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Review

How antibodies use complement to regulate antibody responses

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ABSTRACT

Antibodies, forming immune complexes with their specific antigen, can cause complete suppression or several 100-fold enhancement of the antibody response. Immune complexes containing IgG and IgM may activate complement and in such situations also complement components will be part of the immune complex. Here, we review experimental data on how antibodies via the complement system upregulate specific antibody responses. Current data suggest that murine IgG1, IgG2a, and IgG2b upregulate antibody responses primarily via Fc-receptors and not via complement. In contrast, IgM and IgG3 act via complement and require the presence of complement receptors 1 and 2 (CR1/2) expressed on both B cells and follicular dendritic cells. Complement plays a crucial role for antibody responses not only to antigen complexed to antibodies, but also to antigen administered alone. Lack of C1q, but not of Factor B or MBL, severely impairs antibody responses suggesting involvement of the classical pathway. In spite of this, normal antibody responses are found in mice lacking several activators of the classical pathway (complement activating natural IgM, serum amyloid P component (SAP), specific intracellular adhesion molecule-grabbing non-integrin R1 (SIGN-R1) or C-reactive protein. Possible explanations to these observations will be discussed.

1. Introduction

An important part of our immune system are the antibodies. These large protein molecules are essential in the defense against infectious agents such as bacteria and viruses, but can also be harmful. When reacting against self antigens, antibodies may cause autoimmune diseases and when reacting against non-infectious antigens, such as pollen, allergic disease can be induced. The consequences of recognition of a target structure by an antibody depends on which effector functions the antibody can initiate, and this in turn depends on its isotype or subclass. An antibody's effector functions are primarily mediated via binding to various Fc-receptors or by activation of the complement system. In addition to their role in attacking pathogens, antibodies can regulate the immune response against the antigen they bind to. This is evidenced by the observations that antigens administered to animals together with specific antibodies can induce a dramatically different immune response than when the antigen is administered alone. The phenomenon is known as antibody feedback regulation, and can result in complete suppression or several hundred-fold enhancement of the specific antibody responses (reviewed in Heyman, 2000, 2003, 2013; Hjelm et al., 2006; Nimmerjahn and Ravetch, 2010). Not only passively transferred, but also endogenously produced antibodies affect immune responses. In the experimental situation, specific antibodies are administered in close temporal relationship to the antigen. This leads to enhanced or suppressed responses, usually to the entire antigen, independently of which epitopes the antibodies bind to. Although antibody feedback regulation was discovered already in the end of the 19th century (von Behring and Wernicke, 1892), the underlying mechanisms are incompletely understood. Instead of being presented with a "naked" antigen, the immune system is presented with an immune complex consisting of antigen, antibody and often complement components. Since an immune complex can bind not only to BCRs but also to Fc- and complement receptors, it will have many possibilities to affect immune responses.

Lack of certain factors of the complement system is known to cause severely impaired antibody responses both in animals and humans (Botto et al., 2009; Carroll and Isenman, 2012). Very little is known about how specific antibodies regulate human immune responses, but an interesting example is the so called Rhesus

Abbreviations: BCR, B cell receptor; BSA, bovine serum albumin; CR1/2, complement receptor 1 and 2 (CD35/CD21); CRP, C-reactive protein; FDCs, follicular dendritic cells; KLH, keyhole limpet hemocyanine; MBL, mannose binding lectin; MZ, marginal zone; OVA, ovalbumin; RhD, Rhesus D blood group; SAP, serum amyloid P component; SIGN-R1, specific intracellular adhesion molecule-grabbing non-integrin R1; SRBC, sheep red blood cells; TNP, trinitrophenyl.

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prophylaxis. Pregnant women with the RhD negative blood group can become immunized against fetal RhD positive erythrocytes, acquired via transplacental hemorrhage. This can lead to production of IgG anti-RhD in the mother and passage of these antibodies over the placenta may damage fetal erythrocytes. Administration of small doses of therapeutic IgG anti-RhD during pregnancy or immediately after delivery prevents maternal immunization and has brought the incidence of hemolytic disease of the newborn down dramatically (Clarke et al., 1963; Urbaniak and Greiss, 2000). In contrast, administration of IgM anti-RhD led to an enhanced production of anti-RhD antibodies (Clarke et al., 1963). These findings are paralleled by the ability of IgG to suppress and of IgM to enhance antibody responses to erythrocytes in experimental models, and suggest that the similarities between antibody feedback regulation in humans and animals are considerable.

The focus of the present review will be on current understanding of antibody-mediated feedback regulation in experimental models where complement may be involved. Therefore, only regulation by IgM and IgG is discussed although also IgE has potent immunoregulatory effects (Getahun et al., 2005).

2. Complement and antibody responses to uncomplexed antigens

A role for complement in antibody responses was first recognized when animals depleted of C3 by treatment with cobra venom factor showed a markedly impaired antibody response (Pepys, 1974). Now it is known that hereditary deficiencies or gene targeting leading to lack of C1qA and thereby the entire C1q molecule (Cutler et al., 1998; Rutemark et al., 2011), C2 (Bitter-Suermann et al., 1981), C3 (Fischer et al., 1996; OíNeil et al., 1988), C4 (Fischer et al., 1996; Jackson et al., 1979; Ochs et al., 1983), or CR1/2 (Ahearn et al., 1996; Carlsson et al., 2009; Croix et al., 1996; Fang et al., 1998; Molina et al., 1996; Rutemark et al., 2011, 2012; Thiel et al., 2012), lead to severely impaired antibody responses in many species, including humans (reviewed in (Botto et al., 2009; Carroll, 2004; Carroll and Isenman, 2012). Primary responses, memory responses, thymus dependent and thymus independent responses are affected. The influence of complement is more pronounced against suboptimal antigen doses, but also responses to antigens administered in adjuvants can be impaired.

2.1. Primary importance of the classical pathway for antibody responses

The complement cascade leading to cleavage of C3 can be activated via three pathways: the classical, lectin, and alternative pathways. Antibody responses in mice lacking Factor B of the alternative pathway (Matsumoto et al., 1997; Mehlhop and Diamond, 2006) are normal. Mice lacking mannose-binding lectin (MBL) of the lectin pathway have either normal, moderately higher or moderately lower antibody responses than wildtype mice (Carter et al., 2007; Guttormsen et al., 2009; Lawrence et al., 2009; Ruseva et al., 2009). Noteworthy is that the defect occasionally seen in MBL-deficient animals is not nearly as severe as the defect in C1q-deficient mice (Cutler et al., 1998; Rutemark et al., 2011). Also ficolins can activate the lectin pathway. Mice deficient in ficolin A, ficolin B, both ficolin A and B, or MASP-2 (which completely lack lectin pathway activation but retain activation via the classical and alternative pathways) are more susceptible to *Streptococcus pneumoniae* infection than wildtype mice (Ali et al., 2012; Endo et al., 2012). To our knowledge, no studies of antibody responses have been performed in these animals and therefore firm conclusions on whether the lectin pathway affects antibody responses cannot be drawn. However, the fact that antibody responses are severely impaired in C1q-deficient mice, argues against a major role of either the lectin or the alternative pathway. An overview over the importance of complement factors for antibody responses can be found in Fig. 1.

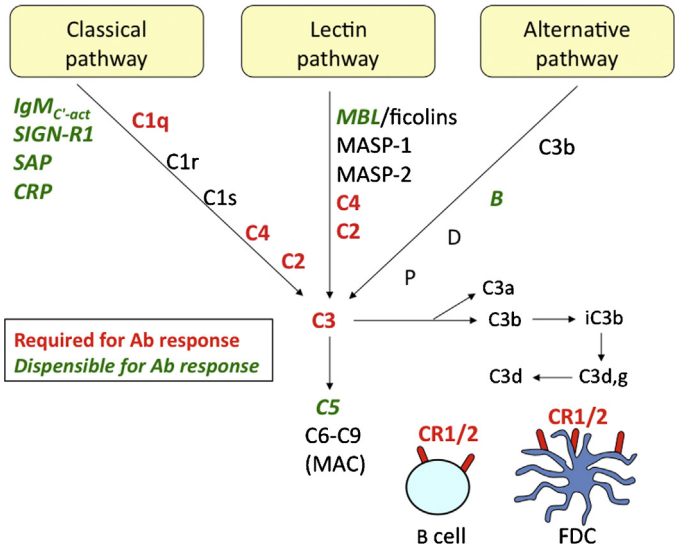

Fig. 1. Involvement of the complement system in antibody responses. Antibody responses in animals lacking the factors and receptors in red (bold) are severely impaired (C1q, C4, C2, C3, CR1/2) whereas antibody responses in animals lacking factors in green (bold italics) are largely normal (complement-activating IgM, SIGN-R1, SAP, CRP, MBL, C5, Factor B). Noteworthy is (i) that disruption of the classical pathway alone leads to impaired antibody responses, although all pathways generate CR1/2 ligands and (ii) that lack of C1q, but not of any of the tested classical pathway activators, leads to impaired antibody responses (adapted from Rutemark et al., 2011).

2.2. Linear relationship between C1q, C2, C4, C3, and CR1/2 in antibody responses?

The phenotype with regard to antibody responses is similar in animals lacking C1q, C2, C4, C3, or CR1/2. Therefore, it is generally assumed that the complement system exerts its regulatory effects via CR1/2, and that the other factors are required merely to generate the C3 split products constituting the ligands for these receptors (iC3b, C3d(g), and C3b for CR1; iC3b and C3d(g) for CR2). Since all three pathways for complement activation are able to generate CR1/2 ligands, it is puzzling that only one is required for antibody responses. One possibility is that there is a quantitative difference in the ability of the activation pathways to cleave C3 and that only the classical pathway generates sufficient amounts of CR1/2-ligands. Another possibility is that C1q plays two parallel roles which are both crucial for antibody responses, one complement-activating and one non-complement activating (Nayak et al., 2012). For the remainder of the discussion we will however assume that the roles of C1q and CR1/2 in antibody responses are linked.

2.3. CR1 versus CR2 in antibody responses

Complement receptors 1 and 2 are primarily expressed on B cells and FDCs. In mice, both receptors are derived from one gene, Cr2, by alternative splicing (Kurtz et al., 1990). Because of this, Cr2 knockout mice lack both receptors and most studies demonstrating the crucial role of CR1/2 on antibody responses have been performed in such animals. The initial observations that CR1/2 were involved in antibody responses were made with blocking monoclonal antibodies (Heyman et al., 1990; Thyphronitis et al., 1991). Treatment of mice with antibodies binding to both CR1 and CR2, but not to CR1