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*J Immunol* 2014; 192:1294-1301; Prepublished online 3 January 2014;
doi: 10.4049/jimmunol.1203023

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Mannan-Binding Protein, a C-Type Serum Lectin, Recognizes Primary Colorectal Carcinomas through Tumor-Associated Lewis Glycans

Motohiro Nonaka,*† Hirotsugu Imaeada,‡ Shogo Matsumoto,* Bruce Yong Ma,*†‡§,¶† Nobuko Kawasaki,* Eiji Mekata,# Akira Andoh,** Yasuharu Saito,†† Tohru Tani,‡ Yoshihide Fujiyama,§ and Toshisuke Kawasaki*

Mannan (mannose)-binding protein (MBP) is a C-type serum lectin that plays a key role in innate immunity. MBP forms large multimers (200–600 kDa) and exhibits broad specificity for mannose, N-acetylgalactosamine, and fucose. MBP exhibits high affinity for unique oligosaccharides that have been isolated from human colorectal carcinoma (SW1116) cells and characterized as highly fucosylated high m.w. type 1 Lewis glycans. In this study, we first demonstrated that MBP recognizes human primary colorectal carcinoma tissues through tumor-associated MBP ligands. We performed fluorescence-based histochemistry of MBP in human colorectal carcinoma tissues and showed that MBP clearly stained cancer mucosae in a Ca2+-dependent manner. Coincubation with plant (Aleuria aurantia) lectin, but not Con A, blocked MBP staining, indicating that fucose, rather than mannose, is involved in this interaction. The expression of MBP ligands was detected in 127 of 330 patients (38.5%), whereas, most significantly, there was no expression in 69 nonmalignant tissues. The MBP-staining pattern in cancer mucosae significantly overlapped with that of Lewis b (Fuc1-2Gal1-3[Fuc1-4]GlcNAc) staining, but the Lewis b staining in normal tissues was not associated with MBP staining. In addition, the MBP staining correlated inversely with the expression of CA19-9 Ag, and MBP stained 11 of 25 (44%) CA19-9 (sialyl Lewis a [NeuAc(2-3)Galβ1-3(Fuc1-4)GlcNAc]) colorectal carcinoma tissues. We found a favorable prognosis in patients with MBP ligand tumors. These results suggest that selective recognition of cancer cells by endogenous MBP seems to be associated with an antitumor effect and that tissue staining with MBP in combination with CA19-9 may serve as a novel indicator of colorectal carcinoma tissues. The Journal of Immunology, 2014, 192: 1294–1301.

Received for publication October 31, 2012. Accepted for publication November 26, 2013.

This work was supported by Grants-in-Aid for Scientific Research B 2070052 (to T.K.) and C 21590543 (to B.Y.M.) and Fellowship 22-9530 (to M.N.) from the Japan Society for the Promotion of Science, Ministry of Education, Culture, Sports, Science and Technology of Japan, as well as by Core-to-Core Program-Strategic Research Networks 17005 sponsored by the Japan Society for the Promotion of Science. Address correspondence and reprint requests to Dr. Toshisuke Kawasaki, Research Center for Glyobiotechnology, Ritsumeikan University, Nishikawachi 1-1-1, Kusatsu, Shiga 525-8577. Japan. E-mail address: tkawasaki@fc.ritsumei.ac.jp

Abbreviations used in this article: AAL, Aleuria aurantia lectin; CEA, carcinoembryonic Ag; CI, confidence interval; CRD, carbohydrate-recognition domain; LE, Lewis; Le−, Lewis a [Galβ1-3(Fuc1-4)GlcNAc]; Le+, Lewis b [Fuc2-1Galβ1-3(Fuc1-4)GlcNAc]; MBP, mannan (mannose)-binding protein; MDCC, mannan-binding protein-dependent cell-mediated cytotoxicity; pAb, polyclonal Ab.
carcinoma patients (38.5%), but they were not expressed in 69 nonmalignant tissues. MBP staining correlated inversely with the expression of CA19-9 among carcinoma patients. Cox proportional hazards regression analysis demonstrated that there was a positive correlation between MBP ligand expression and favorable survival rate. These data indicate the physiological significance of endogenous MBP in colorectal carcinomas, as well as suggest that exogenous MBP is a novel tool for the diagnosis or prognosis of colorectal carcinomas.

Materials and Methods

Patients and cancer tissues

Thirty-five primary colorectal carcinoma tissue specimens including adjacent noncancerous epithelium were obtained from patients who underwent surgery or endoscopic submucosal dissection from 2007 to 2009 at Shiga University of Medical Science Hospital (mean age, 68.9 ± 10.1 y; range, 45–89 y). Informed consent was provided according to the Declaration of Helsinki. Each patient provided written informed consent, and the project was approved by the ethics committees of Ritsumeikan University and Shiga University of Medical Science. The other sets of 196 and 99 colorectal carcinoma tissue specimens were obtained from SuperBioChips Laboratories (Seoul, Korea) (mean age, 58.0 ± 11.9 y; range, 30–86 y) and US Biomax (Rockville, MD) (mean age, 59.9 ± 13.4 y; range, 29–88 y), respectively. Among them, 20 metastatic tissues were available. Survival data were available for 186 patients, and the mean follow-up time was 83.0 ± 45.7 mo (range, 1–120 mo).

Reagents and Abs

MBP was purified as previously described (16). Anti-human MBP mAb was purchased from BioPorto Diagnostics (Gentofte, Denmark). Anti-Lea (MLS103) mAb and anti-Leb (36A) mAb are Abs raised against human colorectal colon cancer cell lines LS180 and SW1116, respectively. MLS103 was a kind gift from Professor S. Fukui, Kyoto Sangyo University (Kyoto, Japan) (17). 36A was prepared in our laboratory (S. Matsumoto, H. Hara, K. Kowahata, M. Kasuda Purne, M. Nonaka, Y. Takishima, H. Toyoda, T. Taki, T. Okumura, N. Kawasaki, and T. Kawasaki, manuscript in preparation). Anti-carcinoembryonic Ag (CEA) mAb was obtained from Abcam (Cambridge, MA), and anti-sialyl Lea (CA19-9) mAb was from Seikagaku Biobusiness (Tokyo, Japan). Anti-CD3ε polyclonal Ab (pAb) was from Santa Cruz Biotechnology (Santa Cruz, CA), anti–HLA-DR mAb and anti–CD83 mAb were from BioLegend (San Diego, CA), and anti–CD163 mAb was from eBioscience (San Diego, CA). Alexa Fluor 488 goat anti-mouse IgG pAb and TO-PRO-3 were from Invitrogen-Life Technologies (Carlsbad, CA). Con A was from Sigma-Aldrich (St. Louis, MO), and Aleuria aurantia lectin (AAL) was from Seikagaku Biobusiness.

Histochemistry

Following deparaffinization and hydration of paraffin-embedded tissue sections, Ag retrieval was performed by steaming in citrate buffer (pH 6). After incubation in blocking buffer (TBS buffer [pH 7.6] containing 1% BSA), the sections were incubated with 2 μg/ml human MBP in the presence of 5 mM CaCl2 or EDTA at room temperature for 1 h and then washed with TBS buffer [pH 7.6] containing CaCl2 or EDTA. Following incubation with 2.5 μg/ml anti-MBP mAb for 1 h, the slides were washed, incubated with Alexa Fluor 488-conjugated secondary pAb and TO-PRO-3 for 1 h, and then observed under a light microscope. For comparative histological analysis, serial tissue sections were subjected to H&E staining, according to standard procedures, and observed under a light microscope.

Immunohistochemical assessment

All tissue sections were evaluated in a coded manner without knowledge of the clinical and pathological parameters. By taking into account both the staining intensity and the percentage of the tumor cut surface area, the total intensity for MBP staining, anti-CD3ε pAb, or anti–HLA-DR mAb was evaluated as negative, 0; weak, 1; moderate, 2; or strong, 3. Carcinoma samples exhibiting significant staining intensity (intensity 2 and 3) were classified as positive expressers of MBP ligands, CD3, or HLA-DR, and the remaining samples were classified as negative expressers of MBP ligands. Assessment was performed by five independent investigators (M. Nonaka, S. Matsumoto, H. Nakao, N. Kawasaki, and T. Kawasaki).

Statistical analysis

The relationship between the expression of MBP ligands and clinicopathological variables was statistically evaluated by means of a χ² test with GraphPad Prism software (version 5.0d, GraphPad, La Jolla, CA). Patients were followed up, the survival curves were estimated by the Kaplan–Meier method, and the resulting curves were compared using the log-rank test. Statistical analyses with multivariate Cox proportional hazards models were performed by EZR software (Saitama Medical Center, Jichi Medical University) (18). To extract a final model of the variables that show a significantly independent relationship with survival, variables were eliminated by stepwise backward selection after including variables (gender, tumor size, nodal status, metastasis, tumor stage, histological differentiation, and MBP ligand positivity) in an initial model. In a stepwise backward-selection procedure, a p value < 0.05 was considered statistically significant.

Results

MBP recognizes cancer cells of human primary colorectal carcinoma

To determine whether whether MBP ligands are expressed on human primary colorectal carcinomas, we performed MBP histochemistry using the three-step staining protocol described in Materials and Methods. Fig. 1A shows a well-differentiated adenocarcinoma of the sigmoid colon that includes adjacent noncancerous mucosa. H&E staining showed that, although the epithelium of the noncancerous mucosa formed straight tubular crypts arranged in parallel, the cancer mucosa showed marked cellular pleomorphism, loss of nuclear polarity, and stratification of nuclei. MBP clearly stained cancer mucosae but not noncancerous mucosae, and a Ca²⁺ chelator, EDTA, abolished the staining (Fig. 1B–D), indicating that the recognition was mediated by the CRD of MBP. This staining was not detected on control treatment without primary incubation with MBP (data not shown).

We examined tissues from a total of 330 patients with adenocarcinomas or mucinous carcinomas. We found that 127 of 330 cases (38.5%) were positive for MBP staining. In contrast, the expression of MBP ligands was not detected in any of the 69 nonmalignant colon tissues (Fig. 2A, 2B). We detected three types of expression patterns among the tumor specimens: intense expression on the apical surface (Fig. 2C), diffuse cytoplasm expression of epithelial cells in adenocarcinomas (Fig. 2D), and mucus expression within malignant glands in mucinous carcinomas (Fig. 2E, 2F). Taken together, these results indicate that MBP can discriminate cancer regions from surrounding noncancerous regions. In other words, MBP ligands are expressed on cancer tissues of human primary colorectal carcinoma mucosae.

Fucose residues are associated with tumor recognition by MBP

Although MBP preferentially binds to high-mannose-type glycans or fucose-containing type-1 Lewis (Le; Lea/Leb) glycans expressed on a broad spectrum of foreign pathogens, only the fucose expression was upregulated in most studies on colorectal carcinomas (19–21). To determine whether a fucose moiety mediates the interaction between MBP and cancer tissues, we performed MBP histochemistry in the presence of a plant lectin: Con A or AAL. Fig. 2E, 2F shows that MBP expression on the apical surface (Fig. 2C), diffuse cytoplasm expression of epithelial cells in adenocarcinomas (Fig. 2D), and mucus expression within malignant glands in mucinous carcinomas (Fig. 2E, 2F). Taken together, these results indicate that MBP can discriminate cancer regions from surrounding noncancerous regions. In other words, MBP ligands are expressed on cancer tissues of human primary colorectal carcinoma mucosae.
showed no inhibitory effect. In contrast, fucose-binding lectin AAL blocked this interaction. This inhibition was detected in most (15 of 16) tumor cases (Fig. 3B), indicating that fucose residues are involved in MBP recognition in primary colorectal carcinoma cells. These results were completely consistent with the binding properties of MBP to a human colon carcinoma cell line, SW1116, as described before (15).

**MBP recognizes colorectal tumor–derived Le^b+ glycans**

As an extension of our previous studies on SW1116 cells, we investigated whether α1,2-fucosylated type-1 Le^b-type) glycans are associated with the expression of MBP ligands on clinical samples by double staining with MBP and anti-Le^b/Le^a mAb. The anti-Le^a mAb, MLS 103, and the anti-Le^b mAb, 36A (see Materials and Methods), used in this study are specifically reactive with Le^a and Le^b oligosaccharides, respectively, as examined using the oligosaccharide microarray method of Fukui et al. (22). We demonstrated that the expression of Le^a glycans showed little correlation with MBP staining (Fig. 4A). In contrast, anti-Le^b mAb stained 15 of 16 (93.8%) cancer tissue specimens that were positive for MBP staining. Moreover, the Le^b expression patterns in five of these cases significantly overlapped with the patterns of MBP staining (Fig. 4A). However, Le^b glycans is commonly known as a blood-type Ag in normal (noncancerous) individuals, and anti-Le^b Abs strongly stained the goblet cells of some noncancerous colon tissues, as reported previously (23–25). In addition, it should be noted that none of these Le^b+ glycans in the noncancerous tissues was costained with MBP, even though those Le^b+ glycans in the cancer tissues from the same patients were extensively costained with MBP (Fig. 4B). Taken together, these findings indicate that tumor-associated anti-Le^b+ glycan Ags are distinct from the conventional blood group Le^b Ags (i.e., the conventional Le^b tetrasaccharide epitope is a necessary component but is not sufficient for the recognition by MBP, and some other neighboring structures should be essential for the high-affinity binding to MBP, this being consistent with our previously
proposed structure of the MBP ligands isolated from SW1116 cells) (15, 26, 27).

MBP ligands are expressed in patients with CA19-9 colorectal carcinomas. MBP binds preferably to a1,2-fucosylated Le^a epitopes (Le^b tetrasaccharide epitope), but the binding is largely abolised when the terminal fucose residue of a Le^b epitope is replaced by a2,3-sialylation (15). CA19-9 (a2,3-sialyl-Le^a) is the frequently applied biomarker that provides prognostic information on pancreatic and gastrointestinal cancers. We investigated the expression profiles on MBP ligands in comparison with those of CA19-9. Interestingly, as shown in Fig. 5, the expression profile of CA19-9 correlated inversely with that of MBP ligands for some cancer patients. Table I summarizes the results of 54 cases. CA19-9 was expressed in 29 of the total 54 cases (53.7%), and predominant portions of the MBP^+ tissues (78.6%) were not stained by anti-CA19-9; instead, large portions of the MBP^− tumor tissues (65%) were CA19-9^+. In contrast, the expression pattern of CEA did not show significant statistical correlation with that of MBP ligands (Table I).

Clinicopathological analysis of expression of MBP ligands in human colorectal carcinomas

Differences in expression patterns between CA19-9 and MBP prompted us to investigate the clinicopathological backgrounds of the patients. We analyzed 196 patients: 77 cases were MBP ligand^+, and 119 patients were negative. Table II shows the statistical analyses of the clinicopathological features of colorectal carcinomas. We found a significant correlation between MBP ligand expression and age (**p = 0.002). The ratio of MBP ligand^+ patients among people aged >60 y (61.0%; 47 of 92) was significantly higher than that for people aged <60 y (39.0%; 30 of 104). The ratio of MBP ligand^+ patients became significantly lower as the tumor differentiation diminished (*p = 0.0118): 51.2% (22 of 43) in well differentiated, 41.1% (51 of 124) in moderately differentiated, and 0% (0 of 9) in poorly differentiated. Moreover, MBP ligand expression was detected more frequently in transverse, descending, and sigmoid colon (52.4%; 53 of 101).
than in cecum and ascending colon (25.0%; 15 of 60) or in rectum (25.7%; 9 of 35) (**p, 0.001).

Correlation between expression of MBP ligands and presence of tumor-infiltrating CD3/HLA-DR+ immune cells

Colorectal tumor often contains nonmalignant immune cells. It was demonstrated that the immune cells that are positive for HLA class II protein HLA-DR frequently infiltrate colorectal tumor and that the HLA-DR expression is associated with lower tumor stages and with a better prognosis (28–30). HLA-DR is expressed broadly on B cells, activated T cells, monocytes/macrophages, dendritic cells, and other nonprofessional APCs. In this study, to determine whether MBP ligand expression correlated with immune infiltration, we performed immunohistochemistry by anti–HLA-DR mAb in combination with MBP staining for 136 cases of cancer tissue (Table III). The percentage of tumor tissues positive for both MBP ligand expression and HLA-DR cells (35 of 136; 25.7%) was significantly higher compared with tissue positive for MBP ligand only (12 of 136; 8.8%) or HLA-DR only (12 of 136; 8.8%) (p < 0.001). HLA-DR+ cells were mostly irregular in shape with surface protrusions, which was reminiscent of monocytic cell lines distinct from round-shaped T or B lymphocytes. Indeed, most HLA-DR+ cells in MBP ligand+ tissues were substantially co-stained by anti-CD83 and anti-CD163 Abs but not MBP (Fig. 6).

Table I. Tissue expression correlation between CEA/CA19-9 and MBP ligands in cancer mucosae

Table II. Clinicopathological features of the study population according to MBP staining in cancer mucosae

Table III. Tissue expression correlation between CD3/HLA-DR and MBP ligands in cancer mucosae

*Analyzed using Fisher exact test.
*p < 0.05.
Expression of MBP ligands is associated with a favorable survival for the patients

We next evaluated the difference in survival rates between patients with MBP ligand⁺ and MBP ligand⁻ carcinomas. Multivariate survival analysis was carried out for 186 patients for 186 patients of which 76 cases (40.9%) had MBP ligand⁺ tumor, using the Cox proportional hazard models with a stepwise backward procedure (Table V). We found that lymph node status (hazard ratio, 5.105; 95% confidence interval [CI], 3.043–8.565; \( p < 0.001 \)) and distant metastasis (hazard ratio, 1.671; 95% CI, 1.239–2.254; \( p < 0.001 \)) were independent predictors of shorter survival. In contrast, MBP ligand expression was demonstrated to be a significant independent factor, with a hazard ratio < 1.0 (hazard ratio, 0.580; 95% CI, 0.353–0.954; \( p = 0.032 \)), indicating that MBP ligand expression correlates independently with a prolonged survival of colorectal cancer patients.

Discussion

Because glycan biosynthesis is a nontemplate-driven process in the endoplasmic reticulum and Golgi body, epigenetic regulation of glycosyltransferase expression during carcinogenesis causes drastic changes in cell surface carbohydrate structures, which may further affect immune functions by creating or masking ligands for endogenous lectins (32). During oncogenic transformation in the gastrointestinal epithelium, changes in the expression patterns of glycosyltransferase genes frequently result in aberrant synthesis of ABH and Lewis (Le)-related carbohydrate Ags (33). The advent of mAb technology has enabled precise definition of such alterations, including upregulation of fucosylated or sialylated lactoseries type 1 or type 2 chain structures (e.g., H/Lewis y/Leb, Le⁺, Lewis x, sialyl-Lea, and sialyl-Lewis x) (33–38). The CA19-9 (sialyl-Lea) epitope is, above all, a well-known tumor marker that is useful for cancer prognosis or monitoring of the colon, pancreas, and other organs (39, 40). However, accumulating evidence revealed that colorectal tumor–associated Le Ags consist of more complex structures than previously believed. In fact, several years ago, we isolated MBP ligand oligosaccharides from an oligosaccharide mixture prepared by hydrazinolysis of a pronase digest of SW1116 cells. They are large, multiantennary N-glycans with highly fucosylated polylactosamine-type structures having Leb–Lea or tandem repeats of the Lea structure at their nonreducing ends (15). A little later, we isolated a major MBP ligand glycoprotein from SW1116 cell lysates using an MBP column and identified them as CD26/dipeptidylpeptidase IV (110 kDa). MALDI mass spectrometry of the N-glycans released from CD26/dipeptidylpeptidase IV (110 kDa).

Table V. Survival analysis by multivariate Cox proportional-hazards model

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal status</td>
<td>5.105</td>
<td>3.043–8.565</td>
<td>(&lt;0.001^{***})</td>
</tr>
<tr>
<td>Metastasis</td>
<td>1.671</td>
<td>1.239–2.254</td>
<td>(&lt;0.001^{***})</td>
</tr>
<tr>
<td>MBP ligand</td>
<td>0.580</td>
<td>0.353–0.954</td>
<td>0.032*</td>
</tr>
</tbody>
</table>

\( ^{*} p < 0.05, \quad ^{***} p < 0.001 \)

Table IV. Expression changes in MBP ligand between primary and metastatic tumor

<table>
<thead>
<tr>
<th>MBP Staining of Metastatic Tumor</th>
<th>MBP Staining of Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n = 7)</td>
<td>Positive (n = 13)</td>
</tr>
<tr>
<td>No. of Cases (%)</td>
<td>No. of Cases (%)</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Positive</td>
<td>3 (23.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Analized using McNemar test.

FIGURE 6. HLA-DR⁺ macrophages and activated dendritic cells infiltrating into MBP ligand⁺ tumor tissues. HLA-DR⁺ cells (red) in MBP ligand⁺ colorectal carcinoma tissues were stained with anti-CD83 mAb, anti-CD163 mAb, or MBP, as described in Materials and Methods. The images were obtained with a confocal laser microscope.

indicating that the majority of HLA-DR⁺ cells are macrophages or activated dendritic cells but not tumor cells.

It also was reported that patients whose tumors are highly infiltrated by CD3⁺ T cells have longer survival compared with those with poorly infiltrated tumors (31). However, in our immunohistochemical study using anti-CD3 Ab, we did not detect a statistically significant correlation between MBP ligand expression and tumor-infiltrating CD3 T cells (\( p = 0.0719 \)). Taken together, these results indicated that MBP ligand expression correlates with immune infiltration of HLA-DR⁺ cells but not CD3⁺ cells.

Expression of MBP ligands in metastatic tumors

To examine whether MBP ligand expression is limited to primary tumor sites, we analyzed 20 primary and corresponding metastatic colorectal cancer tissues (Table IV). We found that 13 of 20 metastatic tumor tissues were negative for MBP ligand, and 7 tissues were positive. Moreover, among 11 patients with MBP ligand+ primary tumor tissues, only 1 patient (9.1%) exhibited MBP ligand expression in the metastatic tumor. In contrast, three of nine patients (33%) lost MBP ligand expression in the metastatic tumors. These results indicate that MBP ligand is expressed in metastatic sites, as well as in primary tumor sites, and the expression may change after metastasis.
cells. MBP binding was inhibited completely by EDTA chelation, which indicates that the binding occurs in a Ca2+-dependent manner and, thus, is mediated through its CRD. In addition, MBP staining was blocked by a fucose-specific lectin, AAL, and partially overlapped with Leα expression in carcinoma tissues. It may be reasonable to assume that the same type of high-affinity interaction between a multimeric protein and multimeric ligands plays an important role in the specific recognition of cancer cells by MBP in human tissues. We also showed that, following metastasis, three tissues changed from MBP ligand+ to MBP ligand−, and one tissue changed from MBP ligand− to MBP ligand+. Although there was no statistical difference in the expression changes (p = 0.3711), it is tempting to speculate that MBP ligand expression may decrease during metastasis.

CA19-9 is one of the most widely used markers for colorectal cancer in clinical practice. The antigenic determinant of CA19-9 recognized by mAb 116NS-19.9 is sialyl-Leα. Because MBP did not bind to sialylated oligosaccharides, it makes sense that the MBP-staining pattern did not overlap with CA19-9 expression in cancer tissues. Our histochemical study revealed that MBP stained 11 of 25 (44%) CA19-9+ colorectal carcinoma tissue samples, and that the percentage of patients who exhibited positive staining with either MBP or anti–CA19-9 Abs was markedly increased (40 of 54; 74%) compared with anti–CA19-9 staining only (53%), suggesting that MBP may be a useful marker for CA19-9+ carcinomas. Furthermore, the expression of MBP ligands in the basolateral, as well as the apical, area of cancer mucosae suggests that MBP ligands on the basolateral surface may enter the blood stream through a neovessel. Accordingly, the establishment of a detection system for MBP ligands in situ may have a clinical benefit.

We demonstrated the good prognosis of MBP ligand+ patients compared with MBP ligand− patients in the multivariate survival analysis. The positivity of MBP staining is entirely independent of nodal status (p = 0.9946), metastasis (p = 0.4113) (Table II), and anti-CD3 staining (p = 0.0719) (Table III), indicating that MBP stains colorectal carcinoma tissues, regardless of those factors. Therefore, the Nα, Mα, or CD3− cohort can be divided into subgroups that do or do not stain positive for MBP, which provides new prognostic information that would not be predicted simply by nodal status, metastasis, or anti-CD3 staining. In addition, this prolonged survival suggests that the expression of MBP ligands may contribute to inhibition of tumor growth or metastasis. We reported previously that SW1116 cell growth in nude mice mostly/regressed within several days after intratumoral and s.c. inoculation of vaccinia virus carrying the MBP gene, and we designated this process as MDCC (14). Therefore, the finding of good survival in MBP ligand+ patients may reflect the antitumor effect of MBP in humans. We showed in this study that immune infiltration by HLA-DR+ cells correlated with MBP ligand expression in the tumor, and most of the HLA-DR+ cells were CD83+ and/or CD163+ monocyctic-lineage cells. This result supports our previous hypothesis that activated immune cells, but not complement activation, induce MDCC. In addition, the finding that MBP ligand expression was observed more frequently as the tumor-differentiation levels increased suggests that MDCC driven by MBP may be effective at an early stage of cancer.

Finally, we found tumor-specific carbohydrate-mediated interaction between endogenous lectin MBP and human primary colorectal carcinoma tissues. The ligand on the tumor cells may be identical or similar to MBP ligand oligosaccharides, which we isolated previously from SW1116 cells. They are highly fucosylated polylactosamine-type structures having Leα−Leβ or tandem repeats of the Leβ structure at their nonreducing ends, and they have a high-affinity interaction with MBP. Our results suggest a possible role for endogenous MBP, as well as its potential usefulness as a novel diagnostic marker or an indicator of better prognoses for colorectal carcinomas. The fact that there was no false positive staining by MBP in noncancerous tissues may stimulate its use in the in situ diagnosis of colorectal cancer tissues and selective removal of cancer cells by endoscopic surgery in the near future.

Acknowledgments
We thank Tomoko Tomimaga and Saori Kamo for secretarial assistance.

Disclosures
The authors have no financial conflicts of interest.

References


