Available online at www.sciencedirect.com
ScienceDirect
Molecular Immunology 44 (2007) 103–110
Molecular Immunology
www.elsevier.com/locate/molimm

Natural antibody mediated innate autoimmune response

Ming Zhang [a], Michael C. Carroll [b,c,*]

[a] Department of Anesthesiology, SUNY-Downstate Medical Center, Brooklyn, NY 11203, United States
[b] The CBR Institute of Biomedical Research Inc., Harvard Medical School, 800 Huntington Ave, Boston, MA 02115, United States
[c] Departments of Pathology and Pediatrics, Harvard Medical School, Boston, MA 02115, USA

Received 26 May 2006; received in revised form 27 June 2006; accepted 28 June 2006
Available online 28 July 2006

Abstract

Recent advance in autoimmunity research reveals that the innate immune system is able to recognize self-targets and initiate inflammatory response in a similar way as with pathogens. This review describes one novel example of this innate autoimmunity, ischemia–reperfusion (I/R) injury. Studies of intestinal, skeletal muscle, and heart I/R models showed that reperfusion of ischemic tissues elicits an acute inflammatory response involving serum complement system which is activated by natural IgM. The recent identification of a monoclonal natural IgM that initiates I/R led to the identification of non-muscle myosin heavy chain type II A and C as the self-targets in two different tissues. New evidence further suggests that IgM binds initially to ischemic antigen providing a binding site for mannan binding lectin (MBL) which subsequently leads to activation of complement and results in tissue injury. Therefore, natural IgM mediated innate autoimmunity is likely responsible for the detrimental consequences in ischemic diseases.

Keywords: Natural antibody; Innate immunity; Complement; Ischemia–reperfusion injury

1. Introduction

The innate immune system includes proteins such as toll-like receptors (TLR), collectins, C-reactive protein (CRP), serum complement, and natural antibody. These molecules represent the first line of host defense against pathogens. They operate through recognition of conserved patterns on the targets on pathogens. However, cross-reactivity may inevitably happen when such conserved patterns exist on host antigens. An example is that heat shock protein 70 presents pathogen-associated molecular patterns (PAMPs) for TLR and triggers sterile inflammatory response (Quintana and Cohen, 2005; Vabulas et al., 2002). This type of response is termed "innate autimmunity", as the initial event is based on the innate recognition of self-molecules (Carroll and Holers, 2005).

In this review, we discuss a recently uncovered model of innate autoimmunity, ischemia–reperfusion injury. This autoimmune injury is clinically relevant and mediated by the recognition of natural antibody against self-proteins exposed by ischemia. This review focuses on the initiation phase of autoimmune injury, so downstream events such as neutrophil infiltration, mast cell activation, or injury mediated by the terminal components of complement are not discussed in depth.

2. Ischemia–reperfusion injury

Ischemia–reperfusion injury is a major complication in many clinical entities. In general, it represents an acute inflammatory response following an ischemic event and subsequent restoration of blood flow (Cotran, 1999). It is primarily responsible for the severity of myocardial infarction, cerebral ischemic events, intestinal ischemia, and many aspects of vascular surgery, trauma, and transplantation (Cotran, 1999). Ischemic heart disease and stroke represent number one and three killers in America, and leading causes of serious disability. Although intestinal ischemia happens much less clinically than heart attack and stroke, its acute form is a lethal complication with high mortality rate of 70–90% (Brandt, 2003).

To understand the pathogenesis and develop therapy for I/R injury, the vast majority of research in this field focus on the

* Corresponding author at: The CBR Institute for Biomedical Research Inc., Harvard Medical School, 800 Huntington Ave, Boston, MA 02115, United States. Tel.: +1 617 278 6660; fax: +1 617 278 6655.
E-mail address: carroll@cbrinstitute.org (M.C. Carroll).

0161-5890/$ – see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.molimm.2006.06.022

cellular response of ischemic tissue. During ischemia, hypoxic cells undergo specific changes including mitochondrial alteration (Halestrap et al., 2004; Madesh et al., 1997; Wu et al., 2004), reactive oxygen species (ROS) generation (Becker, 2004; Grisham et al., 1986; Li and Jackson, 2002; Watts and Kline, 2003), Ca^{2+} (and other ions) imbalance (Piper et al., 2004), activation of kinases, proteases, and lipases (Armstrong, 2004; El-Assal and Besner, 2005; Um et al., 2005; Zheng et al., 2005), damage to membrane protein and lipid (Moore et al., 1995; Spiteller, 1996), NF-κB signaling (Chen et al., 2003; Dawn et al., 2004; Kawano et al., 2006; Misra et al., 2003; Yeh et al., 2000; Zou et al., 2003), activation of poly(ADP-ribose) polymerase (PARP) (Liaudet et al., 2000; Szabo et al., 2004). If cellular injury left unchecked, it will lead to cell death (Eefting et al., 2004; Ikeda et al., 1998; Itoh et al., 2000; Noda et al., 1998; Wu et al., 2002; Zhao, 2004).

Previous studies also noticed that an inflammatory response occurs involving complement, neutrophils (Arndt et al., 1991; Carmody et al., 2004; Kurtel et al., 1992; Schmeling et al., 1989; Sisley et al., 1994; Vinten-Johansen, 2004; Zimmerman et al., 1990), mast cells (Abonia et al., 2005; Frangogiannis et al., 1998; Kanwar et al., 1998; Szabo et al., 1997), and cytokines (Cuzzocrea et al., 2004; Frangogiannis et al., 2002; Mbachu et al., 2004; Sorkine et al., 1995). One hypothesis is that hypoxic cells activate neutrophils which contribute to vascular reperfusion injury by producing reactive oxygen species. However, additional mechanism must be involved since cellular injury can occur in the presence of limited number of inflammatory cells (Koike et al., 1995; Li and Jackson, 2002; Simpson et al., 1993; Szabo et al., 1997).

Our current hypothesis is that injury results from both intrinsic and extrinsic pathways following initial ischemia and reperfusion (Fig. 1) (Zhang et al., 2006a). In the intrinsic pathway ischemia and subsequent reperfusion lead to a number of intracellular changes that render ischemic cells susceptible to a second phase of injury, i.e. the extrinsic pathway, which is mediated by natural IgM and complement. Accordingly, alterations in cell morphology are recognized by the innate immune system resulting in an acute inflammatory response (Carroll and Holers, 2005).

3. Natural antibodies mediate I/R injury

Earlier supporting evidence of this hypothesis emerged from the study by Weisman et al. (1990) who proposed that acute inflammatory attack following reperfusion was dependent on activation of the serum complement system. They found that pretreatment with a soluble inhibitor of complement C3b, i.e. sCR1, can significantly reduce reperfusion injury in a rat cardiac model (Weisman et al., 1990). Similar results were subsequently observed in intestinal (Hill et al., 1992) and skeletal muscle (hind limb) I/R models (Lindsay et al., 1992).

The finding that an intact classical pathway of complement may be required for I/R injury led to the first suggestion that antibody might be involved in mediation of inflammation (Weiser et al., 1996). Indeed, mice deficient in classical pathway components, namely C4, C3, or total immunoglobulin ($RAG^{-/-}$) are equally protected in the hind limb model as well as intestinal model (Weiser et al., 1996; Williams et al., 1999). Moreover, reconstitution of RAG-$1^{-/-}$ mice with IgM from wild-type (WT) mouse sera restored injury (Weiser et al., 1996; Williams et al., 1999). These observations led to a hypothesis that I/R injury is initiated by recognition and binding of pre-existing or natural IgM to neo-epitopes expressed by hypoxic cells (Weiser et al., 1996).

Recent studies extended this hypothesis suggesting that a subset of B lymphocytes, in particular B-l cells, are a major source of pathogenic IgM (Fig. 2) (Fleming et al., 2002; Reid et al., 2002). Notably, mice deficient in complement receptors CD21 and CD35 ($Cr2^{-/-}$) have a pronounced reduction in injury in the intestinal I/R model (Fleming et al., 2002; Reid et al., 2002). The protection is due to lack of specific IgM as reconstitution of either strain with IgM prepared from WT mice restores injury (Fleming et al., 2002; Reid et al., 2002). Alternatively, reconstitution of RAG-$1^{-/-}$ mice with IgM isolated from $Cr2^{-/-}$ mice failed to restore injury to a similar degree as WT IgM (Reid et al., 2002). Thus, these studies demonstrated that I/R injury was not inherent property of all IgM but suggested that it was specific (Reid et al., 2002).

To determine if specific natural IgM mediates the acute inflammatory response in the myocardial I/R, we examined

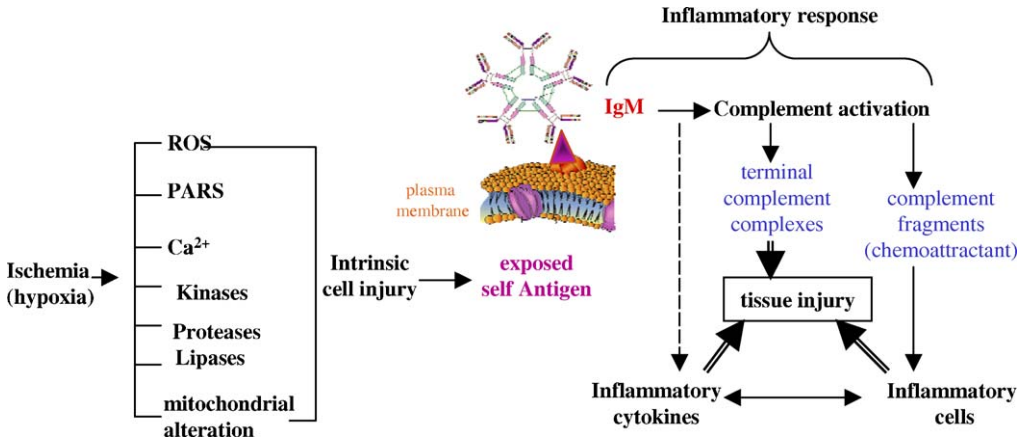

Fig. 1. A model for the initiation of the inflammatory response in I/R injury. Single lines indicate a pathway, double lines indicate an effector-target relationship. PARP, poly(ADP-ribose) polymerase.