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Complement receptor 2, natural antibodies and innate immunity: Inter-relationships in B cell selection and activation

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Abstract

Complement receptor type 2 (CR2) is a receptor that serves as an important interface between the complement system and adaptive immunity. Recent studies have shown that CR2 is also centrally involved in innate immunity, and one key area is the development of potentially pathogenic natural antibodies that target neo-epitopes revealed in ischemic tissue undergoing reperfusion. Mice lacking either total immunoglobulins or CR2 alone are protected from the development of ischemia-reperfusion injury, and this effect can be reversed by introducing CR2-sufficient B-1 cells or by transferring polyclonal natural IgM antibody from wild type mice as well as monoclonal antibodies that recognize phospholipids, DNA or non-muscle myosin. We will report at the XXI ICW an additional membrane-associated protein to which pathogenic IgM antibodies are directed. Whether B cells producing these natural antibodies are differentially selected in CR2-deficient mice is as yet not well understood, and the complement-related mechanism(s) whereby this differential repertoire selection process could occur have yet to be explored in any detail. In addition to this important role in innate immunity, CR2 can also act as a receptor for other components or activators of innate immunity. One such component is interferon-alpha, an anti-viral cytokine that binds CR2 and induces a component of its mRNA signature in B cells through this receptor. Other potential CR2 ligands are DNA and DNA-containing complexes such as chromatin. The biologic role of these CR2 interactions with interferon-alpha and DNA-containing complexes is not well understood, but may be important in the development of the autoimmune disease systemic lupus erythematosus that is characterized by enhanced interferon-alpha levels and loss of self tolerance to DNA-containing self antigens.

Keywords: Complement; Innate immunity; B cells; Ischemia-reperfusion; Natural antibodies

1. Introduction

1.1. Overview of innate and adaptive immunity

Innate immunity is operationally defined as responses by cells of the immune system, primarily directed to pathogens but also to self antigens, that do not include either the phenomenon of immunologic memory, which is manifested by more robust responses to secondary or later exposures, or genetic changes such as recombination and somatic mutation (Medzhidov and Janeway, 2002; Holers et al., 2005). In essence, innate immunity comprises those components that are "hard-wired" into the immune system. In contrast, adaptive immunity is that component of the immune response which includes both memory and changes in gene and/or protein structure during development or in response to antigen, and is focused on T and B cell responses.

T and B cell antigenic responses in adaptive immunity can be directed to both self and non-self antigens. With regard to innate immunity, although it is often thought that this system is directed only to pathogens or foreign antigens, there is substantial evidence that there are major components of the innate immune system, including complement, that are directed to recognize self structures (Holers et al., 2005). Thus, for both innate and adaptive immunity, a major function is the separation of self from non-self, and how this discriminatory capability has evolved and practically works remains a fascinating question. When autoimmunity, or pathologic disease-related loss of self tolerance, develops, this process is characterized in adaptive immunity by the presence of class-switched, high affinity IgG autoantibodies and antigen-specific T cells (Kotzin, 1996). Similarly, "innate autoimmunity" is characterized by uncontrolled

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autoinflammation directed to self tissues (Holers et al., 2005; Stojanov and Kastner, 2005).

Although both innate and adaptive immune systems are also often discussed separately, there are many inter-connections between the two, with bi-directional control. One of the best examples is the complement system, where C3-derived ligands shape the adaptive humoral immune system (Carroll, 1998) and modulate T cell activation through interactions with complement regulatory proteins (Longhi et al., 2006) as well as mediate many of the effector functions of antibodies themselves (Holers, 2003). Thus, each immune response cannot be viewed as a linear function, but is rather a complex and continuously evolving system with many feedback systems.

1.2. Complement is a key component of innate immunity

The complement pathway is one of the major means by which the body recognizes and fights off foreign antigens and pathogens [reviewed in (Fearon and Locksley, 1996; Holers, 2003)]. Although the major function of complement has traditionally been thought to be focused on this process of recognition and elimination of pathogens (Frank et al., 1994; Brown, 1991), it is also now clear that complement also participates centrally in recognition of self antigens such as those that develop during apoptosis (Botto and Walport, 2002). In addition, the complement system through CR2 plays immunoregulatory roles such as enhancing humoral immunity to T-dependent and T-independent foreign antigens (Ahearn et al., 1996; Molina et al., 1996; Carroll, 2000; Haas et al., 2002) (Fig. 1) and in regulating T cell immunity to self and non-self antigens (Kaya et al., 2001; Pratt et al., 2000; Fairweather et al., 2006). Recently, an additional complement receptor designated CRIg for circulating C3b-bound antigens has been found on Kuppfer cells, which likely plays the major role in clearance of pathogens from the blood system (Helmy et al., 2006).

In addition to immunoregulatory functions, other studies have focused attention on the roles that the complement system plays in recognition and effector functions during self tissue injury (Holers, 2003; Thurman and Holers, 2006) and in shaping the development of the natural antibody repertoire by influencing the development of reactivity with certain self antigens (Fleming et al., 2002; Reid et al., 2002; Holers, 2005; Holers et al., 2005; Zhang et al., 2004, 2006). This issue is further explored below in detail.

The two pathways of complement that are most often associated with innate immunity are the lectin and the alternative pathways, although the classical pathway certainly plays a role through recognition of targets directly by C1q, or indirectly through C-reactive protein (CRP) or serum amyloid P (SAP) binding by C1q (Reid et al., 2000). Recently a novel mechanism utilizing the cell surface lectin SIGN-R1 has been described through which this protein can bind C1q and fix C3 in an antibody-independent manner (Kang et al., 2006). Alternative pathway activation is promoted on surfaces that have neutral or positive charge characteristics and do not express endogenous complement inhibitors, or bind the serum-derived complement inhibitor factor H (Zipfel et al., 2002; Muller-Eberhard, 1988).

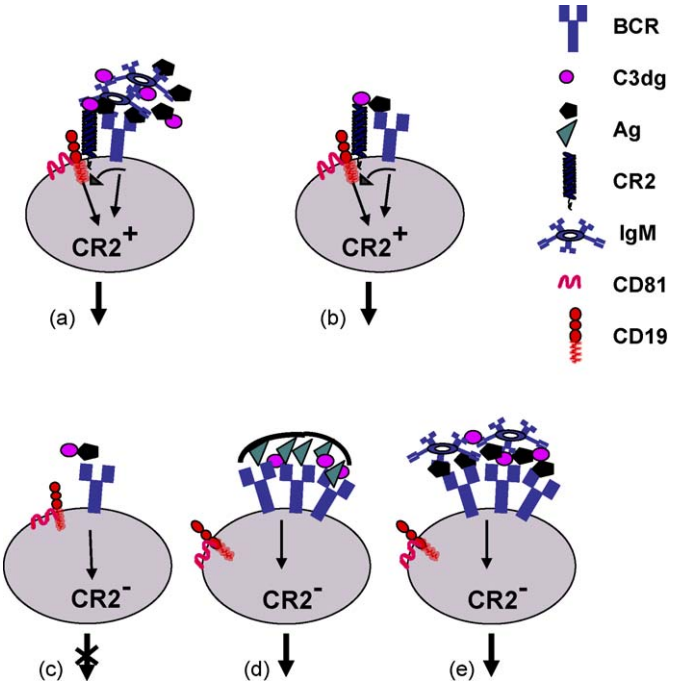

Fig. 1. (a) In the majority of cases, antigens are initially recognized by the BCR as part of immune complexes consisting of pre-existing natural antibodies that bind the antigen as well as covalently attached specific cleavage products of activated complement C3. (b) Alternatively, antigen bound to the IgM BCR can also trigger complement activation and C3 fixation. Because CR2 is non-covalently associated with CD19, the binding of immune complexes to both the BCR and CR2 brings CD19 into proximity of BCR-associated kinases, following which the cytoplasmic tail of CD19 is rapidly and efficiently phosphorylated. The activation of CD19 in this manner multiplies BCR activation several thousand-fold. Thus, CR2-expressing B cells are capable of being activated by very low concentrations of the presented antigen or by an antigen that has a low avidity for the particular BCR. (c) When CR2 is absent, low amounts of antigen or antigen without sufficient avidity will not effectively trigger activation signal. (d) Multivalent antigens cross-linking multiple BCR are capable of activating B cells. (e) Similarly, if the pre-existing IgM recognizes antigens and make multivalent complexes, B cells can receive sufficient activation signals. However, in both cases in CR2 deficient B cells the quality and the strength of the activation signals are insufficient to activate cells effectively.

The lectin pathway is initiated by the binding of mannose binding lectin (MBL) or serum ficolins to repeating carbohydrate moieties found primarily on the surface of microbial pathogens [reviewed in (Reid and Turner, 1994; Matsushita et al., 2000; Fujita et al., 2004)]. In addition, though, the protein cytokeratin, when it is exposed on ischemic endothelial cells (Collard et al., 1998), also activates this pathway, as can antibodies bearing a specific form of agalactosyl carbohydrate designated G0 (Malhotra et al., 1995). Of interest, although the best evidence for the mechanism by which MBL binding leads to C3 activation is that this pathway proceeds through the initial cleavage of C4 and C2, several lines of research suggest that C3 may be directly activated by the lectin pathway without utilizing C4 or C2 (Fujita et al., 2004; Selander et al., 2006).

1.3. Other components of innate immunity

The innate immune system is composed of many redundant pathways, and complement is only one of these many