Genetic assessment of the importance of galectin-3 in cancer initiation, progression, and dissemination in mice

Isabelle Eude-Le Parco1, 2, 3, Gaëlle Gendronneau1, 2, 3, Tien Dang3, Delphine Delacour4, Victor L. Thijsen4, Winfried Edelmann5, Michel Peuchmaur6, and Françoise Poirier1, 3

1Institut Jacques Monod, UMR CNRS 7592, Univ. P6 and P7, 2 Place Jussieu, 75251 Paris Cedex 5, France; 2Department of Pathology, Angiogenesis Laboratory, School for Oncology and Developmental Biology, University of Maastricht, The Netherlands; 3Department of Cell Biology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA; and 4 Assistance Publique-Hôpitaux de Paris (AP-HP) Hôpital R. Debré, Service de Chirurgie Pédiatrique, Paris, France

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The galectin family of β-galactoside binding lectins is involved in normal and pathological processes. Altered expression of galectin-3 has been described in many cancers, and studies of cancer cell lines have implicated this lectin in various aspects of the tumorigenic cascade. The goal of this report was to directly assess the importance of galectin-3 in various aspects of the tumorigenic cascade. The goal of this report was to directly assess the importance of galectin-3 in tumor biology by introducing the null mutation (galectin-3−/−) into mouse lines genetically programmed to develop cancers. We used two mouse models of human intestinal cancer, the ApcΔmin and ApcΔ638N lines, to study tumor initiation and tumor progression. We also crossed the galectin-3−/− mice with PyMT transgenic animals, a model in which primary mammary gland tumors give rise to lung metastases at high frequency. Unexpectedly, we show that the absence of galectin-3 does not affect the evolution of the disease in any of these three situations.

Keywords: Apc mutations/galectin-3 knock-out mice/metastasis/PyMT transgenic/tumor progression

Introduction

Dramatic changes in cellular glycosylation are a hallmark of cancer cells, and significant correlations are now established between some glycosylation patterns and clinical prognosis (Kim and Varki 1997; Hakomori 2002). Consistently, there is now an extensive literature implicating galectins, a family of soluble β-galactoside binding proteins, in cancer (Liu and Rabinovich 2005).

Galectins are small nonglycosylated proteins sharing a conserved carbohydrate recognition domain (CRD) of about 130 amino acids (Hirabayashi and Kasai 1993; Barondes et al. 1994). To date, 15 mammalian galectins have been identified (Cooper and Barondes 1999; Houzelstein et al. 2004). Despite the absence of signal peptide, galectins can be secreted, and they are found either intracellularly or extracellularly, depending on the cell type and cell differentiation state. Galectins intervene in many normal and pathological situations where they play multiple roles, notably in cell interactions, apoptosis, cell cycle, survival, splicing, and intracellular trafficking (Perillo et al. 1998; Hughes 2001; Liu et al. 2002; Delacour and Jacob 2006; Elola et al. 2007).

Galectin-3 is a 30-kDa protein composed of a single C-terminal CRD domain fused to a unique N-terminal collagen-like domain which can mediate oligomerization in vivo (Niiminen et al. 2007). It is widely distributed in normal adult tissues where the major sites of expression are epithelial cells and cells involved in immune response (for review see Dumic et al. 2006). Galectin-3 is also expressed in a variety of tumors (Andre et al. 1999; Danguy et al. 2002; Lahm et al. 2004; van den Brule et al. 2004). An increase in galectin-3 expression has been observed in lymphoma (Konstantinov et al. 1996), as well as in carcinomas of the head and neck (Gillenwater et al. 1996), thyroid (Xu et al. 1995), liver (Hsu et al. 1999), and stomach (Lotan et al. 1994). In contrast, a down regulation has been found in breast carcinomas (Castronovo et al. 1996; Idikio, 1998), uterine carcinomas (van den Brule et al. 1996), and prostate carcinomas (Pacis et al. 2000). Changes in galectin-3 expression have also been reported in colon cancer (Irimura et al. 1991; Lee et al. 1991; Lotz et al. 1993; Schoepner et al. 1995; Nakamura et al. 1999; Hititelet et al. 2003; Legendre et al. 2003). More specifically, studies carried out with tumor cell lines have shown that galectin-3 may be involved at various levels of the tumorigenic cascade, i.e., not only as a cell adhesion or cell migration molecule, but also as a cell cycle regulator, an antiapoptotic factor, and even a proangiogenic agent (Bresalier et al. 1998; Nangia-Makker et al. 2000; Honjo et al. 2001; Ochieng et al. 2004; Takenaka et al. 2004; Nakahara et al. 2005). Finally, there are two reports showing that treatment with galectin-3 inhibitors can reduce tumor development in xenograft assays (John et al. 2003; Johnson et al. 2007). However, despite this wealth of data, most evidence for the importance of galectin-3 in cancer is indirect, as it is based on quantitative correlations or on the behavior of cancer cell lines.

In this report, we aimed to directly assess the importance of galectin-3 in tumor biology by introducing the null mutation (galectin-3−/−) into mouse lines genetically programmed to develop cancers, thereby comparing the evolution of the disease in the presence and absence of galectin-3. In order to study tumor incidence and progression, we used two mouse lines carrying two different mutations in the Apc tumor suppressor gene. Mutations in the Apc gene have been found in many cases of human colorectal cancers, and the mouse mutant lines are good for genetic analysis. Thus, these models have been extensively used for the study of intestinal cancer, the ApcΔmin and ApcΔ638N lines, to study tumor initiation and tumor progression. Additionally, we also crossed the galectin-3−/− mice with PyMT transgenic animals, a model in which primary mammary gland tumors give rise to lung metastases at high frequency. Our results indicate that the absence of galectin-3 does not affect the evolution of the disease in any of these three situations.
models for these cancers (Moser et al. 1990; Su et al. 1992; Fodde et al. 1994; Heyer et al. 1999). In a second set of experiments, we examined the impact of the galectin-3 null mutation on Apc-induced tumors. In some intestinal tumor models, thus, provided a test of the importance of galectin-3 at various stages of the tumorigenic process.

Results

Galectin-3−/− mutants are viable and they live as long as wild-type (wt) control animals under animal house conditions (Colnot et al. 1998). Even though they display various developmental defects in bone (Colnot et al. 2001), kidney (Bichara et al. 2006), and intestine (Delacour et al. 2008) as well as some immunological disorders (Sano et al. 2003; Nieminen et al. 2008), they appear normal and spontaneous tumors have never been observed. The experiments described here were done by breeding galectin-3−/− mice with mice genetically programmed to develop cancers.

Effect of the galectin-3 null mutation on Apc-induced tumors

We first used animals carrying one copy of the ApcMin mutation to study the influence of galectin-3 on the initial steps of tumor formation. Apc encodes a large protein that participates in the Wnt signaling. ApcMin is a nonsense mutation at codon 850. Under normal conditions, Apc sequesters β-catenin in the cytoplasm. Heterozygote ApcMin+ animals develop normally, but the wt Apc allele frequently undergoes a somatic mutation in intestinal cells. In the absence of the functional Apc protein, β-catenin translocates to the nucleus, the Wnt pathway is constitutively activated, and tumors appear (Su et al. 1992).

Two cohorts of ApcMin+/+ animals were generated: a control ApcMin+/+;galectin-3+/+ pool (N = 23) and an ApcMin−/−;galectin-3−/− pool (N = 18). Once adult, the animals were observed weekly and sacrificed when they displayed reduced physical activity, obvious weight loss, and signs of anemia. Survival curves show that the average life span was about 40 weeks in both pools, regardless of the genotype of the mice at the galectin-3 locus (Figure 1A). A full, “swiss-roll”, section of the intestine was prepared for the counting of the tumors and for histopathological examination (Figure 1B). We employed the consensus classification, defined by Boivin et al. (2003), that distinguishes three categories of murine intestinal tumors: (i) low-grade adenomas, (ii) high-grade adenomas, and (iii) adenocarcinomas. This study revealed that, in both groups, 100% of the mice were carrying tumors and all tumors were low-grade adenomas (Figure 1B). The average number of tumors per mouse and the size of the tumors were not significantly different in galectin-3+/+ and galectin-3−/− animals (Figure 1C and D).

The strongest and best characterized modifier gene of the ApcMin mutation is Mom1 (modifier of min) (Gould et al. 1996). Two Mom1 genotypes were present in this experiment, Mom1129/129 and Mom1129/C57. We determined the Mom1 genotype for each mouse, and then used animals presenting the same Mom1 genotype to repeat the comparison of tumor formation with or without galectin-3 in order to exclude any possible impact of this factor on the result. Neither the Mom1129/129 animals nor the Mom1129/C57 animals showed any difference in

![Image](https://academic.oup.com/glycob/article-abstract/19/1/68/1988434)
tumorigenesis depending on the presence or absence of galectin-3 (see supplementary data, Table 1).

We next used a second Apc model system to study the effect of galectin-3 on tumor progression. The Apc<sup>1638N</sup> mutation was generated by introducing a neomycin resistance gene in codon 1638 (Fodde et al. 1994). In this mouse line, an unstable truncated Apc protein is produced, and fewer intestinal tumors appear than in Apc<sup>Min/+</sup> animals. As a result, the animals survive longer and many original low-grade intestinal adenomas evolve into high-grade adenomas and even into adenocarcinomas (Fodde et al. 1994; Heyer et al. 1999). Again, control Apc<sup>+/+</sup>; galectin-3<sup>+/+</sup> individuals (N = 36) were compared with Apc<sup>+/+</sup>; galectin-3<sup>−/−</sup> animals (N = 41). All animals were killed when they were 11 months old and their intestines were processed as before. We found that 88% of the galectin-3<sup>+/+</sup> mice and 92% of the galectin-3<sup>−/−</sup> mice exhibited at least one tumor. When the histological grade of every tumor (N = 65 for galectin-3<sup>+/+</sup> and N = 73 for galectin-3<sup>−/−</sup>) was determined, it appeared that low-grade adenomas, high-grade adenomas, and adenocarcinomas were present in equal proportions in the control (galectin-3<sup>+/+</sup>) and experimental (galectin-3<sup>−/−</sup>) groups (see supplementary data, Table 2). These data indicate that the rate of tumor progression from low-grade to high-grade adenomas and from high-grade adenomas to adenocarcinomas were identical in the presence and absence of galectin-3. All this information (which is detailed in supplementary data, Table 2) was summarized by calculating an arbitrary score value based on the number and the grade of tumors present in each mouse (see Material and methods). This parameter gives a global estimate of the health status of each animal. Figure 2A shows that the advancement of the disease, as represented by the score values, is the same for the two genotypes, thus establishing that tumor progression is not altered in the absence of galectin-3. When we calculated the total size of the tumors present in each mouse, there was again no difference between galectin-3<sup>+/+</sup> and galectin-3<sup>−/−</sup> animals (Figure 2B). Finally, neither the density of vessels nor the inflammatory response seemed affected in the absence of galectin-3 (supplementary data, Figures 1 and 2).

We also examined the distribution of galectin-3 in normal intestine and in tumors (Figure 3). As expected, we found that galectin-3 is normally present in the cytoplasm of differentiated enterocytes located in the upper part of microvilli (Figure 3D). In these cells, staining is intense along the lateral membranes and in the terminal web (Figure 3H). Interestingly, we observed a nuclear shift of galectin-3 in the cells at the surface of low-grade adenomas (Figure 3E and I). In adenocarcinomas, galectin-3 staining was intense not only in the nuclei but also in the cytoplasm of the epithelial-like cells located at the surface of the tumor (Figure 3F and J) or along some cavities inside the tumors (Figure 3G and K).

**Effect of the galectin-3 null mutation on PyMT tumors**

To study the potential effect of the galectin-3<sup>−/−</sup> mutation on metastasis formation in vivo, we used the PyMT transgenic line, in which the polyoma middle T antigen is expressed under the control of the MMTV promoter (Guy et al. 1992). PyMT mice develop large primary tumors in mammary glands which rapidly metastasize to the lungs. Because the primary tumors are superficial in these animals, we could monitor their appearance and progression.
development, on weekly basis. We found that the latency, incidence, and growth of PyMT primary mammary tumors were identical in the control galectin-3+/- (N = 32) and in the experimental galectin-3-/- (N = 38) pools (Figure 4A).

We sacrificed the animals at 5–6 months of age (depending on tumor burden) and compared the incidence of lung metastases in the presence and absence of galectin-3. We found that the number of metastases is similar between the two cohorts, suggesting that the absence of galectin-3 did not affect the dissemination of PyMT primary mammary tumors (Figure 4B). Finally, there was no detectable galectin-3 immunoreactivity in the primary mammary tumors nor in the lung metastases, while it is clearly found in the epithelium of respiratory ducts (data not shown and Figure 4C).

Discussion

The goal of this study was to use the power of mouse genetics to test the importance of galectin-3 in cancer. We focused on intestine cancers induced by mutations in the Apc gene because this gene is mutated in a large proportion of human colon cancers and the mouse models faithfully recapitulate many aspects of the human disease. However, one limitation is that intestinal tumors are not metastatic in mice. Thus, we also used the PyMT transgenic line as it is one of the rare murine models in which metastases form with a high frequency. Taken together, it was possible to assess the impact of the galectin-3-/- mutation on tumor formation, progression, and metastasis.

We showed that, in galectin-3-/- mice, both Apc intestinal tumors and PyMT mammary gland tumors appear at the same frequency as in galectin-3+/- animals. There was no detectable effect of the absence of galectin-3 on tumor formation. In addition, using the mammary tumor model, we found that the time of appearance and the kinetics of tumor growth was unchanged in the galectin-3-/- mutants compared to control mice, thus excluding a subtle transient effect of the mutation on the rate of tumor growth. When tumor progression was examined in Apc1638N animals, we found that the proportions of low-grade adenomas, high-grade adenomas, and adenocarcinomas were not statistically different between the galectin-3+/- and galectin-3-/- individuals, showing that the absence of the lectin did not either influence the speed of transition from benign to malignant tumors in this model. Finally, no effect of the galectin-3 deletion on the frequency of dissemination of PyMT tumors in lungs was detected.

Alterations in galectin-3 expression have been related to neoplastic transformation and metastatic progression of human colon cancers. However, some conflicting results have been published. Several studies reported a significant increase of galectin-3 content in the tumors that progressed to the metastatic stage, relative to the nonmetastatic tumors or normal colon tissue (Irimura et al. 1991; Schoeppner et al. 1995; Nakamura et al. 1999; Hittelet et al. 2003; Legendre et al. 2003), but (Tsuboi et al. 2007) found a reduction in galectin-3 expression associated with the invasion and metastasis of colorectal cancer, while Lotz et al. (1993) described a moderate decrease in galectin-3 mRNA and protein levels in human colon cancer compared to normal mucosa. All these reports measured only correlative links between levels of galectin-3 expression and tumor stage. In contrast, the results obtained in the present genetic study with Apc mutant mice indicate that galectin-3 has, at most, only a marginal effect in this model of the human disease. Since the Wnt pathway is perturbed in 80% of human colon cancers (and most often due to mutations in the Apc gene itself), we conclude that galectin-3 probably does not play a prominent role in these cancers.
A participation of galectin-3 in Wnt signaling via binding to β-catenin and axin has been described in a human breast cancer cell line (Shimura et al. 2004, 2005). Indeed, we found that galectin-3 is translocated to the nucleus of tumor cells at the earliest stage of ApC tumor formation. One possibility is that the absence of the ApC/axin/β-catenin cytoplasmic complex provoked the mislocalization of galectin-3, which would be consistent with the hypothesis of galectin-3 belonging to this large molecular complex. However, we show that the presence of galectin-3 in the nucleus has no detectable consequence on the evolution of the tumors. In addition, galectin-3−/− mice never develop spontaneous tumors, notably in enterocytes (F.P. unpublished results). Taken together, these results suggest that galectin-3 is unlikely to be a major actor in the Wnt signaling pathway.

In the context of the PyMT transgenic line, the galectin-3−/− mutation had also no impact on initiation or growth of the primary tumors. Perhaps more surprisingly, the incidence of lung metastases was unchanged in the galectin-3−/− animals. Using the same experimental approach, Granovsky et al. (2000) have shown that PyMT tumor growth and metastasis formation are strongly repressed in mice deficient in the glycosyltransferase gene, Mght5. They proposed that this drastic tumor suppression effect of the Mght5−/− mutation might be due to the lack of recognition of cell surface receptors, such as EGF receptor or TGFβ receptor, by galectin-3. This interpretation is substantiated by the fact that the EGF receptor seems to bind galectin-3 in an Mght5-dependent manner. If this model was strictly correct, Mght5−/− and galectin-3−/− mutations should have had the same consequences on PyMT tumor formation. As this is clearly not the case, we conclude that other factors, besides galectin-3, must be contributing to the tumor suppressor effect observed in Mght 5−/− mutants.

Recent evidence has brought some fundamental understanding to one role of galectin-3 in enterocytes. It has been shown that galectin-3 is involved in nonraft-dependent protein transport to the brush border of enterocytes. It has been shown that galectin-3 is required for the maintenance of epithelial cell polarity (Delacour et al. 2006) and that protein transport to the brush border of enterocytes is defective in galectin-3−/− mice (Delacour et al. 2008). Moreover, mutant enterocytes display microvilli-like structures along their entire basolateral surfaces, strongly suggesting that galectin-3 is required for the maintenance of epithelial cell polarity (Delacour et al. 2008). It is striking that, at this stage of our studies, these profound architectural defects have not known physiological consequences under standard animal house conditions. For example, one might have predicted that such abnormalities could have rendered the intestinal epithelium more susceptible to intestinal tumorigenesis. Indeed, the emerging idea is that depletion in a galectin is only manifest under stress conditions when the mechanisms ensuring tissue homeostasis are challenged (Gendronneau et al. 2008). One interesting experiment would be to apply different diets to galectin-3 null mutant mice.

That there are no apparent differences in tumor development between galectin-3−/+ and galectin-3−/− animals could possibly be explained by the fact that adaptive mechanisms arise during developmental stages in response to the absence of galectin-3. One possibility is that other members of this gene family might be compensating for the absence of galectin-3. In this respect, it is worth noting that experiments in which tumor cells were injected in galectin-1 null mutant mice have already shown that this galectin is implicated in tumor angiogenesis (Thijssen et al. 2006) as well as in tumor immune response (Toscano et al. 2007).

In conclusion, using three mouse models that have previously been used to reveal the importance of other genes in cancer (Granovsky et al. 2000; Yang et al. 2001), we show that galectin-3 is not a rate-limiting factor in the tumorigenic processes triggered in these genetically induced cancers.

Material and methods

Mice

The galectin-3−/− and Apc1638N/+ lines were respectively generated by Colnot et al. (1998) and Fodde et al. (1994). The ApcMin/+ and PyMT−/+ lines were purchased from Jackson Laboratories (Bar Harbor, ME 04609). galectin-3−/− mice were first crossed with either ApcMin/+, Apc1638N/+ or PyMT−/+ partners. Galectin-3−/− offspring carrying one copy of the cancer inducing allele (F1) were selected. All animals used in these three studies were obtained by crossing the selected F1 with galectin-3−/− mice. Two cohorts of pooled siblings were generated for each comparison. The animals used in the first control cohorts carried one copy of the cancer inducing gene (ApcMin/+ or Apc1638N/+ or PyMT−/+ and two wt alleles of galectin-3 gene (galectin-3−/+); those in the second experimental cohorts carried one copy of the cancer inducing gene (ApcMin/+ or Apc1638N/+ or PyMT−/+ ) and two null alleles of the galectin-3 gene (galectin-3−/−). In the case of ApcMin and Apc1638N crosses, the final mixed genetic background was 75% 129Sv/25% C57B16 and in the case of PyMT crosses, it was 75% 129Sv/25% FVB. The animals used in these experiments originated from several equivalent but independent crosses in order to randomize the effect of mixed genetic background. Mice were housed in a specific pathogen-free facility.

Genotyping

DNA was prepared from tail snips or from spleen samples as described by Miller et al. (1988). The 50 µL reaction mix contained 1 µL of DNA, 200 µM dNTP, 0.4 µM of each of the three primers (see below), 2.5 mM MgCl2, 5% DMSO, and 1.5 U Taq polymerase (Invitrogen, Cergy Pontoise, France) in the manufacturer’s buffer. After an initial step for 3 min at 94°C, 35 PCR cycles were performed as follows: denaturation for 45 s at 94°C, annealing for 30 s at either 55°C (for galectin-3 and ApcMin), 59°C (for Apc1638N), or 60°C (for PyMT), and elongation for 1 min 30 s at 72°C. For the galectin-3 locus, the following primers were used 5′-cagcaagctctgctcgctg-3′ (forward ga3), 5′-tgaaatacttaccgaaaagctgtctgc-3′ (reverse ga3), and 5′-tctggtgcagatcagctgg-3′ (forward neo), which gave a 298-base fragment specific for the wt galectin-3 allele and a 384-base fragment specific for the targeted galectin-3 allele. For ApcMin genotyping, we used the three following primers: 5′-gcctacttccaggt-3′ (MinA), 5′-tccacttgccattgcaagc-3′ (MinB) and 5′-tctgcagaacagagagcagta-3′ (MinC). The MinA/MinB pair gave a 600-base fragment for the wt Apc allele, while the MinB/MinC pair gave a 340-base fragment ApcMin fragment. Apc1638N genotyping was done according to (Fodde et al. 1994), using 5′-tctgcagaacagagagcagta-3′ (1638A), 5′-tgaagagggagtcagctgg-3′ (1638B), and 5′-gggctgtctgctgctgctg-3′ (1638C). The 1638 A/1638C pair allowed the amplification of a 300-base fragment specific for the wt Apc allele, and the 1638A/1638B
immunodetection were performed as described above. Finally, the PyMT transgenic animals were genotyped with four primers: PyMT-A (5'-caaatgaatttcgggtg-3'), PyMT-B (5'-gtcgctagctcccaggtt-3'), PyMT-C (5'-ggaagactgctcacaaggg-3'), and PyMT-D (5'-gggaagctcgagcaggg-3'). The PyMT-A/PyMT-B pair gave a specific WT fragment of 200 bases and the PyMT-C/PyMT-D gave a 556-base fragment specific for the transgene.

Preparation and examination of intestine samples
Mice were killed by cervical dislocation. The small intestine was opened longitudinally and rinsed with the phosphate buffered saline (pH 7.4) solution. A 2 h prefixation step was done in AFA (2% formalin, 5% acetic acid, 75% EtOH) using insect pins for maintaining the intestine in a stretched position on a solid flat bed of paraffin. Using a pair of forceps, the intestine could then be tightly rolled over in a spiral shape before depositing inside a histological cassette. After further overnight incubation in AFA, the samples were embedded in paraffin and full-length intestine sections could be obtained (see “swiss roll” sections in Figure 1B).

Hematoxylin-eosin-stained “swiss roll” sections were examined for histopathological abnormalities following the recommendations proposed by Boivin et al. (2003) for the pathology of mouse models of intestinal cancer. All samples were blindly examined by two independent researchers, and in the case of scoring disagreement, a third independent assessment was performed by a pathologist (M.P.). A score value (S) was attributed to each individual animal according to the following formula: S = LGA + 5 × HGA + 10 × AC, where LGA is the number of low-grade adenomas, HGA is the number of high-grade adenomas, and AC is the number of adenocarcinomas. Immunodetection of galectin-3 on paraffin sections was performed using the rat monoclonal anti-Mac2 antibody (M3/38 hybridoma, Boehringer-Mannheim, Indianapolis, gift from Hakon Leffler, University of Lund, Sweden) and secondary Alexa488-conjugated antibody (Molecular Probes, Invitrogen). Nuclei were visualized with Hoescht 33342 staining. Confocal microscopy was carried out under a LEICA-SP2 microscope (images were processed using LEICA Lite Software). Blood vessels and leukocytes were, respectively, detected using rat anti-mouse CD45 (clone 30F11 B&D, 1:5000 dilution), and ME-9F1 monoclonal antibody (Schrage et al. 2008) kindly provided by Dr A. Hamann was applied overnight at room temperature. Finally, a biotin-labeled secondary antibody was applied for 1 h at room temperature, and staining was performed using the StreptABComplex/horseradish peroxidase kit (DAKO). The sections were counterstained with hematoxylin (Merck), dehydrated, and mounted in Entellan (Merck).

Tumor growth and metastasis in PyMT transgenic mice
The primary tumors were first detected by palpations, and then weekly measured with callipers. Animals were killed by cervical dislocation between 5 and 6 months of age depending on tumor burden. Lungs were dissected out and the number of nodules was counted on a hematoxylin-eosin-stained full section of the lungs examined. Hematoxylin-eosin staining and galectin-3 immunodetection were performed as described above.

Supplementary Data
Supplementary data for this article is available online at http://glycob.oxfordjournals.org/.

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Conflict of interest statement
None declared.

Abbreviations
CRD, carbohydrate recognition domain; Mom1, modifier of min; wt, wild type.

References


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