The Crystal Structure of a Novel Mammalian Lectin, Ym1, Suggests a Saccharide Binding Site*

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Yuh-Ju Sun‡‡, Nan-Chi A. Chang¶‡, Shuen-Iu Hung§, Alice Chien Chang**, Chia-Cheng Chou‡ ‡‡, and Chwan-Deng Hsiao‡‡‡

From the ‡Institute of Molecular Biology, Academia Sinica, Taipei, Taiwan 115, Republic of China, the ¶Department of Life Sciences, National Tsing-Hua University, Hsinchu, Taiwan 300, Republic of China, the §Institute of Microbiology & Immunology and **Institute of Neuroscience, School of Life Science, National Yang-Ming University, Taipei, Taiwan 112, Republic of China, and the ‡‡Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan 114, Republic of China

Ym1, a secretory protein synthesized by activated murine peritoneal macrophages, is a novel mammalian lectin with a binding specificity to GlcN. Lectins are responsible for carbohydrate recognition and for mediating cell-cell and cell-extracellular matrix interactions in microbes, plants, and animals. Glycosaminoglycan heparin/heparan sulfate binding ability was also detected in Ym1. We report here the three-dimensional structure of Ym1 at 2.5-Å resolution by x-ray crystallography. The crystal structure of Ym1 consists of two globular domains, a βα triose-phosphate isomerase barrel domain and a small α + β folding domain. A notable electron density of sugar is detected in the Ym1 crystal structure. The saccharide is located inside the triose-phosphate isomerase barrel domain of the COOH terminal end of the β-strands. Both hydrophilic and hydrophobic interactions are noted in the sugar-binding site in Ym1. Despite the fact that Ym1 is not a chitinase, structurally, Ym1 shares significant homology with chitinase A of Serratia marcescens. Ym1 and chitinase A have a similar carbohydrate binding cleft. This study provides new structure information, which will lead to better understanding of the biological significance of Ym1 and its putative gene members.

Macrophage displays marked heterogeneity during its differentiation, activation, and distribution in various tissues. The list of secretory mediators produced by macrophage has grown to over 100; the mediators endow macrophages, through their abundance, distribution, and versatility, with the ability to influence almost every aspect of the immune and inflammatory responses from the initial breach of epithelium to the ultimate repair of the inflamed tissue (1, 2).

Murine activated peritoneal macrophages elicited by oral infection of nematodes (e.g. Trichinella spiralis) were found to synthesize and secrete a novel protein Ym1 (63). Ym1 has been purified and characterized as a single chain polypeptide with an estimated molecular mass of 45 kDa and a pl of 5.7. Under low salt conditions, Ym1 has a tendency to crystallize at its pl. Protein microsequence data derived from the NH2 terminus and CNBr cleavage fragments have facilitated the cloning of Ym1 from a cDNA library of activated peritoneal macrophages. The nucleotide sequence of a full-length cDNA clone was determined, from which a single open reading frame of 398 amino acids with a 21-amino acid signal peptide typical of secretory protein was deduced. The induced expression of Ym1 by activated macrophages and the profound cellular changes paralleling its appearance suggest that Ym1 may bear functional significance to the development of either host defense against or tolerance to nematode.

The existence of a multigene family was substantiated by data derived from genomic organization and chromosomal mapping studies of Ym1 (3, 63) and the observation that a significance sequence homology (42–57%) exists between Ym1 and several other “chitinase-like” proteins, without known functions, such as HC-gp39 (4, 5), chitotriosidase (6), chitinase A1 (7), gp38k (8), oviductin (9), and DS-47 (10).

Sequence analysis revealed significant homology between Ym1 and microbial chitinases (~30%) (11, 63). However, no measurable chitinase activity was found associated with Ym1. Instead, Ym1 has been identified as a novel animal lectin with a binding specificity toward carbohydrates containing GlcN. In addition, its ability to bind heparin/heparan sulfate was subsequently demonstrated (63).

By selective binding of oligosaccharides, lectins can modulate cell-cell interactions pivotal during developmental processes and immune defense mechanisms against infections and tumor metastasis (12, 13). Some crystal structures of animal lectins have been determined that can be classified to several major groups (14–16), such as galecins (17, 18), C-type animal lectins (19, 20), P-type animal lectins (21–23), I-type animal lectins (24, 25), etc.

Selectins (26, 27) are calcium-dependent C-type lectins that mediate adhesive interactions between leukocytes and the endothelium. Three known selectins, L-selectin (28), P-selectin (29), and E-selectin (30), share structural features composed of carbohydrate recognition domains, an epidermal growth factor domain, and several complement-binding protein domains. The structures of E-selectin and epidermal growth factor domain of P-selectin have been reported by the studies of crystallography and NMR, respectively (29, 30). The three-dimensional structure information of L-selectin is unavailable to date; however, L-selectin has been shown to bind to N-unsubstituted GlcN of

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The atomic coordinates and structure factors (code 1E9L) have been deposited in the Protein Data Bank, Research Collaboratory for Structural Bioinformatics, Rutgers University, New Brunswick, NJ (http://www.rcsb.org/).

‡ To whom correspondence may be addressed. Tel.: 886-2-2826-5414; Fax: 886-2-2826-2503; E-mail: achchang@ym.edu.tw.

‡‡ To whom correspondence may be addressed. Tel.: 886-2-2826-7114; Fax: 886-2-2820-2593; E-mail: achiennchang@ym.edu.tw.

‡‡‡ To whom correspondence may be addressed. Tel.: 886-2-2788-7273; Fax: 886-2-2782-6085; E-mail: mbhsiao@ccvax.sinica.edu.tw.

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heparin/heparan sulfate proteoglycans (28, 31).

Heparin/heparan sulfate is a sulfated, negatively charged glycosaminoglycan that is abundant on cell surface and extracellular matrix. The physiological roles of heparin/heparan sulfate are highly diversified, including cell adhesion, motility, proliferation, differentiation, and tissue morphogenesis. The ability of Ym1 to bind heparin/heparan sulfate may be the functional substrate of Ym1 resulting in vivo (32, 33, 63).

We took advantage of the fact that Ym1 has a tendency to crystallize under low salt conditions to study its biophysical characteristics by x-ray crystallography. The information derived from three-dimensional structure of Ym1 and its carbohydrate binding domain would not only unravel the structure-function relationship of this protein but also further our understanding of other members in the Ym1 gene family.

MATERIALS AND METHODS

Data Collection and Structure Determination—Ym1 was purified and crystallized as described in the accompanying paper by Chang et al. (63). After dialysis, Ym1 crystals were retrieved from the bag and laid onto a 10-ml step gradient of 50, 40, 30, 20, and 10% glycerol in a sterile 15-ml tube. After the tube was allowed to stand at room temperature for 6 h, large crystals that had settled at the bottom of the tube were collected, washed glycerol with deionized and distilled water, and laid 15-ml tube. After the tube was allowed to stand at room temperature for 6 h, large crystals that had settled at the bottom of the tube were collected, washed glycerol with deionized and distilled water, and laid.

The initial model from the electron density map interpretation contained four fragments, Try22–Thr67, Arg75–Leu214, Gly225–Lys293, and Gly294–Leu367. Preliminary refinement was calculated using bulk solvent correction. Torsion angle dynamic restraint and isotropic B factor refinement were applied, and most of the missing side chain and discontinuous backbone were rebuilt. The final model contained 3158 nonhydrogen atoms including 372 residues and 214 oxygen atoms of water molecules. The side chains of Glu71 and Gln72 were invisible from the electron density map. The overall structure folding of Ym1 is shown in Fig. 1. The structure is clearly divided into two globular domains, a large βα barrel (triose-phosphate isomerase (TIM) barrel) domain and a small α + β domain. The TIM barrel domain contains 372 residues, excluding the first 21 leading peptides and the last five COOH-terminal residues. Ribbon drawings of the overall structure folding of Ym1 are shown in Fig. 1.

RESULTS AND DISCUSSION

The Overall Structure—Ym1 contains a single polypeptide chain of 372 residues, excluding the first 21 leading peptides and the last five COOH-terminal residues. Ribbon drawings of the overall structure folding of Ym1 are shown in Fig. 1. The structure is clearly divided into two globular domains, a large βα barrel (triose-phosphate isomerase (TIM) barrel) domain and a small α + β domain. The TIM barrel domain contains...
both the NH$_2$ and COOH termini of Ym1. This domain is built from two separate peptide segments from residues 22–266 and 338–393. The TIM barrel domain includes about 80% of the Ym1 residues. The small $\alpha + \beta$ domain consists of residues 268–336, accounting for another 20% of the total residues of Ym1. There are two disulfide bonds formed by residues Cys$^{266}$–Cys$^{311}$ and residues Cys$^{307}$–Cys$^{372}$. The second disulfide bond is within the interdomain region to stabilize the two domains. A topology diagram of the secondary structure of the polypeptide backbone of Ym1 is shown in Fig. 2 and Table II. Briefly, the polypeptide chain of Ym1 starts in the $\beta 1$ of the TIM barrel domain folding as a $\beta\alpha\beta\beta\alpha\beta\beta\alpha$ secondary topology of seven $\beta$-strands and six $\alpha$-helices and forms the major part of the TIM barrel motif. The chain then traverses from strand $\beta 7$ to the small domain and forms the entire structure of the small domain, which consists of one helix and six-stranded antiparallel $\beta$ sheets, making an $\alpha + \beta$ folding motif. From the residue Asn$^{336}$, the polypeptide chain returns back to the large domain and completes the entire ($\beta\alpha$) TIM barrel motif. The eight-stranded parallel $\beta$-sheet is located inside, and eight parallel $\alpha$-helices are surrounded outside. The TIM barrel is elliptical in a donut shape with axes about 13 and 10 Å inside and about 49 and 42 Å outside.

Sequence and Structure Similarity with “Family 18” Glycosyl Hydrolases—A DALI (43) search for structure similarity to Ym1 showed good agreement with chitinase A of Serratia marcescens (11), a glycosyl hydrolase. Chitinase A comprises three domains, an all- $\beta$-stranded NH$_2$-terminal domain, a catalysis $\beta\alpha$ barrel (TIM barrel) domain, and a small $\alpha + \beta$ folding domain. The superimposition between Ym1 and chitinase A in Ca (Fig. 3a) was shown in Fig. 3a. When the NH$_2$-terminal domain (residues 1–159) was excluded from chitinase A, the superimposition (Fig. 3b) showed a strong similarity in the supersecondary structure. The Ca positions of the TIM and $\alpha + \beta$ domains from two proteins could be superimposed with a root mean square deviation of 0.74 Å. The orientation of Fig. 3b is rotated along the $z$ axis (perpendicular to the plane of the paper) of Fig. 3a by $-90^\circ$. The sequence alignment of Ym1 and chitinase A using BLAST (44) showed that the two proteins have 28% sequence identity and 46% sequence similarity. Although Ym1 shares high structure conservation with the catalytic and small domains of chitinase A, there are three noteworthy structure deviations. First, there is an extra 29-residue insertion (residues 195–224) that forms as two helices in chitinase A, whereas the corresponding region in Ym1 is located between $\beta 2$-1 and $\beta 2$-2. This is the most divergent region between Ym1 and chitinase A. The differences in conformation were found in this region, two $\beta$ strands in Ym1 and two $\alpha$ helices in chitinase A. Second, there is an extra 18-residue loop insertion (residues 234–252) in chitinase A. The corresponding region of Ym1 is around residue Asp$^{72}$, located in the middle of $\alpha 2$. Third, there is a 10-residue insertion (residues 365–375) in Ym1 to form a long loop. The corresponding region of chitinase A is located between $\beta 5$ and $\alpha 5$-1.

In addition to chitinase A, concanavalin B (45) and narbonin (46) also share structure similarity with Ym1 according to DALI (43) structure alignment results. Both proteins also belong to the “family 18” glycosyl hydrolases, which contain a similar TIM domain motif and share sequence homology as shown in Fig. 4 and Table III. However, all of these proteins show different biological functions. Chitinase A exhibits glycolytic activity, Ym1 demonstrates glycosaminoglycan binding ability but no glycosyl hydrolase activity (63), and concanavalin B and narbonin both lack chitinase activity.

Saccharide Binding Environment in “Family 18” Glycosyl Hydrolases—The remarkably symmetrical eight-stranded $\beta/\alpha$-barrel structure was first found in the glycolytic enzyme, TIM (47). The typical arrangement of structural elements in the $\beta/\alpha$ TIM barrel domain consists of eight alternating $\alpha$-helices and $\beta$-strands coiled into a barrel. Structurally, the presence of a highly symmetrical, eight-stranded $\beta/\alpha$-barrel structure in many unrelated enzymes seems to have significance for similar substrate binding sites (48). The saccharide substrate of Ym1 might be bound in a fashion similar to that of chitinase A, since Ym1 shares significant sequence and structure conservation with chitinase A. From Perrakis’s study (11), the substrate-binding site of chitinase A is formed by a long groove, located at the carboxyl-terminal end of the $\beta$-strands of the TIM barrel. Many studies on glycosyl hydrolases have delineated that two residues (e.g. in chitinase A of S. marcescens, glutamic acid (Glu$^{315}$) and aspartic acid (Asp$^{391}$)) participate in sugar binding when glycosidic bonds are hydrolyzed (11). Despite the possibility that glycosyl hydrolases may mediate their activities through different protein folding patterns or mechanisms of catalysis, these two residues are key to substrate binding (49).

The key residues of the catalytic domain of chitinases in “family 18” glycosyl hydrolases have been identified. Site-directed mutagenesis studies conducted in chitinase A1 of Bacillus circulans clearly demonstrated that both Asp$^{200}$ and Glu$^{204}$ are essential for chitinolytic activity of the enzyme (7). The mutation of glutamic acid to glutamine completely abolished the enzymatic activity. Conversion of Asp to Asn also significantly reduced the activity (7). It was intriguing to find that the corresponding residue Glu$^{315}$ of Serratia chitinase A is not only key to substrate binding but also essential for its catalytic activity (7, 11). The three essential residues Asp$^{311}$, Glu$^{315}$, and Asp$^{391}$ are highly conserved in majority of chitinases known to date.

The corresponding residues in Ym1 are Asn$^{136}$, Gln$^{140}$, and Asp$^{211}$, located at $\beta 4$ and the COOH-terminal ends of $\beta 4$ and $\beta 6$. 

![Ribbon diagrams (60, 61) of Ym1 in side view orientation (a) and top view orientation (b). The proposed saccharide substrate-binding site is shown as a ball and stick. The $\alpha$-helices are shown as cylinders in violet, and the $\beta$-strands are shown as arrows in cyan. The amino and carboxyl termini are labeled.](http://www.jbc.org/)

**Fig. 1.**
in the TIM barrel, respectively. Amidated residues, Asn136 and Gln140, may explain why Ym1 neither binds chitin nor exhibits chitinase activity. Similar residue substitutions and the lack of chitinase activity were noted in concanavalin B (His127, Gln131, Asn190) (45) and narbonin (Asp 128, Glu132, Asn194) (46). Structurally, the three key residues are located at a similar, if not identical, position in the TIM barrel in all four chitinase-like proteins (shown in Fig. 4 and Table III). In chitinase A, the Cα distance between Glu 315 and Asp 391 is 13.1 Å, whereas the corresponding Cα distance for Ym1 (Gln 140, Asp 213), concanavalin B (Gln131, Asn190), and narbonin (Glu 132, Asn194) is 13.6, 11.7, and 10.4 Å, respectively.

**Identification of a Putative Saccharide Binding Site in Ym1**—Although no oligosaccharide was added during the crystallization process, from the \( \text{Fo} - \text{Fc} \) difference Fourier map (Fig. 5), surprisingly, an extra saccharide density was observed at the top of the β barrel of the TIM domain. This location of the saccharide is highly conserved with the oligosaccharide-binding site in many glycosyl hydrolases (50). Since Ym1 has GlcN binding ability (63), we have tentatively modeled the monoglucosamine into this electron density map. The orientation of the sugar ring cannot be definitively determined at the current level of resolution. However, based on its similarity to the location and shape of the saccharide density observed in chitinase A complexed with GlcNAc (11), the six carbon atoms were positioned into the tentative orientation as shown in Fig. 5. The sugar ring of the putative glucosamine appeared to fit snugly into the electron density map and sat right between the two putative key residues, Gln140 and Asp213. The orientations of Gln140 and Asp213 of Ym1 were very similar to that of the two corresponding residues, glutamic acid and aspartic acid, key to sugar binding of many glycosyl hydrolases (50). The sugar ring was modeled with its O1 and O5 atoms oriented toward Gln140 OE1 and Gln 140 NE2 with distances of 2.9 and 3.2 Å, respectively. The O6 of GlcN is 3.6 Å apart from Asp 213. The charged residue Asp138 might also participate in sugar binding, for its OD1 is modeled 2.7 Å away from the N2 atom of the putative GlcN (Fig. 5). In addition, several aromatic residues, such as Tyr27, Phe58, Trp99, Tyr212, and Trp360, surrounding the binding pocket might contribute to the hydrophobic interactions for sugar binding. It should be pointed out that the face of the glucosamine sugar ring (GlcN) is packed against the ring of Trp360 as seen in other lectin-saccharide interactions (14, 15). All surrounding hydrophobic residues are involved in van der Waals interactions about 4.0 Å from the sugar. As shown in Table III, these important hydrophobic residues are highly conserved in chitinase-like proteins, i.e., chitinase A, concanavalin B, and narbonin. The average temperature factor for

![FIG. 2. A topology diagram of Ym1 is consisting of two domains, the TIM domain and a small α + β domain. The α-helices are shown as cylinders in lavender and labeled α1–α8 for the TIM domain and αC for the small domain. The β-strands are shown as arrows in cyan and labeled β1–β8 for the TIM domain and βA, βB, βD, βE, and βF for the small domain. The amino and carboxyl termini are labeled.](image-url)
the putative sugar binding pocket is about 15 Å² for those residues surrounding the Ym1 protein and 20 Å² for atoms of the proposed glucosamine, respectively. The locations of these residues are evenly distributed into β1, β2, β3, β6, and β8 secondary structures. This might provide the basis for explaining why the (βα)8 TIM barrel motif plays an important role in sugar binding. However, the small domain of Ym1, which is mainly β structure, is not involved in the saccharide binding. Thus far, we have been unable to assign any definitive function for this domain.

Comparison of the Substrate Binding Pocket between Ym1 and Chitosanase—Although Ym1 exhibits a binding activity toward glucosamine, the sequence and three-dimensional structure of Ym1 do not share any significant similarity with chitosanase. Chitosanase hydrolyzes chitosan, a polymer of GlcN produced by partial or full deacetylation of chitin. To our knowledge, chitosanases from Streptomyces N174 (6) and B. circulans (51) are the only ones in “family 46” glycosyl hydrolases with known crystal structures. The chitosanase molecule is dumbbell-shaped, containing two globular domains linked by
a bent helix. The chitosan-binding pocket of chitosanase is located in the two helices and the three-stranded $\beta$-sheet between the two domains (52). Two essential residues, Glu22 and Asp40 in Streptomyces N174, participate in the catalytic mechanism of the chitosanase enzymatic reaction (52, 53). The putative glycosaminoglycan binding site of Ym1, however, is located inside the TIM barrel domain and at the carboxyl-terminal end of the $\beta$-strands. To understand the interaction of glycosaminoglycan and proteins, we have examined the binding surfaces of Ym1 and performed the electrostatic surface potential calculations on Ym1 and chitosanase. Fig. 6 shows two color-coded images produced according to the electrostatic surface potential of Ym1 and chitosanase generated by the program GRASP (54). The surfaces of the possible substrate binding cleft of Ym1 and chitosanase exhibited polarized negative potentials, as shown in red. These results indicate that the substrate binding cleft is appropriate for a positively charged substrate such as GlcN or chitosan. Consequently, in vivo Ym1 may bind to $N$-substituted glycosaminoglycan ligand, structurally similar to chitosan, which is not present in mammals.

Carbohydrate-binding Proteins and Ym1—Since Ym1 has the glucosamine binding activity and the heparin/heparan sulfate proteoglycans might be the functional substrate of Ym1 in vivo (32, 33, 63), we examined the available structure information of several carbohydrate-binding proteins. For example, mannoside-binding protein (19, 20) and E-selectin (30) both be-
long to the \( \alpha/\beta \) class with C-type lectin-like folding. The carbohydrate ligands are bound around the loop 3 and 4 regions, the relatively shallow depressions of the molecular surface (55). The carbohydrate binding activity is \( \text{Ca}^{2+} \)- and pH-dependent (55).

Three-dimensional structures of some heparin/heparan-binding proteins have been determined (56–59), such as human heparin-binding protein (57) and fibroblast growth factor (56). Heparin-binding protein (57) consists of a close \( \beta \)-barrel of six antiparallel \( \beta \)-strands, a typical serine protease fold; fibroblast growth factor (56) is composed entirely of \( \beta \)-sheet structure, composed of a three-fold repeat of a four-stranded antiparallel \( \beta \)-meander motif as a trefoil fold structure. The heparin/heparan sulfate binding is mediated by the electrostatic interaction between the positively charged residues of protein and the negatively charged groups of heparin/heparan sulfate.

Structurally, Ym1 does not exhibit any three-dimensional homology with the aforementioned carbohydrate-binding proteins. Ym1 contains a large \( \beta \alpha \) barrel domain, a typical TIM motif folding, and a small \( \alpha + \beta \) fold domain. The saccharide binding site of Ym1 is found inside the TIM domain at the COOH terminal end of the \( \beta \)-strands. The biological relevance of heparin/heparan sulfate binding of Ym1 is not defined at this stage.

Ym1 and Chitinase-like Proteins—Chang et al. (63) discussed the Ym1 sequence related to secretory proteins, including HC-gp39, chitotriosidase, gp38k, and DS-47. gp38k has been identified as a heparin-binding glycoprotein (8). From our molecular modeling studies (data not shown), the three-dimensional structures of these chitinase-like proteins are quite similar to Ym1, except for several loop insertions on DS-47 and a longer COOH-terminal region on chitotriosidase. Under “Identification of a Putative Saccharide-binding Site in Ym1,” we proposed that residues Gln\(^{140} \) and Asp\(^{213} \) of Ym1 are the essential residues that participate in sugar binding. From the sequence comparison, Asp\(^{213} \) of Ym1 is completely conserved within this superfamily. However, residue Gln\(^{140} \) varies greatly and might perform different functions. Hydrophobic residues Leu\(^{140} \) and Ile\(^{140} \) in HC-gp39 and gp38k substitute the corresponding residue, Gln\(^{140} \) of Ym1, respectively. In DS-47, Gln\(^{160} \) is the same as that of Ym1. In chitotriosidase, Gln\(^{140} \) is replaced by Glu\(^{140} \), which is conserved in “family 18” glycosyl hydrolases. This may explain why only chitotriosidase has the chitinase activity. Furthermore, several hydrophobic residues, such as Tyr\(^{27} \), Phe\(^{58} \), Trp\(^{99} \), Tyr\(^{212} \), and Trp\(^{360} \) of Ym1, are highly conserved within this superfamily. These hydrophobic residues may play significant functional roles, since they are seated in the \( \beta \) strands of the TIM barrel domain and located around the position of the putative sugar-binding pocket in Ym1.

Another noteworthy similarity among this superfamily is the disulfide bond linkage. Two Cys pairs, Cys\(^{26} \)-Cys\(^{51} \) and Cys\(^{307} \)-Cys\(^{372} \), were determined in the Ym1 crystal structure from a total of six cysteine residues. Surprisingly, both disulfide bonds are strictly conserved in all of these chitinase-like proteins. It should be noted that Cys\(^{49} \) may form the third disulfide bond with Cys\(^{394} \). However, due to the quality of the electron density map, the third possible disulfide bond could not be determined in the structure. Meanwhile, residues Cys\(^{49} \) and Cys\(^{394} \) are not conserved in these secretory proteins. Based on the Ym1 crystal structure and the sequence comparison of these chitinase-like proteins, we suggest that they may share structure similarity and saccharide binding activity like Ym1.

Conclusion—In the present study, we determined the crystal structure of Ym1 by x-ray diffraction method. Ym1 is composed...
of two domains, a large \(\beta/\alpha\) barrel (TIM barrel) domain and a small \(\alpha + \beta\) fold domain. Surprisingly, the three-dimensional structure of Ym1, rather than being similar to the known animal lectins, is highly homologous to chitinase structure. Although no chitinase activity can be detected in Ym1, Ym1 has a similar structure to that of the “family 18” glycosyl hydrolases, which consist of a \((\beta_3\alpha)\) topology.

We have observed a saccharide binding site in the Ym1 crystal structure and elucidated the saccharide binding environment. The substrate monosaccharide is located inside the TIM barrel similar to that of Ym1. The heparin/heparan sulfate glycoconjugates may have the functional substrate of Ym1 in vivo. Ym1 may be a novel heparin/heparan sulfate-binding protein with a common TIM barrel folding. The three-dimensional structure of Ym1 presented here provides important information toward understanding how Ym1 binds with its biological targets.

The glucosamine binding ability of Ym1 suggests that it may belong to the chitinase-like animal lectins, and it may have other important biological functions yet to be discovered. There is no structure information available for other chitinase-like proteins (e.g., HC-gp39, chitotriosidase, gp38k, and DS-47). Results from the present study should provide a framework for understanding the possible structure conformation and related biological functions of these Ym1 superfamly proteins. We suggest that these Ym1 superfamly proteins may also have saccharide binding activity similar to Ym1 and may share a structure conformation similar to that of Ym1.

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