J Immunol. 2002 Dec 1;169(11):6417-26. Function of the lectin domain of Mac-1/complement receptor type 3 (CD11b/CD18) in regulating neutrophil adhesion.
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A lectin function within CD11b mediates both cytotoxic priming of Mac-1/complement receptor type 3 (CR3) by beta-glucan and the formation of transmembrane signaling complexes with GPI-anchored glycoproteins such as CD16b (FcgammaRIIIb). A requirement for GPI-anchored urokinase plasminogen activator receptor (uPAR; CD87) in neutrophil adhesion and diapedesis has been demonstrated with uPAR-knockout mice. In this study, neutrophil activation conditions generating high-affinity (H-AFN) or low-affinity (L-AFN) beta(2) integrin adhesion were explored. A role for the Mac-1/CR3 lectin domain and uPAR in mediating H-AFN or L-AFN adhesion was suggested by the inhibition of Mac-1/CR3-dependent adhesion to ICAM-1 or fibrinogen by beta-glucan or anti-uPAR. The formation of uPAR complexes with Mac-1/CR3 activated for L-AFN adhesion was demonstrated by fluorescence resonance energy transfer. Conversely, Jurkat cell LFA-1 H-AFN-adhesion to ICAM-1 was not associated with uPAR/LFA-1 complexes, any requirement for GPI-anchored glycoproteins, or inhibition by beta-glucan. A single CD11b lectin site for beta-glucan and uPAR was suggested because the binding of either beta-glucan or uPAR to Mac-1/CR3 selectively masked two CD11b epitopes adjacent to the transmembrane domain. Moreover, treatment with phosphatidylinositol-specific phospholipase C that removed GPI-anchored proteins increased CD11b-specific binding of (125)I-labeled beta-glucan by 3-fold and this was reversed with soluble recombinant uPAR. Conversely, neutrophil activation for generation of Mac-1/CR3/uPAR complexes inhibited CD11b-dependent binding of (125)I-labeled beta-glucan by 75%. These data indicate that the same lectin domain within CD11b regulates both the cytotoxic and adhesion functions of Mac-1/CR3. PMID: 12444150

Immunol Res. 2002;25(3):219-27. Role of the lectin domain of Mac-1/CR3 (CD11b/CD18) in regulating intercellular adhesion. Ross GD. The James Graham Brown Cancer Center, Department of Pathology, University of Louisville, KY 40292, USA. gordon.ross@louisville.edu

Leukocyte diapedesis requires that Mac-1/CR3-dependent adhesion be regulated so that cells can move from one attachment site to another. The high affinity adhesion state of Mac-1/CR3 is generated when it forms a lectin-dependent complex with the receptor for urokinase plasminogen activator (uPAR; CD87). The extensively glycosylated uPAR binds to the same C-terminal lectin domain of CD11b that had previously been shown to prime Mac-1/CR3 for cytotoxic degranulation in response to beta-glucan. uPAR and beta-glucan compete for a lectin site that is near to the CBRM1/23 epitope (residues 943-1047) at the C-terminus of CD11b, and thus the lectin domain is critical to both the adhesion and cytotoxic functions of Mac-1/CR3. Adhesion is reversed when the uPA enzyme is captured by its receptor (uPAR), causing uPAR to bind to CD11b at a second site (residues 424-440) that is in between the N-terminal I-domain and the divalent cation binding region. PMID: 12018461

Crit Rev Immunol. 2000;20(3):197-222. Regulation of the adhesion versus cytotoxic functions of the Mac-1/CR3/alphaMbeta2-integrin glycoprotein. Ross GD. Department of Pathology, University of Louisville, KY 40292, USA.

Mac-1/CR3 functions as both an adhesion molecule mediating the diapedesis of leukocytes across the endothelium and a receptor for the iC3b fragment of complement responsible for phagocytic/degranulation responses to microorganisms. Mac-1/CR3 has many functional characteristics shared with other integrins, including bidirectional signaling via conformational changes that originate in either the cytoplasmic domain or extracellular region. Another key to its functions is its ability to form membrane complexes with glycosylphosphatidylinositol (GPI)-anchored receptors such as Fc gammaRIIIB (CD16b) or uPAR (CD87), providing a transmembrane signaling mechanism for these outer membrane bound receptors that allows them to mediate cytoskeleton-dependent adhesion or phagocytosis and degranulation. Many functions appear to depend upon a membrane-proximal lectin site responsible for recognition of either microbial surface polysaccharides or GPI-linked signaling partners. Because of the importance of Mac-1/CR3 in promoting neutrophil inflammatory responses, therapeutic strategies to antagonize its functions have shown promise in treating both autoimmune diseases and ischemia/reperfusion injury. Conversely, soluble beta-glucan polysaccharides that bind to its lectin site prime the Mac-1/CR3 of circulating phagocytes and natural killer (NK) cells, permitting cytotoxic degranulation in response to iC3b-opsonized tumor cells that otherwise escape from this mechanism of cell-mediated cytotoxicity. PMID: 10968371

Immunopharmacology. 2000 Jan;46(1):39-54. Critical role of Kupffer cell CR3 (CD11b/CD18) in the clearance of IgM-opsonized erythrocytes or soluble beta-glucan. Yan J, Vetvicka V, Xia Y, Hanikyrova M, Mayadas TN, Ross GD. Department of Pathology, University of Louisville, KY 40292, USA.

Liver macrophages (Kupffer cells) play a major role in blood clearance of both C3-opsonized immune complexes and therapeutic beta-glucan polysaccharides. Human Kupffer cells express three types of C3-receptors: CR1 (C3b-receptor; CD35), CR3 (iC3b- and beta-glucan-receptor), and CR4 (iC3b-receptor; CD11c/CD18). Studies of isolated macrophages have suggested that CR3 is the major receptor mediating capture of either C3-opsonized erythrocytes (E) or beta-glucans. In this investigation, the organ distribution and function of CR3 in the clearance of IgM-opsonized E and soluble CR3-binding polysaccharides were explored in normal vs. CR3-knockout (CR3-KO) mice. Analysis of intravenously (i.v.) injected 125I-anti-CR3 showed that the major vascular reservoir of CR3 was the liver, followed by spleen and lungs. By contrast, clearance of 125I-anti-CR1 appeared to be mediated predominantly by splenic B lymphocytes, as only subsets of splenic macrophages or Kupffer cells were found to express CR1. Clearance of IgM-opsonized 51Cr-E occurred rapidly to the livers of normal mice but was nearly absent in CR3-KO mice. Soluble 125I-beta-glucan exhibited rapid clearance to the liver in normal mice, whereas clearance in CR3-KO mice was significantly reduced. In conclusion, Kupffer cell CR3 plays a crucial role in the clearance of both IgM-opsonized E and beta-glucans. PMID: 10665778

J Immunol. 1999 Sep 15;163(6):3045-52. Beta-glucan, a "specific" biologic response modifier that uses antibodies to target tumors for cytotoxic recognition by leukocyte complement receptor type 3 (CD11b/CD18). Yan J, Vetvicka V, Xia Y, Coxon A, Carroll MC, Mayadas TN, Ross GD. Division of Experimental Immunology, Department of Pathology, University of Louisville, KY 40292, USA.

Beta-Glucans were identified 36 years ago as a biologic response modifier that stimulated tumor rejection. In vitro studies have shown that beta-glucans bind to a lectin domain within complement receptor type 3 (CR3; known also as Mac-1, CD11b/CD18, or alphaMbeta2-integrin, that functions as an adhesion molecule and a receptor for factor I-cleaved C3b, i.e., iC3b) resulting in the priming of this iC3b receptor for cytotoxicity of iC3b-opsonized target cells. This investigation explored mechanisms of tumor therapy with soluble beta-glucan in mice. Normal mouse sera were shown to contain low levels of Abs reactive with syngeneic or allogeneic tumor lines that activated complement, depositing C3 onto tumors. Implanted tumors became coated with IgM, IgG, and C3, and the absent C3 deposition on tumors in SCID mice was reconstituted with IgM or IgG isolated from normal sera. Therapy of mice with glucan- or mannan-rich soluble polysaccharides exhibiting high affinity for CR3 caused a 57-90% reduction in tumor weight. In young mice with lower levels of tumor-reactive Abs, the effectiveness of beta-glucan was enhanced by administration of a tumor-specific mAb, and in SCID mice, an absent response to beta-glucan was reconstituted with normal IgM or IgG. The requirement for C3 on tumors and CR3 on leukocytes was highlighted by therapy failures in C3- or CR3-deficient mice. Thus, the tumoricidal function of CR3-binding polysaccharides such as beta-glucan in vivo is defined by natural and elicited Abs that direct iC3b deposition onto neoplastic cells, making them targets for circulating leukocytes bearing polysaccharide-primed CR3. Therapy fails when tumors lack iC3b, but can be restored by tumor-specific Abs that deposit iC3b onto the tumors. PMID: 10477568

Immunopharmacology. 1999 May;42(1-3):61-74. Therapeutic intervention with complement and beta-glucan in cancer. Ross GD, Vetvicka V, Yan J, Xia Y, Vetvickova J. Department of Pathology, University of Louisville, KY 40292, USA. gordon.ross@louisville.edu

Complement (C) has two major effector systems available for host defense. The membrane attack complex (MAC) generated from components C5-C9 can form membrane-penetrating lesions that lead to cell death by causing a rapid loss of cytoplasmic components. The MAC is only effective against pathogens with outer phospholipid membranes, and cannot kill gram-positive bacteria or yeast whose membranes are protected by cell walls. The most important effector mechanism of C is the opsonization of microbial pathogens with the serum protein C3 that leads to their high avidity attachment to the C3-receptors of phagocytic cells. Pathogens that activate complement are first coated with the C3b fragment of C3, which is rapidly proteolyzed into the iC3b fragment by serum factor I. These iC3b fragments serve to promote the high avidity attachment of the 'iC3b-opsonized' pathogens to the iC3b-receptors (CR3, CD11b/CD18) of phagocytic cells and natural killer (NK) cells, stimulating phagocytosis and/or cytotoxic degranulation. Host cells, including neoplastic tumor cells, have been endowed with natural mechanisms for self-protection against both the MAC and the cytotoxic activation of CR3. This review discusses a novel type of immunotherapy for cancer that uses soluble yeast beta-glucan to override the normal resistance of iC3b-opsonized tumor cells to the cytotoxic activation of phagocyte and NK cell CR3, allowing this important effector mechanism of the C system to function against tumor cells in the same way that it normally functions against bacteria and yeast. Moreover, the cytotoxic activation of beta-glucan-primed NK cell CR3 by iC3b-opsonized tumors is shown to be accompanied by a tumor-localized secretion of the cytokines TNFalpha, IFNalpha, IFNgamma, and IL-6. PMID: 10408367 J

Immunol. 1999 Jun 15;162(12):7285-93. Generation of recombinant fragments of CD11b expressing the functional beta-glucan-binding lectin site of CR3 (CD11b/CD18). Xia Y, Ross GD. Division of Experimental Immunology and Immunopathology, Department of Pathology, University of Louisville, KY 40292, USA. y0xia001@gwise.louisville.edu

CR3 (Mac-1; alphaMbeta2 integrin) functions as both a receptor for the opsonic iC3b fragment of C3 triggering phagocytosis or cytotoxicity and an adhesion molecule mediating leukocyte diapedesis. Recent reports have suggested that a CR3 lectin site may be required for both cytotoxic responses and adhesion. Cytotoxic responses require dual recognition of iC3b via the I domain of CD11b and specific microbial surface polysaccharides (e.g., beta-glucan) via a separate lectin site. Likewise, adhesion requires a lectin-dependent membrane complex between CR3 and CD87. To characterize the lectin site further, a recombinant baculovirus (rBv) system was developed that allowed high level expression of rCD11b on membranes and in the cytoplasm of Sf21 insect cells. Six rBv were generated that contained truncated cDNA encoding various CD11b domains. Immunoblotting of rBv-infected Sf21 cells showed that some native epitopes were expressed by five of six rCD11b fragments. Lectin activity of rCD11b proteins was evaluated by both flow cytometry with beta-glucan-FITC and radioactive binding assays with [125I]beta-glucan. Sf21 cells expressing rCD11b that included the C-terminal region, with or without the I-domain, exhibited lectin activity that was inhibited by unlabeled beta-glucan or anti-CR3 mAbs. The smallest rCD11b fragment exhibiting lectin activity included the C-terminus and part of the divalent cation binding region. The beta-glucan binding affinities of the three C-terminal region-containing rCD11bs expressed on Sf21 cell membranes were not significantly different from each other and were similar to that of neutrophil CR3. These data suggest that the lectin site may be located entirely within CD11b, although lectin site-dependent signaling through CD18 probably occurs with the heterodimer. PMID: 10358177

J Immunol. 1999 Feb 15;162(4):2281-90. The beta-glucan-binding lectin site of mouse CR3 (CD11b/CD18) and its function in generating a primed state of the receptor that mediates cytotoxic activation in response to iC3b-opsonized target cells. Xia Y, Vetvicka V, Yan J, Hanikyrova M, Mayadas T, Ross GD. Division of Experimental Immunology and Immunopathology, Department of Pathology, University of Louisville, KY 40292, USA. y0xia001@gwise.louisville.edu

Mouse leukocyte CR3 (Mac-1, alphaMbeta2 integrin) was shown to function as a receptor for beta-glucans in the same way as human CR3. Soluble zymosan polysaccharide (SZP) or pure beta-glucans labeled with FITC or 125I bound in a saturable and reversible manner to neutrophils, macrophages, and NK cells. This lectin activity was blocked by anti-CD11b mAb M1/70 or 5C6 and did not occur with leukocytes from CR3-/- (CD11b-deficient) mice. SZP preparations containing primarily mannose or glucose bound to CR3, and the binding of 125I-labeled beta-glucan to CR3 was competitively inhibited by beta-glucans from barley or seaweed, but not by yeast alpha-mannan. Also, as with human CR3, the lectin site of mouse CR3 was inhibited by alpha- or beta-methylglucoside (but not D-glucose), alpha- or beta-methylmannoside, and N-acetyl-D-glucosamine. Phagocytosis of zymosan and serum-opsonized zymosan was partially inhibited by anti-CR3 and was reduced to <40% of normal with leukocytes from CR3-/- mice. As with neutrophils from patients with CD18 deficiency, neutrophils from CR3-/- mice exhibited no phagocytosis of particulate beta-glucan. SZP or beta-glucans primed CR3 of neutrophils, macrophages, and NK cells for cytotoxicity of iC3b-opsonized tumor cells that otherwise did not trigger killing. beta-Glucan priming for cytotoxicity was inhibited by anti-CR3 and did not occur with leukocytes from CR3-/- mice. The primed state of macrophage and NK cell CR3 remained detectable for 18 to 24 h after pulsing with beta-glucans. The similarity of mouse and human CR3 in response to beta-glucans highlights the utility of mouse tumor models for development of therapeutic beta-glucans. PMID: 9973505

Clin Exp Immunol. 1999 Feb;115(2):229-35. Regulation of CR3 (CD11b/CD18)-dependent natural killer (NK) cell cytotoxicity by tumour target cell MHC class I molecules.
Vetvicka V, Hanikyrova M, Vetvickova J, Ross GD. Division of Experimental Immunology and Immunopathology, Department of Pathology, University of Louisville, KY, USA.

Phagocyte and NK cell CR3 functions as both an adhesion molecule and an iC3b receptor mediating cytotoxic responses to microorganisms. Cytotoxic activation of iC3b receptor function requires ligation of both a CD11b I-domain site for iC3b and a lectin site located in the C-terminus of CD11b. Because tumours lack the CR3-binding polysaccharides of bacteria and fungi, iC3b-opsonized tumours do not stimulate CR3-dependent cytotoxicity. Previous studies showed that NK cells could be induced to kill iC3b-opsonized tumours with small soluble beta-glucans that bound with high affinity to CR3, bypassing the absence of similar polysaccharides on tumour membranes. Because CR3 signalling requires several tyrosine phosphorylation events, it appeared possible that CR3-dependent killing of autologous tumour cells might be suppressed by NK cell inhibitory receptors for MHC class I (KIR and CD94/NKG2) whose action involves recruitment of SHP-1 and SHP-2 tyrosine phosphatases. In the current study, Epstein-Barr virus (EBV)-transformed B cells were used as targets following opsonization with iC3b. Soluble beta-glucan primed CR3 for killing of iC3b-coated B cells, but autologous class I-bearing targets were 84% more resistant than class I-deficient Daudi cells. Blockade of target cell class I with a MoAb specific for a domain recognized by both KIR and CD94/NKG2 resulted in comparable killing of class I+ B cells. By contrast, another MoAb to class II had no effect on cytotoxicity. These data suggest that NK cell recognition of class I suppresses CR3/tyrosine kinase-dependent cytotoxicity in the same way as it suppresses cytotoxicity mediated by other tyrosine kinase-linked receptors such as FcgammaRIIIA (CD16). PMID: 9933447

J Immunol. 1997 Jul 15;159(2):599-605. Targeting of natural killer cells to mammary carcinoma via naturally occurring tumor cell-bound iC3b and beta-glucan-primed CR3 (CD11b/CD18). Vetvicka V, Thornton BP, Wieman TJ, Ross GD. Department of Pathology, University of Louisville, KY 40292, USA.

Previous reports have suggested that malignant cells frequently generate a humoral immune response that is ineffective in tumor destruction. Despite coating tumors with IgM and IgG that activate the C system via the classical pathway, normal membrane regulators of C (e.g., membrane cofactor protein and CD59) prevent cytotoxicity. Moreover, C3 deposition on tumors does not result in cytotoxic recognition by phagocytes or NK cells bearing C3 receptors capable of mediating destruction of C3-opsonized bacteria or yeast. The current investigation showed that freshly excised mammary tumors bore IgM, IgG, and C3 detectable by flow cytometry. Normal sera contained natural IgM and IgG Abs reactive with breast tumor cell lines, and IgG Ab titers were increased in patients with breast cancer. Breast tumor cell lines incubated in normal serum from AB+ individuals activated the classical, but not the alternative, pathway of C and became coated with C3. Despite exhibiting membrane-bound C3, serum-opsonized breast tumor cell lines were not killed by CR3 (CD11b/CD18)-bearing NK cells. Priming of NK cell CR3 with small soluble yeast beta-glucan polysaccharides enabled CR3-dependent killing of these same C3-bearing tumor cell lines. Tests of mammary carcinoma cells from freshly excised tumors demonstrated that they also bore sufficient amounts of opsonic C3 for cytotoxic recognition by NK cells bearing polysaccharide-primed CR3, whereas they were largely resistant to NK cells bearing unprimed CR3. This study demonstrates the potential utility of using naturally occurring opsonic C3 on tumor cells for specific immunotherapeutic targeting by NK cells and phagocytes bearing polysaccharide-primed CR3. PMID: 9218574

J Clin Invest. 1996 Jul 1;98(1):50-61. Comment in: J Clin Invest. 1996 Jul 1;98(1):1-2.

Soluble beta-glucan polysaccharide binding to the lectin site of neutrophil or natural killer cell complement receptor type 3 (CD11b/CD18) generates a primed state of the receptor capable of mediating cytotoxicity of iC3b-opsonized target cells. Vetvicka V, Thornton BP, Ross GD. The Division of Experimental Immunology and Immunopathology, Departmentof Pathology, University of Louisville, Kentucky 40292, USA. ovetv01@ulkyvm.louisville.edu

When phagocyte CR3 binds to iC3b on bacteria or yeast, phagocytosis and degranulation are triggered because of simultaneous recognition of iC3b via a CD11b I-domain binding site and specific microbial polysaccharides via a lectin site located COOH-terminal to the I-domain. By contrast, when phagocyte or natural killer (NK) cell CR3 adheres to iC3b on erythrocytes or tumor cells that lack CR3-binding membrane polysaccharides, neither lysis nor cytotoxicity are stimulated. This investigation showed that soluble CR3-specific polysaccharides such as beta-glucan induced a primed state of CR3 that could trigger killing of iC3b-target cells that were otherwise resistant to cytotoxicity. Anti-CR3 added before sugars prevented priming, whereas anti-CR3 added after sugars blocked primed CR3 attachment to iC3b-targets. Polysaccharide priming required tyrosine kinase(s) and a magnesium-dependent conformational change of the I-domain that exposed the CBRM1/5 activation epitope. Unlike LPS or cytokines, polysaccharides did not up-regulate neutrophil CR3 expression nor expose the mAb 24 reporter epitope representing the high affinity ICAM-1-binding state. The current data apparently explain the mechanism of tumoricidal beta-glucans used for immunotherapy. These polysaccharides function through binding to phagocyte or NK cell CR3, priming the receptor for cytotoxicity of neoplastic tissues that are frequently targeted with iC3b and sparing normal tissues that lack iC3b. PMID: 8690804

Clin Exp Immunol. 1993 May;92(2):181-4. CR3 (CD11b, CD18): a phagocyte and NK cell membrane receptor with multiple ligand specificities and functions. Ross GD, Vetvicka V. Department of Microbiology and Immunology, University of Louisville, KY 40292.

The C3 receptor CR3 is expressed on phagocytic cells, minor subsets of B and T cells, and natural killer (NK) cells. It has important functions both as an adhesion molecule and a membrane receptor mediating recognition of diverse ligands such as intercellular adhesion molecule-1 (ICAM-1) and fixed iC3b. The receptor is capable of undergoing an activation event that regulates both its specificity for various ligands and its ability to mediate phagocytosis or extracellular cytotoxicity. Certain bacteria express carbohydrates or lipopolysaccharides (LPS) that can bind to and activate CR3, allowing the receptor to assume its activated state. Soluble beta-glucan derived from the yeast Saccharomyces cerevisiae is a particularly potent stimulator of CR3, and produces an activated state of the receptor that permits neutrophil phagocytosis of iC3b-coated erythrocytes or NK, cell cytotoxicity of iC3b-coated tumour cells, that are normally resistant to NK cells. PMID: 8485905

Complement. 1987;4(2):75-86. Role of complement receptor type three and serum opsonins in the neutrophil response to yeast. Cain JA, Newman SL, Ross GD.

Previous studies have suggested that neutrophil complement receptor type three (CR3) has two binding sites: (1) a site for fixed iC3b that does not trigger ingestion or a superoxide (O2-) burst, and (2) a function-triggering site for the beta-glucan component of yeast (Saccharomyces cerevisiae) cell walls. In the present study it was found that yeast (Y) coated with C3b (YC3b) or iC3b (YC3bi), prepared with purified complement in an IgG-free system, were avidly ingested ans stimulated a vigorous O2- burst, whereas sheep erythrocytes (E) bearing C3b or iC3b, were not ingested and did not give an O2- burst. YC3b and YC3bi contained an amount of fixed C3 that was approximately equal to serum-opsonized Y (OY), and produced O2- bursts comparable to OY. Experiments utilizing rabbit F(ab')2 anticomplement receptor type one (anti-CR1) to block fixed C3b binding to CR1, and monoclonal anti-CR3 (MN-41 or OKM1) to block fixed iC3b and Y cell wall binding to CR3, indicated that the O2- burst response to OY was primarily due to fixed iC3b and Y cell wall binding to CR3. Fixed C3b (that represented 33% of the fixed C3 on OY) and IgG anti-Y antibodies that bound to CR1 and Fc receptors, respectively, were found to contribute little to the response. Although YC3b did bind avidly to neutrophil CR1, the results suggested that the O2- burst response to YC3b was triggered after the initial YC3b binding by the secondary attachment of Y cell wall components to CR3. When neutrophils were treated with anti-CR3, 90% of neutrophils bound YC3b (via CR1), but phagocytosis and an O2- burst were completely absent. Similar findings were made with OKM1-treated neutrophils and YC3bi. Responses of OKM1-treated neutrophils were inhibited because only the iC3b-binding site of CR3 was ligated by the YC3bi. Thus, fixed C3b or iC3b on Y mediate avid binding of Y to neutrophils via CR1 or the iC3b-binding site of CR3, respectively, but ingestion and an O2- burst response are only triggered when glucans in the Y cell wall secondarily bind to neutrophils via the beta-glucan binding site of CR3. PMID: 3040333

Complement. 1987;4(2):61-74. Specificity of membrane complement receptor type three (CR3) for beta-glucans. Ross GD, Cain JA, Myones BL, Newman SL, Lachmann PJ.

The binding of the iC3b receptor (CR3) to unopsonized zymosan was shown to result from CR3 attachment to cell wall beta-glucans. A specificity of neutrophil responses for beta-glucan was first suggested by a comparison of yeast (Saccharomyces cerevisiae) cell wall components for stimulation of a neutrophil superoxide burst. **Neutrophils responded poorly to heat-killed yeast, but gave increasingly better responses to cell wall polysaccharides devoid of proteins** (zymosan) and nearly pure beta-glucan particles derived from zymosan. Zymosan triggered a burst that was **29% as great** as that stimulated by phorbol myristate acetate (PMA), and beta-glucan particles stimulated a burst that was **72% as great** as that produced by PMA. Phagocytic responses to yeast were also inhibited by soluble glucans but **not by soluble mannans**. Three types of experiments demonstrated a role for CR3 in these responses. First, neutrophil ingestion of either yeast or yeast-derived beta-glucan particles was blocked by monoclonal anti-CR3, fluid-phase iC3b, or soluble beta-glucan from barley. Monocyte ingestion of beta-glucan particles was also blocked by anti-CR3, but not by anti-CR1 or anti-C3. Second, the neutrophil superoxide burst response to either zymosan or beta-glucan particles was blocked by anti-CR3 or fluid-phase iC3b, and was completely absent with neutrophils from 3 patients with an inherited deficiency of CR3. Third, CR3 was isolated from solubilized neutrophils by affinity chromatography on beta-glucan-Sepharose. PMID: 3040332