Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Common Scaffolds, Diverse Recognition Profiles

A paper in this issue of *Structure* reports the crystal structure of griffithsin, a lectin from red algae, and demonstrates its ability to bind and neutralize the SARS coronavirus, providing a link in understanding the evolution of lectins in this family. (Ziółkowska et al., 2006).

Lectins, as a family of proteins, owe their involvement in a spectacular range of biological processes to their ability to specifically bind carbohydrates (Lis and Sharon, 1998). There is considerable diversity in the sequences and folds found in different lectin families, and more interestingly, there is also significant diversity in the quaternary structures and oligosaccharide recognition profiles found within the same family (Vijayan and Chandra, 1999). Every new structure-function study, therefore, is a precious addition to the lectin knowledge base.

The structure of griffithsin reported in this issue is the first detailed structural study of an algal lectin. The β-prism-I fold that its subunits adopt appears to be a popular fold among known lectins across different plant classes, ranging from monocotyledonous cereals to higher plants such as *Arabidopsis thaliana* (Raval et al., 2004). The quaternary structures of the lectins in this family available in the PDB, commonly known as jacalin-related lectins (JRLs), also span a wide range including different types of dimers found in calsepa, banana, and the Japanese chestnut, the latter in fact resembling a hexamer; tetramers found in jacalin, artocarpin, and *Maclura pomifera* agglutinin; and an octamer found in heltuba. Remarkably, these variations occur despite strong sequence and fold conservation in the family and can be structurally explained by small sequence changes at subunit interfaces.

A new dimeric arrangement is found in griffithsin, one that involves swapping of two β strands with those from the other subunit in the dimer. Interestingly, a similar arrangement was observed previously in the crystal structures of another family of lectins, those from bulbs such as snowdrop and garlic. Understandably, this type of swapping enhances the intersubunit interactions, rendering subunit association much stronger. In some sense, this also suggests the dimer and not an individual subunit as the minimum biological unit, hence exerting a strong selective pressure for evolution of stable dimers. This is particularly important in view of the observations that variation in quaternary structure appears to have provided a strategy for generating diversity in carbohydrate recognition (Vijayan and Chandra, 1999).

Each subunit of griffithsin has three sugar binding sites. There is also a 3-fold sequence motif and structural repeat within each subunit, a scenario again very similar to that found in bulb lectins but unlike that in many other JRLs. Most JRLs have only one well-established binding site in their subunits; however, the recent structure of banana lectin (Singh et al., 2005) indicated two clear binding sites with weak hints about a possible third. The 3-fold internal repeat in sequence, completely missing from JRLs of higher plants (Sankaranarayanan et al., 1996), is quite visible in the monocotyledonous banana and has become clearer in the more primitive griffithsin. These two features put together are suggestive of a gene-triplication event early in lectin evolution, which has diverged sufficiently in higher plants beyond easy recognition. Thus, the study of griffithsin from an alga has provided an important clue to understanding the evolutionary trace of this class of lectins.

The importance of multivalency in the function of lectins is well recognized (Weis and Drickamer, 1996). It is commonly believed that multiple binding sites on each monomer are occupied simultaneously by different sugars of oligosaccharide molecules, thereby enhancing affinity in a cooperative fashion. Although there are some reports to show that different residues of the same oligosaccharide molecule can bind to two or more sites on a single lectin molecule, affinity enhancement is better explained by the formation of supramolecular assemblies formed through the crosslinking of the lectin molecules through the sugars (Sacchettini et al., 2001). Such crosslinking, which could be a generic feature of all lectins, is enabled by the multiple binding sites present on lectin molecules. Extensive computational studies carried out for garlic lectin indicated that a mannosyl nona-saccharide of the type typically present on cell surfaces cannot simultaneously occupy more than one site on a given subunit or even in a dimer, but instead crosslinks different protein molecules, with the sugars forming the required bridges (Ramachandraiah et al., 2003). Different types of crosslinks are enabled by either a different number of binding sites on the same subunit or by different quaternary structures of the same fold.

These variations become very useful in catering to a large number of different oligosaccharides present on different organisms, against some of which the plant may be required to defend itself. Ziółkowska et al. (2006) present data to show inhibition of both replication and cytopathicity of the SARS coronavirus by griffithsin, possibly due to its binding to the glycosylated spike protein, in addition to the previously reported binding and inhibition of HIV (Mori et al., 2005). While the modes of binding at the monosaccharide level are likely to be the same in both cases, it would be interesting to understand the modes of recognition at the oligosaccharide level, for which the structure of griffithsin reported here provides a framework. Regardless of that, these data highlight the scope of lectins as useful markers in the detection and typing of different viruses.

Given that the role of plant lectins as defense molecules is becoming well established, it leaves us wondering whether lectins constitute primary defense systems in themselves, simple yet capable of recognizing a wide range of complex sugars. In any case, the fact that such diversity in recognition can be generated over a common scaffold provided by the structure of individual lectin subunits with multiple binding sites in them illustrates

the evolution of one of the most efficient biological systems in the cell. They also have immense potential to be used in medicine, both for diagnosis as well as therapy, especially in cancers and bacterial or viral infections, which may be realized as oligosaccharide binding profiles and preferences become better understood.

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When Size Matters

Erythrocruorins are very large extracellular hemoglobins found in some invertebrates. In this issue of *Structure*, Royer et al. (2006) report the structure of the 3.6 MDa, 180-mer of *Lumbricus* (earthworm) hemoglobin consisting of 144 globin and 36 linker chains.

Erythrocruorins are high molecular mass (1,500,000 to 4,000,000 Da) hemoglobins found in the hemolymph of many annelid worms and some other nonvertebrates (for a superb review on the great diversity and adaptations of nonvertebrate hemoglobins, see Weber and Vinogradov [2001]). They are similar to vertebrate hemoglobins, the best characterized proteins in biochemistry, in that they bind one molecule of oxygen per heme and function as oxygen carriers. The "How" and "Why" questions about the existence and nature of these large assemblages has intrigued scientists for nearly two centuries. *Lumbricus* erythrocruorin prepared by Hünfeld in 1840 was the first protein crystallized (Reichert and Brown, 1909). Thus, the report of the structure of erythrocruorin 166 years later in this issue of *Structure* by Royer and colleagues is a remarkable milestone.

These molecules have many interesting structural and functional features. Svedberg and Eriksson-Quensel (1934) discovered that the extracellular hemoglobins of the earthworm, *Lumbricus terrestris* (LtHb), and related annelids are gigantic molecules with masses greater than 3×10^6 Da, ~50 times the mass of human hemoglobin. They honored these gigantic hemoglobins by naming them erythrocruorins to distinguish them from their smaller brethren. Early studies with electron microscopy showed them to have a hexagonal bilayer structure with a large central hole (Levin, 1963), which is filled in erythrocruorins of some other annelids. Among their most intriguing functional properties are unusually high cooperativity of oxygen binding and use of calcium as an allosteric factor.

The determination of the size and polypeptide composition of erythrocruorins has had a tortuous history. The molecules were initially believed to be composed wholly of heme-containing globin subunits, but some disturbing observations did not fit this picture: the iron content was significantly lower than expected, and heme-free subunits were found experimentally. Although the four unique globin subunits (*a*, *b*, *c*, and *d*) had the expected masses of 14–17 kDa, small quantities of 24–35 kDa subunits were also present, but these were regarded either as contaminants or ill-defined aggregates of the globin subunits. Vinogradov et al. (1986) resolved this problem with clear evidence for unique nonglobin, nonheme structural subunits called "linkers" that line the central hole to form an internal "bracelet" to which the hemoglobin subunits are attached. A total of four different linkers have since been identified as constituents of LtHb: L1, L2, L3, and L4 (a minor component similar to L3) (see Kao et al., 2006).

In this issue of *Structure,* Royer and colleagues report the crystal structure of this enormous molecule to a resolution of 3.5 Å, and they have determined the positions of the 144 globin subunits and 36 linkers in the assemblage. This is the largest three-dimensional protein structure reported to this resolution. It is significantly larger than the 50S ribosomal subunit and is comparable in size to many viruses (Figure 1). The disulfide-linked globin heterotrimer (*abc*), together with the fourth globin subunit (*d*, a monomer) and three unique linkers (L1, L2, L3: excluding the minor component L4), are the five players in the choreography of the assembly process. How do they assemble into the full-sized molecule? What is the smallest functional unit? Why are four