



Animal and Bacterial Lectins

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Many of the important biological functions of carbohydrates result from their recognition by sugar-binding proteins or lectins. In the same way that carbohydrates do not all serve the same function, lectins in animal and bacteria mediate a variety of different functions. The different roles of animal lectins involve interaction with sugar structures endogenous to the animal or with sugars on bacterial and fungal cell surfaces. Conversely, many bacterial lectins are designed to mediate interactions with animal cells. Before considering the variety of functions performed by animal lectins, it is useful to divide them into groups that are based on shared structural features.

CLASSIFICATION OF ANIMAL LECTINS

Many animal lectins are complex proteins consisting of multiple different types of protein modules. Fortunately, the sugar-binding activity of most lectins can be ascribed to a single type of module within the overall polypeptide. It is useful to group the lectins based on similarities in their carbohydrate-recognition domains (CRDs). So far, three major groups of CRDs have emerged. P-type CRDs selectively bind mannose 6-phosphate, S-type CRDs in the galectins bind β -galactosides, and C-type CRDs bind a variety of different sugars in a Ca^{2+} -dependent fashion. Examples of proteins containing each of these types of CRDs are discussed briefly, to indicate the types of biological processes that they mediate. More details about most of these functions can be found in a recent review⁽¹⁾.

MANNOSE 6-PHOSPHATE RECEPTORS

The mannose 6-phosphate receptors recognize mannose 6-phosphate recognition markers on endogenous glycoproteins within animal cells, and direct their intracellular routing to lysosomes⁽²⁾. Two different membrane-bound receptors seem to be capable of leading lysosomal hydrolases from the trans-Golgi network to the lysosome. In addition, one of the receptors is able to mediate uptake of hydrolases from the medium surrounding the cell. The selective attachment of the mannose 6-phosphate marker onto the hydrolases and not onto other proteins in the secretory pathway results from the selective recognition of the hydrolases by a transferase which attaches N-acetylglucosamine phosphate to high-mannose structures. Terminal mannose 6-phosphate is then revealed by removal of the N-acetylglucosamine. One of the receptors is a dimer of identical polypeptides, each of which contains a single CRD. The second, larger receptor contains 15 CRD-like modules in a single polypeptide; however, it appears that only two of these CRDs have mannose 6-phosphate-binding activity. Thus, each receptor is designed to recognize two mannose 6-phosphate residues in an oligosaccharide attached to a hydrolase.

SELECTINS

Perhaps the best studied animal lectins are the selectin cell adhesion molecules. These membrane receptors contain C-type CRDs adjacent to epidermal growth factor-like modules and various numbers of complement homology repeats. The selectins mediate interactions between circulating leukocytes and endothelial cells at sites of inflammation and in lymph nodes. They are responsible for an initial, weak interaction between the rapidly moving leukocyte and the stationary epithelium, causing the leukocyte to roll along the surface. The CRDs in the selectins recognize specific endogenous carbohydrate structures.

CLEARANCE RECEPTORS

A number of the lectins that contain C-type CRDs are membrane receptors that mediate endocytosis of glycoproteins. The best studied example is the mammalian hepatic asialoglycoprotein receptor, which removes glycoproteins from circulation when sialic acid residues are removed to expose terminal galactose. Most serum proteins contain complex N-linked oligosaccharides; exposure to a low level of neuraminidase activity, perhaps at the surface of epithelial cells, would result in random loss of sialic acids followed by clearance into the liver. The mannose receptor of macrophages and liver endothelial cells also causes clearance of proteins, in this case by binding to exposed high mannose structures. Such clearance may be important in the case of lysosomal hydrolases that have been released from cells and have lost their mannose 6-phosphate recognition markers. This receptor also contributes to the clearance of tissue plasminogen activator from circulation.

COLLECTINS AND MANNOSE RECEPTORS

C-type CRDs are also involved in recognition of exogenous sugars, such as those found on the surfaces of potential microbial pathogens. Since the outer walls of these organisms are often rich in mannose and N-acetylglucosamine, sugars that are not found in such high abundance on animal cell surfaces, these lectins can discriminate, in a crude way, between self and nonself. The collectins, which include serum mannose-binding protein and two of the pulmonary surfactant apoproteins, consist of C-type CRDs linked to collagenous domains. The mechanism of Ca^{2+} -dependent sugar binding by the CRD of mannose-binding protein has been established at the molecular level (see Figure⁽³⁾). In overall architecture, the collectins resemble complement component C1q, and at least some of these lectins can initiate fixation of complement and act as opsonins. These properties allow the collectins to mediate a simple, antibody-independent immune response. Since mutations in the collagenous domain of serum mannose-binding protein can lead

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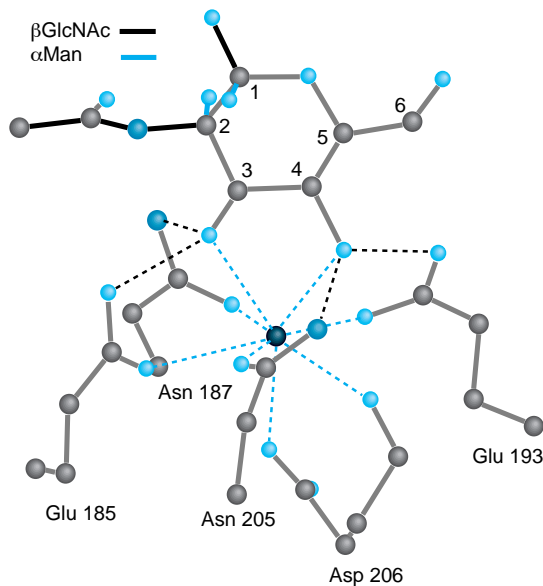


Diagram showing how both mannose and N-acetylglucosamine can bind to serum mannose-binding protein through a network of hydrogen bonds (black dashes) and direct coordination to Ca^{2+} (blue dashes).

to recurrent, severe infections in young children, it appears that this form of immune protection is particularly important during the period from 6 months to 2 years of age. The macrophage mannose receptor may also participate in sugar-based immune protection, by directly mediating phagocytosis of microorganisms. It is the only known lectin with multiple C-type CRDs in a single polypeptide chain, perhaps reflecting its ability to bind to large, particulate ligands.

GALECTINS

While all of the C-type CRDs function at cell surfaces or in the extracellular environment, the galectins have an unusual dual localization, both inside the cytoplasm and nucleus as well as outside the cell. They are found in a wide variety of cell types, and all bind a relatively similar spectrum of β -galactosides. Galectins contain CRDs that are distinct in structure from those in the C-type lectins, and do not require calcium for sugar-binding activity. Although similar in overall structure to the legume lectins of plants, the mechanism of sugar binding is distinct⁽⁴⁾. In most cases, the galectin molecules display multivalent sugar binding, either as a result of multiple CRDs being present in one polypeptide or through oligomerization of single CRDs. Functions have been suggested for galectins both inside and outside the cell. Inside the cell, one of the galectins is found associated with ribonuclear protein particles, and changes its localization between nucleus and cytoplasm

during the cell cycle, suggesting a possible role in regulation of RNA transcription or transport. The appearance of galectins at cell surfaces at specific stages in development indicates a function related to cellular differentiation, such as during myotube fusion to form muscle.

BACTERIAL LECTINS

The bacterial lectins that have been best characterized structurally are toxins. Pertussis toxin, which is responsible for whooping cough, and cholera toxin, *Escherichia coli* heat-labile toxin and verotoxin, which cause diarrhea, have distinct target cells and mechanisms of action. However, they all consist of membrane-binding subunits that interact with sugars on eukaryotic cell surfaces, and enzymatically active subunits that move into the cytoplasm and modify activity of critical cellular components. The sugar-binding membrane anchor subunits are very diverse in amino acid sequence and bind to various sugar receptors, but in three dimensions all form pentamers which seem to have similar protein folds^(5,6). A second group of bacterial lectins, less well understood at the molecular level, mediate adhesion of the bacteria themselves to eukaryotic host cells⁽⁷⁾. These interactions are important for enteric bacteria, which must adhere to the intestinal lining, and for various strains which live as intracellular parasites in macrophages.

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