Characterization of a Novel Member of the Macrophage Mannose Receptor Type C Lectin Family*

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The recognition of a diversity of carbohydrates by the various calcium dependent (type C) lectin family members has been shown to be critical for a variety of processes ranging from cell adhesion to antigen presentation. Examination of the expressed sequence tag (EST) data base for novel type C lectins using E-selectin as a probe resulted in the identification of a distantly related short polypeptide sequence containing many of the conserved residues found in these carbohydrate-binding proteins. Cloning of the full-length murine cDNA containing this region revealed that this protein is a novel member of the family that includes the macrophage mannose, the phospholipase A2, and the DEC 205 receptors, with a cysteine-rich domain, a fibronectin type 2 domain, eight type C lectin domains, a transmembrane domain, and a short cytoplasmic carboxyl terminus. Genomic Southern analysis suggests that this is a conserved protein, and examination of a human homologue revealed a high degree of sequence homology with the murine form. Northern blot analysis revealed expression of a large transcript in a number of different human and murine tissues and tumor cells and an alternatively spliced smaller transcript with a divergent 5′ sequence was expressed specifically in the human fetal liver. Analysis of the genomic structure revealed that the gene encoding this lectin was interrupted by a large number of introns, and the intron structure was similar to the macrophage mannose receptor gene. Finally, in situ hybridization analysis demonstrated that the transcript encoding this lectin was found in a number of highly endothelialized sites as well as in chondrocytes in cartilaginous regions of the embryo.

A number of different animal and plant lectin families exist, but it is the calcium-dependent, or type C, lectins that have recently garnered the most attention. For example, the recognition of carbohydrate residues on either endothelial cells or leukocytes by the selectin family of calcium-dependent lectins has been found to be of profound importance to the trafficking of leukocytes to inflammatory sites (1). The biophysical analysis of these adhesive interactions has suggested that lectin-carbohydrate binding evolved in this case to allow for the adhesion between leukocytes and the endothelium under the high shear conditions of the vasculature (2). The crystal structures of the mannose binding protein (3, 4) and E-selectin (5), together with various mutagenesis analyses (6–9), is consistent with the supposition that the type C lectins are, in general, involved with the rapid recognition of clustered carbohydrates.

A particularly unusual group of type C lectins is that represented by the macrophage mannose (10, 11), phospholipase A2 (12–14), and DEC 205 (15) receptors. While most of the members of the type C lectin group contain only a single carbohydrate binding domain, these three receptors contain either 8 (macrophage mannose and phospholipase A2 receptors) or 10 (DEC 205 receptor) lectin domains, and it is likely that these domains cooperate with each other to enhance ligand avidity (16, 17). All three of these molecules appear to be type 1 transmembrane proteins, and they all appear to mediate various endocytic phenomena. Thus, this family will hereafter be referred to as the endocytic type C lectins (11, 15, 18). Both the macrophage mannose and DEC 205 receptors appear to mediate the endocytosis of large particulate (the macrophage mannose receptor) (11) or highly glycosylated molecular (the DEC 205 receptor) complexes (15). In both cases, the endocytosis of glycosylated complexes by these receptors is involved with the transport of either particles or glycoproteins to the endosomal pathway where they are degraded and, in the case of the DEC 205 receptor, efficiently presented to cells of the immune system (15). Interestingly, it is likely that the phospholipase A2 receptor is also involved with the endocytic uptake of extracellular proteins (12–14, 18). However, the function of this receptor, other than as a high affinity mediator of phospholipase binding, is unknown, and its tissue expression pattern appears to be far broader than the other two receptors in this family (14). In summary, all three of the members of this family of type C lectins appear to be involved with the binding and uptake of either large particulate or molecular complexes into the endocytic pathway of the cell, and in the case of both the macrophage mannose and DEC 205 receptors, these interactions appear to be via protein-carbohydrate recognition.

Here, we describe a search of the expressed sequence tag (EST)1 cDNA data base with the lectin domain of E-selectin, which resulted in the identification of an EST with distant, but significant, homology to this type C lectin motif. Characterization of the cDNA clone containing this E-selectin-related region revealed that it is a novel member of the family of endocytic type C lectins. The novel protein contains domains that are distantly related, but similar in overall structure, to those found in the other members of this lectin family. In addition, it appears to be expressed specifically in some highly endothelialized regions of the embryo and adult as well as by actively growing and differentiating chondrocytes in the embryo. These data suggest that this lectin represents a novel member of the endocytic lectin family that may be involved with the endocytosis of glycosylated complexes by both the endothelium and chondrocytes.

1 The abbreviations used are: EST, expressed sequence tag; PCR, polymerase chain reaction; RACE, rapid amplification of cDNA ends.

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**MATERIALS AND METHODS**

Isolation of cDNAs Coding the Murine and Human Lectins—According to the EST sequence, two 33-mers were synthesized (5’ CCG GAA TTC CGG TTT GTT GCC ACT GGG AGC AGG 3’ and 5’ CCC AAG CTT GAA GTG TGC AGA GCC ACA GTT CTC 3’) for PCR (94 °C, 1 min; 60 °C, 1 min; and 72 °C, 1 min, for 35 cycles) using 5 μl of a human heart cDNA library (Clontech) as template. The 260-base PCR product was cloned (TA cloning kit, Invitrogen) and used as a probe to screen a human heart cDNA library as well as to probe Northern and Southern blots (Clontech). The same pair of primers was also used to amplify a mouse heart cDNA library with lower annealing temperature (55 °C) and a mouse product with the same size (260 base pairs) was obtained. Screening of approximately 500,000 plaques from cDNA libraries was done using standard procedure with a randomly labeled DNA probe. Since the positive clones were isolated after two more rounds of rescreeing, the size of the inserts was identified by PCR using two primers from the jgt10 vector, and the inserts were subcloned. DNA sequencing was performed on an Applied Biosystems automated DNA sequencer. To clone the 5’ region of the transcripts, 5’ RACE (rapid amplification of cDNA ends) was performed using the most 5’ end of the known sequence and the protocol for 5’ RACE supplied by the manufacturer (marathon-ready cDNAs, Clontech) was followed. RACE products were subcloned and sequenced as described.

Northern and Southern Blot Analyses—The DNA probes were prepared by agarose gel purification (gel extraction kit, Qiagen) and random labeling (Pharmacia Biotech Inc.). Blot hybridization was performed as described in manufacturer’s instruction using commercially supplied blots (Clontech).

Characterization of the Fetal Liver Transcript—Sequencing of the RACE products using human fetal liver marathon-ready cDNA (Clontech) as template revealed a novel 5’ region not found in the original heart-derived clones. To further characterize this transcript, PCR was performed on heart, lung, and fetal liver using a common downstream primer with two different upstream primers. One upstream primer is from the lectin sequence, which is not present in fetal liver clone and the other is from fetal liver unique sequence. The PCR products were analyzed on agarose gel and hybridized by an oligonucleotide common to both transcripts.

Isolation of Genomic Clones Encoding the Murine Lectin—A 129 mouse-derived embryonic cell (ES) genomic library was used for the screening by two lectin cDNA sequences. One is from the 5’ end of the lectin coding sequence and the other one is from the 3’ end of the cDNA. Screening of 500,000 plaques yielded three kinds of lectin genomic clones; positive for the 5’ end probe, the 3’ end probe, and both. Recombinant phage DNA was isolated from plate lysates (Wizard Lambda Prep Kit, Promega) and digested by NotI/HindIII. Genomic DNA inserts were subcloned into a NotI-digested pBluescript SK vector using rapid DNA ligation kit (Boehringer Mannheim), after heat inactivation of the restriction enzyme. The approximate locations of introns and exons were identified using dot-blot hybridization with specific oligonucleotide probes and PCR analysis of λ clones using exon-specific probes. Physical mapping of the lectin gene was performed using restriction enzyme digestion of genomic clones followed by Southern blot hybridization with exon-specific oligonucleotide probes.

In Situ Hybridization—In situ hybridization was performed essentially as described previously (19). Briefly, antisense and sense riboprobes for this clone were generated by use of the PCR to derive templates for subsequent in vitro transcription. In preparation for hybridization, sections were treated sequentially with 4% paraformaldehyde (10 min) and proteinase K (0.5 μg/ml, 15 min) and then prehybridization buffer consisting of 10% dextran sulfate, 2 × SSC (sodium chloride/sodium citrate) and 50% formamide. Probes were added at a final concentration of 106 cpm/ml, and the sections were incubated overnight at 55 °C. Posthybridization washes consisted of 2 × SSC containing 1 mM EDTA, before and after a 30-min treatment with ribonuclease (20 μg/ml). A high-stringency washing containing 0.1 × SSC containing EDTA was performed in a large volume for 2 h at 55 °C. Sections were then washed in 0.5 × SSC, dehydrated in increasing concentrations of ethanol, and then vacuum-desiccated. Slides were covered with NTB2 nuclear emulsion (Eastman Kodak Co.) and exposed for up to 5 weeks. After the slides were developed they were counterstained with hematoxylin and eosin and evaluated by epiluminescent microscopy for positive hybridization. Serial sections of the tissues hybridized with the sense probes served as negative controls.

**RESULTS**

The EST data base is a large collection of random cDNA sequences from a diversity of libraries. In order to examine if any novel type C lectins were contained within the sequences of the EST data base, it was “probed” in silico with the lectin domain of E-selectin. As can be seen in Fig. 1, a sequence (T11885) was identified which showed low homology (~ 23%) to a region of the E-selectin lectin domain. While this homology appeared to be quite distant, the residues that were identical were included in the subset of amino acids that have been shown previously to be conserved in the vast majority of type C lectins (20). In addition, searching the GenBank™/EMBL data base with the novel EST-derived E-selectin related sequence resulted in only type C lectin homologies (data not shown), again consistent with the novel sequence being a member of this family of proteins.

Because the novel EST sequence was originally derived from a human heart cDNA library, a similar library was used for PCR analysis using primers deduced from the EST sequence. This resulted in a DNA fragment containing the same sequence as that found for the data base entry, and this fragment was used to probe the human heart library. In addition, a murine fragment was also isolated using similar techniques, and this fragment was used for the isolation of a cDNA from a murine heart library. Fig. 2 illustrates the full-length sequence obtained for the murine cDNA clone. As can be seen from this figure, this large transcript encoded a protein of 1,479 residues with a molecular mass of approximately 167 kDa. The human sequence revealed approximately 90% amino acid sequence homology with the murine protein (data not shown). The ATG signal sequence, a cysteine-rich domain, a fibronectin type II domain, and an endocytosis domain were conserved in the vast majority of type C lectins containing multiple lectin domains, which also mediate endocytosis (Fig. 3). These levels of sequence homology are similar to those found when these three lectin-like receptors are compared with each other, consistent with the supposition that the novel cDNA described here is a new member of this family. Further homology analysis by domains revealed that the highest sequence homologies between these four related proteins were found in the fibronectin type II and lectin-like domains 1–3, consistent with the possibility that these domains might be functionally important (Fig. 4). In addition, analysis of the cytoplasmic domain of the novel type C lectin also revealed that it contained a conserved tyrosine residue (residue number 1,451) in a context similar to the NSYY motif that has been found previously to be important for the endocytosis of the phospholipase A2 receptor (18). In summary, the novel receptor described here is related to three described previously lectins with an overall structure that consists of a signal sequence, a cysteine-rich domain, a fibronectin type II domain, 8 type C lectin domains (10 such domains in the DEC
FIG. 2. The DNA and derived protein sequence of the cDNA encoding the E-selectin homologous sequence. Illustrated is the entire DNA sequence and derived protein sequence of the cDNA clones and RACE products derived using the T11885 DNA sequence as a probe. The region homologous to the original EST stretches from amino acids 995 to 1,061.
205 receptor), a transmembrane domain, and a short cytoplasmic domain (Fig. 4).

Analysis of the Genomic Structure of the Novel Type C Lectin—Southern blot analyses with a small region of the novel type C lectin revealed that it was encoded by a single copy, highly conserved gene, in agreement with the high degree of sequence homology between the murine and human cDNAs (Fig. 5). The gene encoding the murine form of the novel type C lectin, with the exception of the signal sequence and cysteine-rich domain exons, which could not be isolated from our library,

![Fig. 3. Protein homologies between the novel type C lectin, the macrophage mannose receptor, the phospholipase A2 receptor, and the DEC 205 receptor. Illustrated are the conserved residues in the three members of the endocytic type C lectin family (boxed). Overlined are shown the signal sequence, cysteine-rich, fibronectin type II, type C lectin, transmembrane, and cytoplasmic domains. The ninth and tenth type C lectin domains of the DEC 205 receptor were deleted to allow for a clearer alignment.](http://www.jbc.org/Downloaded from http://www.jbc.org/)

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was characterized using a combination of Southern blotting and PCR analysis of cDNA clones using exon-specific probes predicted from the human and murine macrophage mannose receptor gene structures (21, 22). As can be seen from Fig. 5, the gene was interrupted by a minimum of 28 introns and was spread across at least 39 kilobase pairs of DNA. This genomic structure is therefore highly reminiscent of that found for the human and murine macrophage mannose receptors (21, 22), both of which were interrupted by a similar number of introns at similar sites. These data are thus consistent with the supposition that the members of this family of type C lectins were all derived from an original progenitor gene, which was then duplicated and mutated to give rise to these four different proteins with different functions.

Northern Blot Analysis of Transcripts Encoding the Novel Type C Lectin—A diverse collection of murine and human tissues were analyzed for expression of the transcript encoding the novel type C lectin. As can be seen from Fig. 6, the transcript was found to be expressed in the earliest murine embryonic stage examined (day 7) and its expression continued throughout embryonic development. Analysis of human fetal tissues revealed that the transcript was highly expressed in lung and kidney. Interestingly, a truncated transcript was found to be expressed predominately in the fetal liver (see below). Analysis of adult murine tissues revealed that high levels of expression were detected in the heart, lung, and kidney, with lower levels in the brain and muscle. Interestingly,
The transcript in the adult liver in both humans and mice appears to be absent, further supporting the specificity of the smaller transcript to the fetal liver. Analysis of expression in human tissues revealed that there were also high transcript levels in the heart as well as in prostate, testis, ovary, and intestine, with lower levels in brain, placenta, lung, kidney, pancreas, spleen, thymus, and colon. Analysis of expression in various transformed cells (Fig. 6) revealed that the novel lectin was transcribed in at least two different hematopoietic cell lines, in contrast to its apparent lack of expression in human peripheral blood leukocytes. In addition, several other transformed cell lines derived from various tumors were also positive for the expression of this lectin. In summary, analysis of expression of the novel type C lectin suggests that it is expressed in a diversity of tissues and throughout development, although it appears to be absent from adult liver and is found as a smaller transcript in fetal liver.

The expression of a smaller transcript in human fetal liver, together with the complex genomic structure described above, suggested that this RNA might have been produced through alternate splicing. Analysis of RACE clones derived from the fetal liver revealed that the smaller transcript appeared to have a divergent 5' sequence. In order to further characterize this transcript, a human fetal liver library was screened, and the resultant positive phage were sequenced. One positive phage was found that appeared to encode a partial cDNA, which corresponded to the smaller transcript. Thus, as can be seen from Fig. 6, the resultant sequence is identical to the original, full-length lectin until nucleotide 61, where a divergent sequence is found leading to the 5' end of the transcript. This is the identical splice site seen from Fig. 7, the resultant sequence is identical to the original, full-length lectin until nucleotide 61, where a divergent sequence is found leading to the 5' end of the transcript. This is the identical splice site found for intron number 18 in the mannose receptor (21, 22), which interrupts a region in the collagenous terminus of the fifth lectin domain, consistent with alternate splicing. In order to demonstrate that this transcript exists, as well as to investigate its tissue specificity, specific primers were designed from the original transcript as well as from the smaller, alternately spliced transcript (Fig. 7). As can be seen from Fig. 7, analysis of lung, heart, and fetal liver RNA revealed that the alternately spliced, small transcript was specific to the fetal liver, although this tissue also appeared to make the full-length transcript as well. In addition, analysis of a tissue Northern blot with a 30-mer oligonucleotide specific for the novel region in this transcript revealed a signal only in the fetal liver corresponding to this small RNA (data not shown). Because the size of the transcript on Northern blots suggests that this alternately spliced transcript should extend for only a relatively short distance 5' to the clone isolated here, it is not clear at this time if this transcript encodes a protein.

In Situ Hybridization Analysis of the Novel Type C Lectin—In order to examine the types of cells which expressed the transcript encoding the novel type C lectin, in situ hybridization analyses were performed using murine neonatal and adult tissues. As can be seen from Fig. 8, this transcript was found in two very divergent tissue types. For example, the Northern blot analysis of murine adult tissues as well as human fetal tissues (Fig. 7) suggested a high level of expression of the transcript in lung, and Fig. 8 illustrates that this RNA was found to be clearly expressed in the lung. Although it is difficult to tell at the resolution of the in situ experiments the exact cellular location of the transcript, because of the highly vascularized nature of the lung, it is possible that it is expressed by the lung endothelium. The transcript was also found at a number of other highly endothelialized sites, including, for example, the choroid plexus and the kidney glomerulus (Fig. 8), but it was not universally expressed at detectable levels in all endothelium. In addition, examination by PCR of endothelial cell lines derived from murine yolk sac also demonstrated expression of the lectin (data not shown). The figure also illustrates that the transcript was found to be highly expressed by chondrocytes at sites of active cartilage deposition. As can be seen in this figure, the collagenous region of the larynx produced a high level of this transcript as did other bone forming regions in the neonate, including the developing sternal bones as well as the...
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support the contention that the selectins are also important for
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with mutations in various selectin genes precipitates profound
in affected individuals (24, 25), and the production of animals
occurring human mutations in the circulating mannose-bind-
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binding and engulfment of pathogenic organisms by macro-
the endothelium under the conditions of vascular flow (1), the
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bone forming sites in the embryo as well as in the adult.

FIG. 8. In situ hybridization analysis of neonatal and embry-
onic tissues with the novel type C lectin. A, lung hybridized with
antisense probe; B, lung hybridized with sense probe; C, kidney glom-
erulus hybridized with antisense probe; D, choroid plexus hybridized with
antisense probe; E, developing sternum hybridized with antisense
probe; F, developing sternum hybridized with sense probe; G, develop-
ing tooth hybridized with antisense probe; H, developing cartilage of the
larynx hybridized with antisense probe.

devolving teeth. These data suggest that, in contrast to the
restricted expression of the previously reported members of
this family, the novel type C lectin described here appears to be
expressed in a diversity of highly endothelialized regions and
bone forming sites in the embryo as well as in the adult.

DISCUSSION

The recognition of carbohydrates by various calcium-depend-
ent, or type C, lectins has been acknowledged recently as a
major aspect of a number of physiological phenomena. These
include, for example, the adhesion of various leukocytic cells to
the endothelium under the conditions of vascular flow (1), the
binding and engulfment of pathogenic organisms by macro-
phages (11), and the recognition of transformed cells by natural
killer (NK) cells (23). The importance of these types of interac-
tions have been significantly highlighted by both naturally
occurring as well as induced mutations. For example, naturally
occurring human mutations in the circulating mannose-bind-
ing protein result in sensitivity to various pathogenic infections
in affected individuals (24, 25), and the production of animals
with mutations in various selectin genes precipitates profound
defects in leukocyte trafficking (26, 27). While neither natu-
really occurring nor induced mutations have yet been reported
for the family of endocytic type C lectins, various in vitro data
support the contention that these lectins are also important for
a range of potentially critical functions. We here describe a
novel member of the endocytic lectin family, which contains
many of the structural features of the previously described
members, but which reveals several differences in expression
sites with potentially important functional implications.

Comparison of the overall structure of the novel receptor
reported here suggests that it is clearly a member of the endo-
cytic type C lectin family. Thus, the novel receptor contains
regions that are homologous to the cysteine-rich, fibronectin
type II, and multiple lectin domain motifs found in the other
three members of this lectin family, in addition to a signal
sequence and transmembrane domain, which would orient the
receptor as a type I transmembrane protein (10–14). Interest-
ingly, the cytoplasmic domain is also homologous with the
other members of this family, and this homology includes a
conserved tyrosine within a context similar to the NSYY motif,
which is critical for endocytosis (18). Thus, while the levels of
conservation between these family members appears to be
quite low (~30–35%), their overall predicted protein domain
structures as well as the exon structures of at least the genes
for the human and murine mannose macrophage receptors (21,
22) as well as the novel receptor reported here suggest that
they are clearly a related family of receptors. It is therefore
likely that this novel receptor is involved with the uptake of
ligands for the purpose of an endocytic response.

With respect to ligand recognition by the novel receptor,
previous work has implicated the type C lectin domains as
being critical for the binding activity of the other members of
this family. For example, various deletion analyses of both the
macrophage mannose receptor (16, 17) and the phospholipase

two lectin motifs of the novel protein, consistent with a role for
these motifs in carbohydrate recognition. Interestingly, this is
in contrast with the macrophage mannose receptor, where the
fourth lectin-type domain appears to be the one that is most
critical for carbohydrate recognition (16, 17). These data thus
support the contention that the related lectin reported here is
also involved with the recognition of a highly glycosylated
ligand(s) in order to mediate an endocytic uptake.

While the data reported here suggest that the mechanisms of
ligand recognition by the novel endocytic type C lectin may be
related to those described previously for the other family
members, analysis of the expression patterns of this new protein
suggest that it potentially performs a novel task(s). The expres-
sion patterns of two of the members of the endocytic lectin
family, the macrophage mannose receptor and the DEC 205

2 K. Drickamer, personal communication.
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receptor, reveal a highly restricted transcription of these proteins in macrophages and liver endothelial cells (the macrophage mannose receptor, Ref. 10) or in dendritic cells and thymic epithelium (the DEC 205 receptor, Ref. 15), and these patterns correlate with the known functions of these receptors in immune system function. A broader expression pattern is observed for the phospholipase A2 receptor (12–14). This endocytic receptor is expressed in various tissues of the embryo and the adult, including the heart, lung, kidney, skeletal muscle, and liver in the adult mouse and the kidney in the embryonic human. This pattern is somewhat reminiscent of the novel receptor described here, especially the expression in the adult heart, lung, and kidney. However, there are several differences between these two receptors, including the expression of the novel receptor in the embryonic lung as a large transcript and in the fetal liver as a smaller transcript. In addition, the novel receptor is not expressed at all in adult liver, in contrast to the phospholipase A2 receptor. These differences in expression patterns are consistent with potential differences in function between these two more widely expressed lectin-like receptors.

The cell types that express the novel endocytic lectin give some clues as to its possible function. The relatively widespread transcription in adult tissues is consistent with endocytic function, and the in situ hybridization analysis also supports this contention. These data suggest that the novel lectin might function as a vascular carbohydrate-binding protein. In contrast, other members of this family, including the macrophage mannose receptor and the DEC 205 receptor, appear to function as mediators of the immune system, and they are expressed on a subset of adult immune system cells. However, because the embryo is in a sterile environment, it is unlikely that the currently described lectin is involved with this type of function. One possible function that this lectin could perform in the vasculature might be to transport highly glycosylated proteins across the blood vessel. This function is similar to that hypothesized for the macrophage mannose receptor expressed on endothelial cells of the liver. The high level of expression of the novel lectin in chondrocytes also suggests interesting possibilities. In contrast to endothelial cells, these cells are not directly exposed to the blood stream, so it is unlikely that the lectin binds to identical ligands in the case of these matrix-depositing cells. Expression of the lectin was detected in regions of mineralization, such as the sternal and tooth regions, as well as sites of cartilage deposition, such as the lar ynx. These data suggest that the lectin might be involved with the synthesis of cartilage or other types of extracellular matrix produced by the chondrocytes. If the novel lectin described here is indeed found to be involved with endocytosis, then one possible function in chondrocytes might be the uptake of highly glycosylated precursor proteins that are degraded and utilized for extracellular matrix production. A contrasting possibility might be that the chondrocytes utilize this lectin to remodel the extracellular matrix by the endocytosis of highly glycosylated proteins.

In summary, the data reported here provide evidence for a novel member of the endocytic type C lectin family. This glycoprotein appears to be expressed in a wide variety of tissues in the embryo and adult, and it is transcribed by chondrocytes and, possibly, endothelial cells. While these data are consistent with an important role for this novel lectin during development and in the adult, a number of studies are required before the possible relevance of this lectin to endocytic function and cartilage formation are firmly established.

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