/j.molimm.2015.01.028