Glycan-binding proteins are categorized into two groups, lectins and sulfated glycosaminoglycan-binding proteins. SUEL-related lectins are members of a superfamily of proteins containing a carbohydrate-recognition domain (CRD), which is structurally similar to sea urchin egg lectin (SUEL). Here I review the structure and function of this family of proteins.

Key words: lectin; SUEL; rhamnose; carbohydrate-recognition domain

The sea urchin Anthocidaris crassispina expresses two lectins. One is echinoidin,1 which has been purified from coelomic fluids and belongs to a member of the C-type lectins, requiring Ca<sup>2+</sup> for its glycan-binding activity. The other is termed SUEL,2 which was first reported to show specificity to β-galactoside,2 but later was found to show higher avidity to l-rhamnose.3 In 1991, the amino acid sequence of SUEL was reported.4 At that time, the lectin gave no homology to any lectins, and thus it was proposed to be a novel type of lectin. SUEL exists as a disulfide-linked homodimer of the subunit, which consists of 105 amino acid residues. The dimeric form was found to be essential for hemagglutination activity, indicating that the subunit contains a single sugar-binding site. In 1998, a rhamnose-binding lectin termed STL2 was isolated from eggs of the steelhead trout (Oncorhynchus mykiss), and its amino acid sequence was determined.5 STL2 appeared to consist of two tandemly repeated domains homologically to SUEL.5 Since then, rhamnose-binding lectins isolated from other fish eggs have been found to contain two or three tandemly-repeated SUEL-like domains. More recently, two galactose-binding lectins with two tandemly-repeated SUEL-like domains have been reported: PPL from the mantle of the penguin wing oyster (Pteria penguin),6 and PFL1 from the skin mucous of the ponyfish (Leiognathus nuchalis).7 The SUEL-like domain has also been found in mouse Latrophilin-1, which exhibits binding affinity to l-rhamnose.8 Thus, lectins of this category are not restricted to marine organisms, but are widely distributed throughout organisms. Since most of the lectins belonging to this family show specificity to l-rhamnose, this family has often been called rhamnose-binding lectins (RBLs). However, some lectins categorized in this family are now known to show binding affinity to other glycans, such as Galα1-4Galβ1-4Glc (Gb3) and β-galactose. Hence, they might more suitably be called SUEL-related lectins.

I. SUEL-Like Domain

The SUEL-like domain corresponds to the CRD. Figure 1 shows multiple alignments of the SUEL-like domains of fish egg lectins and SUEL. The typical SUEL-like CRD consists of approximately 100 amino acid residues and contains eight conserved cysteine residues (Fig. 1, highlighted in red). The CRD also contains conserved Tyr-Gly-Arg in the N-terminal domain, and Asp-Pro and Lys in the C-terminal domain (Fig. 1, highlighted in blue). The positions of disulfide linkages have been determined in several SUEL-related lectins by amino acid sequencing,9 mass spectrometry,10 NMR spectroscopy,8 and X-ray crystallography.11 Four disulfide bonds interconnect the backbone within each domain, as follows: C1–C3, C2–C8, C4–C7, and C5–C6 (Fig. 1, top). The crystal structure of chum salmon egg lectin CSL3 shows that the lectin has a king dumbbell shape, in which two lobes are connected through linkers, where each lobe corresponds to the SUEL-like CRD.11 Each domain has two anti-parallel β-sheets with two (β2 and β4) and three (β1, β3, and β5) strands, and three helices (α1-3). As expected, each domain of CSL3 is structurally similar to the N-terminal domain of mouse Latrophilin-1, whose structure has been determined by NMR spectroscopy.8

II. Diversity of the SUEL-Related Lectins

The SUEL-like domain is widely distributed throughout organisms including humans, mice, fish, plants, C. elegans, and bacteria according to Pfam (http://pfam.sanger.ac.uk/, Gal Lectin, PF02140) and InterPro (http://www.ebi.ac.uk/interpro/index.html, β-galactoside/ l-rhamnose binding SUEL lectin, IPR000922) databases. However, only limited numbers of proteins containing the SUEL-like domain have been reported to have sugar-binding activity (Table 1).
III. Classification of SUEL-Related Lectins

Based on protein architecture, SUEL-related lectins can be classified into three types: proto, tandem, and chimera, similarly to the classification proposed for galectins (Fig. 2). The prototype consists of a single CRD. SUEL belonging to this category forms a covalently-linked dimer via an extra cysteine residue located at the N-terminus, and thus shows hemagglutination activity.4) The tandem repeat-type contains two or three tandemly repeated CRDs in a single polypeptide. All of the known SUEL-related lectins from fish eggs belong to this type. Steelhead trout egg lectins (STLs) form noncovalently-linked dimmers as revealed by cross-linking experiments.12) Consistently, a chum salmon egg lectin, CSL3, was found to form a homodimer.

![Fig. 1. Multiple Alignment of SUEL-Related Lectins.](image)

Chum salmon egg lectins (CSL1, P66177; CSL2, P66178; CSL3, P66179), steelhead trout egg lectins (STL1, NP_001117668; STL3, NP_001117669), a catfish egg lectin (SAL, Q9PVW8), white-spotted char egg lectins (WCL1, NP_001117667; WCL2, NP_001117668; WCL3, NP_001117669), Tribolodon brandti egg lectins (TBL1, BAF45138; TBL2, BAF45139; TBL3, BAF45140), a ponyfish skin mucous lectin (PFL1, BAE02882), and a sea urchin egg lectin (SUEL, P22031) were aligned using Clustal W (ver1.83). N, M, and C represent the N-terminal, middle, and C-terminal domains, respectively. The positions of disulfide linkages and the secondary structure of CSL3 are shown at the top. The conserved Cys are highlighted in red. Conserved Tyr-Gly-Arg, Asp-Pro, and Lys are highlighted in blue. Amino acid residues of CSL3-N forming hydrogen bonds with α-L-rhamnose are bold and underlined.

![Fig. 2. Classification of the SUEL-Related Lectins by Domain Architecture.](image)

<table>
<thead>
<tr>
<th>Type</th>
<th>Domain structure</th>
<th>Lectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proto</td>
<td></td>
<td>SUEL, BsRBL1-5</td>
</tr>
<tr>
<td>Tandem</td>
<td></td>
<td>STL2, STL3, CSL2, CSL3, WCL3, TBL1, TBL2, SML, PPL, PPL1</td>
</tr>
<tr>
<td>Chimera</td>
<td></td>
<td>Latrophilin-1, C21orf63, EVA-1</td>
</tr>
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</table>

![Fig. 3. Structural Comparison between α-L-Rhamnose and α-D-Galactose.](image)

The hydroxy groups of α-L-rhamnose and α-D-galactose at C2, C3, and C4 are highlighted in red.
of the 20-kDa subunit by noncovalent interactions, as shown by X-ray crystallography. 11) The chimera-type consists of both SUEL-like and non-SUEL-like domains. Human C21orf63 and mouse latrophilin-1 belong to this type. C21orf63 is a type-I transmembrane receptor containing two tandemly-repeated SUEL-like extracellular domains, a transmembrane domain, and an intracellular domain. 13) Latrophilin-1 is also a type-I transmembrane receptor with a SUEL-like domain at the N-terminus. 14)

### IV. Sugar-Binding Specificities of SUEL-Related Lectins

The sugar-binding specificities of SUEL-related lectins are summarized in Table 1. SUEL and fish egg lectins commonly show monosaccharide specificity to α-L-rhamnose. Recently, the detailed sugar-binding specificities of CSLs and SFL were analyzed by frontal affinity chromatography, which provides quantitative interaction data in terms of $K_D$ in a high-throughput manner. 15,16) Among more than 100 oligosaccharides, including a series of N-glycans and glycolipid-type glycans, CSLs and SFL exhibited the highest affinity to Gb3. 15,16) Consistently, the number of hydrogen bonds of CSL3 formed with Gb3 (10 hydrogen bonds) is higher than with α-L-rhamnose (6 hydrogen bonds) predicted by X-ray crystallography, 11) confirming the result, obtained by frontal affinity chromatography that they show higher affinity to Gb3 than α-L-rhamnose. Amino acid residues of CSL3 involved in the formation of hydrogen bonds with α-L-rhamnose predicted from X-ray crystallography are as follows: Glu7, Tyr27, Asn74, Asp79, Gly83, and Lys86 (Fig. 1). In association with Gb3, two extra amino acid residues, Arg39 and Gln43, are involved. They form hydrogen bonds with the second sugar, β-D-galactose (Gal), and the third sugar, D-glucose (Glc), from the non-reducing end. 11) The mechanism of specificity to both α-L-rhamnose and Gb3 can be explained by the hydroxyl orientations: the hydroxyl orientations of α-L-rhamnose at C2, C3, and C4 correspond to those of the inverted form of β-D-galactose at C4, C3, and C2 respectively (Fig. 3). 8)

The SUEL-like domain of mouse latrophilin-1 also showed binding affinity to α-L-rhamnose, but at low affinity ($K_D = 1.8 \text{ mM}$) analyzed by NMR spectroscopy. 8) Consistently, the amino acid residues of CSL3 involved in hydrogen bond formation with α-L-rhamnose are highly conserved in Latrophilin-1, 8,11) while some members of this family exhibit different specificities. For example, PPL has been reported to show binding specificity to α(2-6) sialylated and asialo N-glycans. 5) Recently, the sugar-binding specificity of human C21orf63 was screened by glycoconjugate microarray. 17) No binding was observed for α-L-rhamnose. Instead, C21orf63 showed binding activity to heparin and heparan sulfate through the second SUEL-like domain. 17) One explanation of the failure to detect the binding signal to α-L-rhamnose is that the sensitivity of the glycoconjugate microarray might not be high enough to detect low binding affinity to the monosaccharide. No sugar-binding activity has been reported for the nematode C21orf63 homolog, EVA-1, a receptor for the SLT-1/Slit neuronal axon guidance cue. 13) It would be interesting to determine whether the SUEL-like domains of EVA-1 show sugar-binding activity.

### V. Tissue Distributions of SUEL-Related Lectins

The developmental expression of SUEL during embryogenesis has been studied in detail. 2,18) Before fertilization, SUEL is stored in cortical granules in the cytoplasm of unfertilized eggs. Upon fertilization, it is released into the hyaline layer at the peripheral region, where the molecule might have a role in cell adhesion or pathogen recognition. The tissue distribution of steelhead trout egg lectins (STLs) has also been reported. 19,20) STL1 is expressed exclusively in the liver of Pteria penguin and is then transported to the oocytes, whereas STL2 and STL3 are female-specific proteins, which are expressed exclusively in the oocytes and accumulate in the cortical vesicles. 19,20) The expression profile of STLs during embryonic development has been examined by northern blotting. 19) STL2 and STL3 mRNA were detected in the previtellogenic or vitellogenic oocytes, but not in the fertilized eggs and larvae of fishes. 19) Similarly to STL2 and STL3, Tribolodon brandti egg
lectins, TBLs, are also expressed mainly in the ovary.21) Some SUEL-related lectins present in other tissues. PFL1 is localized in the skin mucus,7) and PPL in the mantle.6) Human C21orf63 mRNA is ubiquitously expressed in various tissues.17) Expression of mouse latrophilin-1 is restricted to the brain.14) Thus, the SUEL-related lectins tend to be localized selectively in specific tissues, but the localization varies depending on the protein and the organism.

VI. Putative Functions of the SUEL-Related Lectins

Due to the specific localization of SUEL in the hyaline layer of embryonic cells, it has been implicated in morphogenesis by regulation of cell-cell interactions.2,18) SUEL-related lectins from fish eggs have been proposed to play important roles in innate immunity through specific binding to α-rhamnose, which often constitutes a major component of the bacterial cell wall. STLs from steelhead trout eggs have been reported to agglutinate gram-negative and gram-positive bacteria through specific binding to lipopolysaccharide (LPS) and lipoteichoic acid (LTA) respectively.21) Similar functions have been proposed for CSLs and PPL.6) A high concentration of STL2 was detected on the surface coat of spores of the fish parasite Glugea plecostomae,23) which is the causative agent of gill disease in salmonids, suggesting a role for this molecule in self-defense against parasites. Similarly, SFL from ayu eggs agglutinates the spores of the ayu pathogen Glugea plecostomae through specific binding to GB3.16) CSLs from chum salmon eggs bind to a peritoneal macrophage cell line, RTM-5, and a fibroblastic-like cell line, RTG-2, followed by induction of proinflammatory cytokines.15) Furthermore, CSLs have been reported to play roles as opsonins, which enhance phagocytosis.15) Fish egg lectins have also been reported to have apoptosis-inducing activity, although their functional significance in fishes remained to be elucidated.15,24) Mouse latrophilin-1, a target receptor for α-latrotoxin, has been implicated in synaptic function, although the role of the SUEL-like domain has yet to be clarified.14) Nematode EVA-1 has been reported to function as a coreceptor for SLT-1/Slit and to influence axon migration functions.13) However, the role of the SUEL-like domain in this receptor is not known.

VII. Concluding Remarks

Lectin, a term derived from the Latin “legere,” meaning “to select,” was first discovered in 1888 by Peter Hermann Stillmark from seed extracts of the poisonous plant Ricinus communis. Since then, lectins have been found throughout organisms such as animals, plants, bacteria, and virus. Based on structural and/or sequence similarities, lectins are classified into more than 40 families. As reviewed here, SUEL-related lectins are defined as a lectin family, since they recognize glycans via evolutionarily conserved SUEL-like CRDs. It would be interesting to see whether the SUEL-like domains found in various organisms have sugar-binding activity, and if so, to clarify their biological functions mediated by their sugar-binding activity.

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References