The β-Glucan Receptor, Dectin-1, Is Predominantly Expressed on the Surface of Cells of the Monocyte/Macrophage and Neutrophil Lineages

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The β-Glucan Receptor, Dectin-1, Is Predominantly Expressed on the Surface of Cells of the Monocyte/Macrophage and Neutrophil Lineages

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We recently identified dectin-1 (βGR) as a major β-glucan receptor on leukocytes and demonstrated that it played a significant role in the non-opsonic recognition of soluble and particulate β-glucans. Using a novel mAb (2A11) raised against βGR, we show here that the receptor is not dendritic cell-restricted as first reported, but is broadly expressed, with highest surface expression on populations of myeloid cells (monocyte/macrophage (Mφ) and neutrophil lineages). Dendritic cells and a subpopulation of T cells also expressed the βGR, but at lower levels. Alveolar Mφ, like inflammatory Mφ, exhibited the highest surface expression of βGR, indicative of a role for this receptor in immune surveillance. In contrast, resident peritoneal Mφ expressed much lower levels of βGR on the cell surface. Characterization of the nonopsonic recognition of zymosan by resident peritoneal Mφ suggested the existence of an additional β-glucan-independent mechanism of zymosan binding that was not observed on elicited or bone marrow-derived Mφ. Although this recognition could be inhibited by mannan, we were able to exclude involvement of the Mφ mannose receptor and complement receptor 3 in this process. These observations imply the existence of an additional mannenn-dependent receptor involved in the recognition of zymosan by resident peritoneal Mφ.


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eukocyte β-glucan receptors were first described nearly 20 yr ago as opsonin-independent receptors for particulate activators of the alternative complement activation pathway (1, 2). These receptors are thought to mediate the potent biological effects of β-1,3-α-glucans, including anti-tumor and anti-infective properties (3–7). Receptors for these fungal-derived polymers have been reported on cells of the monocyte/macrophage (Mφ)-lineage (including microglia), neutrophils, NK cells, and fibroblasts (8, 9). To date four β-glucan receptors have been identified as candidates mediating these activities, namely complement receptor 3 (CR3; CD11b/CD18) (10, 11), lactosylceramide (12), selected scavenger receptors (13), and dectin-1 (βGR) (14).

We identified dectin-1 (βGR) as a β-glucan receptor after screening a retroviral cDNA library derived from the M6 cell line RAW264.7 with the β-glucan-rich particle zymosan (14). βGR consists of a single C-type, lectin-like, carbohydrate recognition domain, a short stalk, and a cytoplasmic tail possessing an immunoreceptor tyrosine-based activation motif (15). The receptor recog

nized particles such as zymosan, Saccharomyces cerevisiae, and heat-killed Candida albicans in a β-glucan-dependent manner (14). The receptor could also bind to T cells, promoting cellular proliferation in the presence of suboptimal concentrations of anti-CD3 (15). T cell recognition was β-glucan independent, indicating the presence of a second binding site on this receptor (14). The human homologue of βGR has also been cloned (16–19) and was found to exhibit similar properties (18).

We recently assessed the role of βGR in the recognition of soluble and particulate (zymosan) β-glucans by macrophages (20). Using a novel anti-βGR mAb (2A11) that has the ability to block the β-glucan binding activity of the receptor, we found that βGR was a major receptor on Mφ for the nonopsonic recognition of these carbohydrates, defining βGR as the missing leukocyte β-glucan receptor. Furthermore, we demonstrated that CR3 played no obvious role in this process (20), in contrast to previous reports (10, 21). βGR was initially considered dendritic cell (DC) restricted (15), a finding not consistent with the distribution ascribed to the leukocyte β-glucan receptor activity. However, we isolated βGR from a mouse Mφ cell line and observed βGR transcript in murine and human Mφ and peripheral blood neutrophils (14, 18, 20). Given the potential importance of the leukocyte β-glucan receptor in innate immunity, we sought to clarify the expression pattern of βGR and performed a comprehensive analysis of the distribution of this receptor in mice. We show, using mAb 2A11, that βGR is predominantly expressed on cells of the M6/Mφ and neutrophil lineages, but also on DC, as previously noted. Furthermore, a subset of splenic T cells that expressed the Gr-1 Ag also expressed βGR, albeit at low levels. Examination of βGR expression on various freshly isolated primary Mφ showed that alveolar and peritoneal inflammatory Mφ expressed high levels of the receptor, whereas resident peritoneal cells expressed relatively low levels. As βGR is responsible for the nonopsonic recognition of zymosan by other Mφ populations (20), we studied zymosan...
recognition by the low \( \beta GR \)-expressing resident peritoneal cells. While \( \beta GR \) was responsible for \( \beta \)-glucan-dependent zymosan recognition by these cells, a second \( \beta \)-glucan-independent, mannan-inhibitable, nonopsonic recognition mechanism was also present.

**Materials and Methods**

**RNA analysis**

For RT-PCR analysis, total RNA from various cell lines (RAW264.7, J774, P388D1, and NIH-3T3) and primary cell types (BMDDMD) were prepared using the guanidine isothiocyanate-based RNA isolation kit (Stratagene, La Jolla, CA). First-strand cDNA synthesis was performed using the Advantage RT-for-PCR kit with an oligo(dT) primer (Clontech, Palo Alto, CA), as described by the manufacturer. The \( \beta GR \) transcript was subsequently amplified using primers corresponding to the region of the cDNA encoding residues 66–244 of the primary protein sequence. Dihydrofolate reductase-specific primers (Stratagene) were used as a positive control. Commercially available membranes containing poly(A) mRNA isolated from various mouse tissues were purchased from OriGene Technologies (Rockville, MD) and were probed as described by the manufacturer using a full-length \( \beta GR \) cDNA probe.

**Tissue and cell preparation**

All mice used in this study were C57BL/6J, unless otherwise stated, and were between 8 and 12 wk of age. Animals were kept and handled in accordance with institutional guidelines. Splenocytes were harvested by standard methods using a combination of digestion with Liberase Blendzyme II in RPMI (Roche, Indianapolis, IN) and mechanical dissociation. Femurs were collected, and fresh bone marrow was disaggregated using Blendzyme II in RPMI (Roche, Indianapolis, IN) and mechanical dissociation. Enzymatic activity was quenched with RPMI/20% FCS, and -methylglucoside, and mannan; all from Sigma (St. Louis, MO) and used at 100 \( \mu \)g/ml or Abs (2A11 (20); 3C6 (23), which has been shown to block the CR3-mediated lectin activity (26); or an irrelevant rat IgG2b control; all used at 100 \( \mu \)g/ml) were added to the chilled cells 20 and 60 min, respectively, before the addition of zymosan. After incubation, unbound zymosan was removed by extensive washing with medium, and cells were lysed with 3% Triton X-100. FITC in lysates was quantified using a Titer-Tek Fluoroskan II (Labsystems Group, Bangstoke, U.K.) as previously described (14, 18).

**Results**

Expression of \( \beta GR \) mRNA in macrophages and multiple mouse tissues

We studied the expression of \( \beta GR \) by RT-PCR in several \( \text{M}_\Phi \) cell lines and in primary \( \text{M}_\Phi \) and DCs. All \( \text{M}_\Phi \) cell lines as well as bone marrow-derived \( \text{M}_\Phi \) and DC showed evidence of \( \beta GR \) expression, whereas \( \beta GR \) transcript was not detectable in the mouse fibroblast cell line NIH-3T3 (Fig. 1A). Using the full-length coding sequence to screen a multiple tissue Northern blot, we found \( \beta GR \) expression in most murine tissues with the exception of brain, muscle, and skin (Fig. 1B). Notably there was only one discernible transcript detectable in these tissues.
Distribution of βGR surface expression in the spleen

We examined the surface expression of βGR using 2A11 on freshly isolated splenocytes (Fig. 2). CD11c\textsuperscript{high} DC were found to express βGR (population 1) in a similar pattern to that reported previously (15). Notably, however, other CD11c\textsuperscript{low} cells in the spleen, particularly those expressing CR3, exhibited high surface expression of βGR (population 2). To further delineate which cell types were expressing βGR, the cells were subdivided into six populations based on their expression of CR3 and Gr-1 (an mAb recognizing Ly-6G and Ly-6C) and their FSC/SSC profiles (Fig. 2B). Gr-1\textsuperscript{high}CR3\textsuperscript{high}SSC\textsuperscript{high} neutrophils (population 3) exhibited high surface expression of βGR, as did Gr-1\textsuperscript{low}CR3\textsuperscript{low}SSC\textsuperscript{low} M\textsuperscript{−} (population 4B), which also expressed F4/80 (data not shown). A second, unidentified, population of Gr-1\textsuperscript{low}CR3\textsuperscript{high} spleenocytes with very high SSC (population 4A) did not show evidence of βGR surface expression. CR3\textsuperscript{−}Gr-1\textsuperscript{−} spleenocytes, a mixed population containing DC (CD11c\textsuperscript{high}), NK cells, and other M\textsuperscript{−} (both CD11c\textsuperscript{−}), showed heterogeneity in expression of βGR (population 5). NK cells, which have been shown to recognize β-glucans (8) and are identified by high expression of the DX5 Ag (CD49b) (28), did not show significant labeling with the 2A11 Ab (data not shown). Gr-1\textsuperscript{low}CR3\textsuperscript{−} splenocytes (population 6), previously reported to be a T cell subset (29), expressed CD3 and low levels of surface βGR (Fig. 2C). Analysis of all splenic T cells (CD3\textsuperscript{+}) and B cells (B220\textsuperscript{−}) for βGR surface expression, however, indicated that only a distinct subset of T cells exhibited significant surface expression of βGR (Fig. 2C). βGR\textsuperscript{+}CD3\textsuperscript{−} T cells were predominantly Gr-1\textsuperscript{−} and CD8\textsuperscript{+}, but CD4\textsuperscript{−} cells were also observed (data not shown). Splenic autofluorescent F4/80\textsuperscript{−} M\textsuperscript{−} also expressed βGR, but at very low levels (data not shown). Plasmacytoid DC in the spleen, which were identified by their Gr-1\textsuperscript{−}B220\textsuperscript{−}CD11c\textsuperscript{−}CR3\textsuperscript{−} phenotype and analyzed in 129/SvEv and BALB/c mice because of the

FIGURE 2. Distribution of βGR surface expression on freshly isolated splenocytes. A, CD11c\textsuperscript{high} DC (population 1; purple) were confirmed to express βGR, but highest surface expression was observed on most CR3\textsuperscript{−}CD11c\textsuperscript{low/neg} splenocytes (population 2; brown). B, Gr-1\textsuperscript{high}CR3\textsuperscript{high}SSC\textsuperscript{high} neutrophils (population 3; red) exhibited high surface expression, as did Gr-1\textsuperscript{low}CR3\textsuperscript{−}SSC\textsuperscript{−}M\textsuperscript{−} (population 4B; light green), which were also F4/80\textsuperscript{−} (data not shown). CR3\textsuperscript{−}Gr-1\textsuperscript{−} splenocytes (population 5; yellow), a mixed population that contains DC, M\textsuperscript{−}, and NK cells, showed heterogeneous βGR expression. Gr-1\textsuperscript{−}CR3\textsuperscript{−} spleenocytes (population 6; pink) also exhibited βGR surface expression, albeit at a relatively low level, and these cells were confirmed to express CD3. C, Analysis of all T cells (gated on CD3\textsuperscript{+}; orange) showed that only a subset of T cells expressed βGR. B220\textsuperscript{−} B cells (gray) had no obvious βGR surface expression. Unshaded histograms, Control Ab staining; shaded histograms, correspond to the marker indicated.
exhibited the highest cells.

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Control Ab staining; shaded histograms, receptor-expression of fi

We and others have observed expression of Gr-1 high SSC high and peripheral blood Mo (identi

expression. Thioglycolate-elicited and resident alveolar Mo expressed very high levels of βGR. Resident peritoneal Mo expressed significantly less surface βGR than the other Mo studied, but expression was markedly increased after 1 day in culture. Unshaded histograms, Control Ab staining; shaded histograms, receptor-specific staining. Peritoneal Mo were distinguished from other cells by high expression of F4/80 and CR3, and alveolar Mo were identified as previously described (22).

Surface expression of the βGR on myeloid cells in the bone marrow

Since we have previously observed the βGR transcript in human bone marrow (18), we examined murine bone marrow for the expression of βGR (Fig. 3B). Gr-1 high CR3 - neutrophils were subdivided into two populations. Approximately one-third of the bone marrow Gr-1 high neutrophils had high βGR surface expression; the remaining two-thirds showed intermediate or marginal expression (populations 1 and 2, respectively; Fig. 3B). The βGR high neutrophils had higher SSC and higher CR3 surface expression than the βGR low neutrophils (data not shown), suggesting that the βGR high neutrophils may be in a more advanced state of maturation. This is consistent with the high βGR surface expression detected on circulating peripheral blood neutrophils (Fig. 3A). The Gr-1 low subgroup of bone marrow cells that has been reported to include cells of the Mo/Mo lineage, myeloid precursors, and hematopoietic stem cells (31) contained cells with the highest βGR surface expression (population 3). The expression of CR3 and F4/80 indicated that these high βGR-expressing cells most likely belonged to the Mo/Mo lineage (data not shown). Additional unidentified Gr-1 low and Gr-1 - bone marrow cells also showed evidence of βGR expression, but these were not characterized further (Fig. 3B).

Expression of βGR by isolated primary Mo

Freshly isolated resident and thioglycolate-elicited peritoneal Mo were assayed for surface expression of βGR. We also looked for βGR expression on alveolar Mo, as we had found a high level of transcript in the lung (Fig. 1). Both freshly isolated alveolar Mo and thioglycolate-elicited Mo expressed high surface levels of βGR, whereas resident peritoneal Mo exhibited lower expression (Fig. 4). Interestingly, we observed an up-regulation of βGR on the surface of resident peritoneal Mo after 1 day of culture (Fig. 4). Surface expression of βGR on thioglycolate-elicited Mo was relatively unaffected by 1 day of culture (data not shown). Since the Mo MR is also a candidate receptor for the nonopsonic recognition of zymosan by resident peritoneal Mo (see below), we analyzed the surface expression of this receptor on the same cells. Similar to βGR, we found the highest surface expression of the MR on thioglycolate-elicited Mo, moderate expression on resident alveolar Mo, but only very limited expression on the surface of

FIGURE 4. Primary Mo express βGR. Freshly isolated 4-day thioglycolate-elicited peritoneal Mo (Mo thic), resident peritoneal Mo (Mo res), and alveolar Mo (Mo alv), and resident peritoneal Mo that had been cultured for 1 day (d1 Mo res) were assayed for surface expression of βGR, MR, CR3, and F4/80 (not shown). Thioglycolate-elicited and resident alveolar Mo expressed very high levels of βGR. Resident peritoneal Mo expressed significantly less surface βGR than the other Mo studied, but expression was markedly increased after 1 day in culture. Unshaded histograms, Control Ab staining; shaded histograms, receptor-specific staining. Peritoneal Mo were distinguished from other cells by high expression of F4/80 and CR3, and alveolar Mo were identified as previously described (22).

FIGURE 3. Expression of βGR by peripheral blood and bone marrow cells. A, Peripheral blood neutrophils (Gr-1 high) and M (F4/80 - CR3 - SSC low), gated from total peripheral blood leukocytes as shown in the insets, both showed significant levels of surface staining with 2A11 (shaded histograms) compared with a rat IgG2b control (unshaded histograms). B, Bone marrow was analyzed for the expression of βGR, Gr-1, CR3, and F4/80. Dot plots show βGR expression in relation to Gr-1 staining. Gr-1 high neutrophils are subdivided into two populations by high and low βGR surface expression. βGR high neutrophils (population 1) had higher SSC and CR3 surface expression than βGR low neutrophils (population 2), indicating that βGR high neutrophils may be more mature (data not shown). Gr-1 low βGR high cells (population 3) in the bone marrow, most likely of the Mo/Mo lineage, exhibited the highest βGR surface expression.

relative scarcity of these cells in C57BL/6 (30), also exhibited low, but detectable, levels of βGR expression (data not shown).

Expression of βGR on peripheral blood leukocytes

We and others have observed expression of βGR/defectin-1 on both human and mouse PBL by Northern blot (17, 18). We confirmed these observations by FACS by identifying a significant population of PBL that expressed βGR (data not shown). Consistent with the data obtained from the spleen, peripheral blood neutrophils (identified as Gr-1 high SSC high) and peripheral blood M (identified as CR3 - F4/80 SSC low) exhibited high surface expression of βGR (Fig. 3A).
resident peritoneal cells (Fig. 4). Unlike βGR, however, the expression of MR on resident peritoneal cells was relatively unaffected by 1 day of culture (Fig. 4). As reported previously, we found that alveolar Mφ expressed negligible CR3 (22) (Fig. 4) and low levels of F4/80 (data not shown).

Surface expression of βGR during peritoneal inflammation

To study the expression of βGR in an inflammatory context, we examined peritoneal exudate cells 18 h after the i.p. administration of thioglycollate, a model of sterile peritonitis. F4/80+CR3+GR-1+ Mφ, F4/80−CR3+Gr-1+ neutrophils, and F4/80−CR3+Gr-1− SSChigh eosinophils (32) were then tested for βGR surface expression (Fig. 5). Elicited peritoneal Mφ exhibited the highest βGR expression, and significant amounts were also present on the inflammatory neutrophils. In contrast, recruited eosinophils showed no obvious surface expression of βGR (Fig. 5).

Non-opsonic binding of zymosan to resident peritoneal Mφ

We observed that freshly isolated resident peritoneal Mφ had a lower level of surface βGR expression than that on other Mφ studied (Fig. 4). As we had previously shown that βGR was a major receptor for zymosan on thioglycollate-elicited and BMDM (20), we wanted to determine whether this was also true for resident peritoneal Mφ. We compared the contribution of βGR on both resident and elicited Mφ and found that the binding of unopsonized zymosan to elicited Mφ was significantly inhibited by β-glucans, as previously reported (Fig. 6) (20). βGR was still a major receptor for zymosan on resident Mφ, but it contributed less to this process than in the thioglycollate-elicited cells. Furthermore, we found that mannan had an inhibitory effect on the binding of zymosan to the resident Mφ, but not to the thioglycollate-elicited cells (Fig. 6A). The combination of β-glucans and mannan did not have an additive effect (data not shown). As with the elicited Mφ, methylglucoside failed to inhibit the initial binding of zymosan to resident peritoneal Mφ, suggesting no involvement of CR3 in this process (data not shown). These results implied that a secondary β-glucan-independent, mannan-inhibitable, nonopsonic binding mechanism was operational on resident Mφ, but was not present on other Mφ examined.

FIGURE 5. Expression of βGR during inflammation. Sterile peritonitis was induced by i.p. administration of thioglycollate broth 18 h before analysis. Peritoneal exudate cells were examined by FACS with the Mφ/GR-neutrophil marker F4/80 and the neutrophil marker Gr-1 for the expression of βGR. F4/80−Gr-1+ Mφ (Mφ), Gr-1−F4/80+ neutrophils (Neut) also expressed βGR, but F4/80−Gr-1− SSChigh eosinophils (Eo) did not show evidence of surface expression of this receptor.

To find out which specific receptors were involved, we performed Ab blocking experiments on the resident peritoneal Mφ (Fig. 6B). The anti-βGR mAb, 2A11, blocked the nonopsonic binding of zymosan to resident peritoneal Mφ to the same degree as the soluble β-glucans laminarin (Fig. 6B) and glucan phosphate (data not shown), consistent with βGR being a major β-glucan receptor on Mφ. Anti-CR3 (5C6, which blocks the lectin activity of CR3 (26)) or the soluble β-glucans, laminarin and glucan phosphate (not shown). Only 2A11 inhibited nonopsonic zymosan binding to resident peritoneal Mφ. Data are expressed as the mean ± SD percentage of binding to control untreated Mφ, measured as relative fluorescence units (RFU).

Discussion

We recently demonstrated that βGR is a principal β-glucan receptor on primary Mφ (20). As our data (14, 18, 20) did not agree with the previously reported DC-restricted expression of dectin-1 (15), and as the leukocyte β-glucan receptor is believed to be more broadly expressed (8), we re-examined the distribution of dectin-1 using the novel anti-βGR mAb 2A11. While we confirmed expression of dectin-1 by splenic DC, we discovered that a significant proportion of CR3+ splenocytes exhibited higher surface expression of βGR. These cells were of the Mφ/Mφ lineage and...
neutrophils. Furthermore, we also found that peripheral blood M₃ and neutrophils expressed high surface levels of βGR. In the bone marrow, cells of the M₁/M₅ lineage were also the major surface expressers of βGR, but heterogeneous expression was evident on Gr-1⁺ high neutrophils. This heterogeneity appeared to be related to maturation, as βGRGr-1⁺ cells had higher levels of CR3 and higher SSC. Overall, these results were consistent with the expected distribution of the β-glucan receptor (8). Although NK cells are thought to recognize β-glucans (33), we detected no obvious surface expression on freshly isolated splenic NK cells. We cannot exclude, however, that expression of βGR on the surface of these cells may be regulated by activation. Surprisingly we also observed surface expression of dectin-1 on the Gr-1⁻ subset of splenic T cells, although it is not without precedent that NK-like C-type lectins can be expressed on T cells (reviewed in Ref. 34). It is plausible that the expression of βGR, as a T cell binding receptor, on a subset of T cells may be part of a novel mechanism for the regulation of the T cell response by specific subsets of T cells as well as by APC.

We have postulated that βGR may play a fundamental role in the immunomodulatory effects of β-glucans and the host response to fungal pathogens (14), and so looked for expression of this receptor on inflammatory cells. Consistent with this, in a model of peritoneal inflammation, elicited M₅ and neutrophils exhibited high βGR surface expression. Although freshly isolated resident peritoneal M₅ exhibited low 2A11 binding, the levels of the receptor were up-regulated within 1 day of culture (Fig. 4), indicating that βGR surface expression on M₅ can be regulated. High levels of βGR were also detected on the CR3⁻ resident alveolar M₅, highlighting the important role this receptor may play in immune surveillance and host defense at this portal of entry, where the availability of complement and Ig is restricted.

Our recent studies with elicited M₅ (both thioglycolate and Bio-Gel) and BMDMβ indicated that βGR was a major nonopsonic receptor for binding of the β-glucan-rich particle zymosan (20). The observation of lower βGR surface expression on resident peritoneal M₅ compared with the other M₅ we have studied prompted us to determine whether βGR was the major β-glucan receptor on this cell type. Although, we found that β-glucan-dependent binding of unopsonized zymosan to resident peritoneal M₅ was mediated by βGR, these cells also exhibited a second nonopsonic, mannan-inhibitable binding mechanism that was not found on all other M₅ examined (20). The surface expression pattern of the M₅ βGR was not consistent with a role for the MR in this process. Our observations have hence uncovered the existence of a second β-glucan-independent, nonopsonic mechanism of binding zymosan used by resident peritoneal M₅ (but not by other M₅ tested) that was inhibitable by mannan. This additional receptor could represent the mannan-dependent yeast receptor previously observed on resident peritoneal M₅ (35, 36) and implicates this receptor as a pattern recognition receptor with a potentially important role in host defense. The presence of this receptor activity specifically on resident peritoneal M₅ may also explain the controversy surrounding the contribution of a mannan-dependent receptor to yeast/zymosan recognition (35–37). Candidate receptors that may play a role in this process and have demonstrated mannose binding capabilities are DC-SIGN/DC-SIGNR (38) and NKCL (39).

In summary, we have shown that the major surface expression of βGR is on cells of the M₁/M₅ lineage and neutrophils and to a lesser extent on splenic DC. We have also observed low surface expression of βGR on a specific subset of splenic T cells. This analysis of the surface expression of βGR has provided novel insights into the biology of this receptor and into the recognition of β-glucans by leukocytes.

Acknowledgments

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10. Acknowledgments

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