Review Article

Role of lectins in clinical settings

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ABSTRACT

Lectins are a diverse class of proteins derived from either plants, microbial or animal sources and may be soluble or membrane bound. It is a tetramer made up of four nearly identical subunits. In humans, lectins have been reported to cause digestive distress, carbohydrate, and other disorders. This review intends to put forward basic foundation in carbohydrate structure and function, lectin biology and the implications of glycobiology in human health and disease, particularly in cancer therapeutics. These topics are among the hundreds included in the field of glycobiology and form the cornerstone of glycobiology.

Key words: Applications, biological significance, lectins, structure

INTRODUCTION

It is difficult to discuss carbohydrates without reference to lectins. The term lectin is derived from the Latin word "legere" meaning "to bind" or "to pick." Lectins are defined as proteins that preferentially recognize and bind carbohydrate complexes protruding from glycolipids and glycoproteins[1] Lectins are abundant in nature, and were first isolated in 1888 by Stillmark at Estonia University.[2] Lectins are found in most plants but are particularly high in legumes and grains[3,4] Seafood such as shellfish, eel, halibut, and flounder also have high lectin contents. The amount of lectin concentration generally accounts for 1–3% of the protein content of the specific food, and in the case of plants, the amount is dependent upon the degree of plant maturation.[2]

Lectins are nonimmunologic protein-polysaccharide molecules having a strong binding affinity for the complex carbohydrates, which are abundant on cell surfaces.[3] Lectins bind in a manner similar to antibodies, forming an irreversible covalent bond. The binding of lectins can often be inhibited by specific monosaccharides.[3-5] An example of a high molecular weight polysaccharide, which conveys a protective effect is arabinogalactan, found in a variety of foods and herbal medicines. This class of molecules has been shown to occupy the binding sites of various microorganisms, preventing them from attaching to cellular surfaces and making it easier for the immune system to eliminate them.[4]

The aim of this review is to highlight instructionally useful discussion on structure and function of lectins and their role in human health and disease, particularly in cancer, metastasis and its therapeutics.

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BACK TO HISTORY

The beginnings of lectinology date back to 1888 when Herrmann Stillmark described the agglutination properties of ricin; however, the modern age of lectinology started nearly 100 years later (Bies, 2004; Sharon and Lis, 2004). Lectins were initially found and described in plants, but in subsequent years multiple lectins were isolated from microorganisms and also from animals (Sharon and Lis, 2004). During the past several years, however, many primary and three-dimensional structures of lectins have been elucidated. Structural studies conducted on animal lectins suggested that the carbohydrate binding activity of most lectins was generated by limited amino acid residues designated as the carbohydrate recognition domain (CRD) (Sharon and Lis, 2004) Table 1.

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Table 1: Historical background

1949	Liener	Toxicity of *Phaseolous vulgaris* hemagglutinins
1949	Jaffe	Thermoinactivation of *Phaseolous vulgaris* hemagglutinins
1952	Watkins and Morgan	Inhibition of lectins by simple sugars
1954	Boyd and Sharpleigh	Introduction of the term lectin
1960	Nowell	Mitogenic stimulation of lymphocytes by *Phaseolus Vulgaris* lectin
1963	Aub	Agglutination of malignant cells by lectins
1964	Muclenaere	Parallel inactivation of hemagglutinating
1965	Agrawal and Goldstein	Affernity chromatography for lectin purification
1966	Boyd	Lectins in algae
1970	Asperg *et al.*	Use of Con A for affernity purification of glycoproteins
1974	Ashwell and Morel	Role of animal lectins in endocytosis of glycoproteins
1976	Gallo	Interleukins 2 dissolved in medium of lectin stimulated lymphocytes
1977	Ofek *et al.*	Role of bacterial lectins in endocytosis of glycoproteins
1981	Reisner *et al.*	Use of lectins in bone marrow transplantation
1984	Yajko *et al.*	Combined use of lectin and enzyme in clinical identification of microorganism
1987	Harban- Mendoza *et al.*	Control of root- knot nematodes by lectin
1988	De Oliveira *et al.*	Root letin as a specificity determinant in *Rhizobium*- legume symbiosis
1990	Yamauchi	Con A expression in *E. Coli* cells

Until recently, most work on the medical significance of lectins has focused on their role as causes of disease or as immune system modulators.[4-6] In the 1950s, 1960s, and early 1970s, specific investigations of their role in causing certain diseases were undertaken by a variety of authors.[7-10] Most investigations of lectins have been primarily focused on their diagnostic role as markers of specific disease states, but some later studies[11] have begun to look at their potential as therapeutic agents.

STRUCTURE OF LECTINS

According to Goldstein *et al*., lectins are mainly made up of carbohydrate binding proteins or glycoproteins of nonimmune origin, which binds the cell or precipitates, glyco-conjugates. The specific capacity of lectins to bind with the cell surface mainly depends on the monosaccharide or simple oligosaccharides [Figure 1].[7-10]

Some lectins structurally differentiated as:[1-3]

1. Erythrine C lectins
2. Concavalin C lectins
3. Ulex europeus lectins
4. C-type lectins (CTLs).

Lectins are classified into four groups, based on their affinity to bind with:

- Glucose
- Galactose and N-acetyl-D-galactosamine

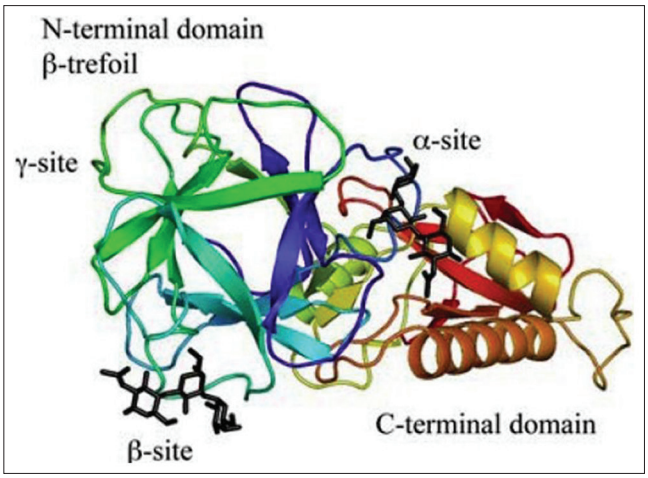

Figure 1: Structure showing the three potential sugar-binding sites α, β, and γ

- L-fucose
- Sialic acids.

Another classification of lectins based on lectin-like protein is [Figures 2 and 3]:

- Type I: Depending upon structural and evolutionary sequence similarities. Includes - beta prism lectin (B-type), calcium dependent lectins (C-type), fibrinogen/collagen domain containing lectins (F-type), garlic and snow drop lectins (G-type), hylauronic bonding protein (H-type), immunoglobulin superfamily lectins (I-type), alpha mannosaccaridase-related lectin (M-type), nucleotide phosphohydrolases (N-type), racin lectin (R-type), tachupleus tridentatus (T-type), wheat germ agglutinin (W-type), xanopus egg lectin (X-type)
- Type II: Depending upon proteins without established evolutionary. Includes: Annexins, pentraxins, G-domains, CD11b/CD 18 (beta integrins, CR3).

Lectin families

Within the animal lectins, several highly conserved CRD amino acid sequences have been identified, thus allowing investigators to categorize the majority of these lectins into structurally related families and superfamilies (Sharon and Lis, 2004). CTLs are the most abundant of all animal lectins, and the CTL superfamily is grouped into three families: Selectins, collectins, and endocytic lectins (Sharon and Lis, 2004)[1] [Figures 2-4].

Structure of lectins

The binding of lectins is:[7]

- Reversible
- Noncovalent
- Surface containing conjugate acts as lectin recertor
- Specificity: Based on hapten inhibition test
- All lectin molecules possess: Two/more carbohydrate binding sites (essential for agglutination).

Properties

- Most of the plant and animal lectins are resistant to both heating and digestion.
- Many of these lectins are highly stable, thermally (at 70°C for > 30 min), but these lectins do not completely degrade with cooking. Some of them are relatively resistant to digestive enzymes and acids
- Some lectins are degraded and others pass through gut, about 1–5% are re-absorbed into the blood stream in animals, which sufficient to cause an immune response.[7]

Biological significance of lectins

The biological role of lectins is based on conjecture rather than knowledge. The question of the possible physiological role of lectins has intrigued investigators from the beginning.[8] Due to their proprietory role in adhesion and agglutination, lectins have been considered as important in both symbiotic and pathogenic interaction between some microorganisms and hosts. The microbial lectins may play a role in adhesion.[7]

Lectins serve as means of attachment of different kinds of cells as well as of viruses to other cells via the surface carbohydrates of the cells to be attached. In some cases, cell surface lectins bind to particular glycoproteins, whereas in other cases the carbohydrates of cell surface glycoproteins or glycolipids serve as sites of attachment for biologically active molecules that have specificity towards carbohydrate, for example, microorganisms, various plant toxins, galactic etc., as shown in Figure 5.[8]

Endogenous lectins mediate biological processes such as [Figure 5]:

- Cell-cell self-recognition

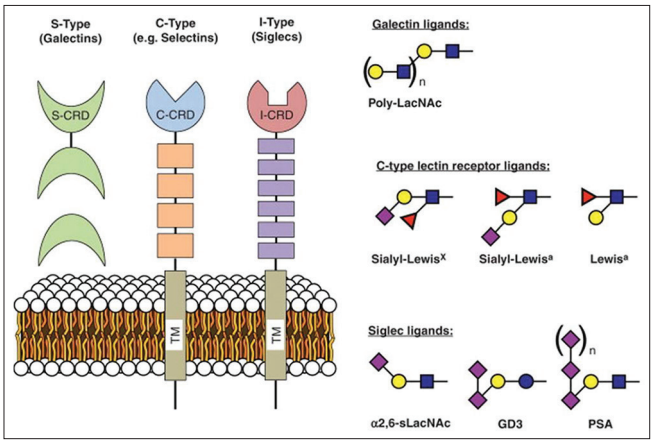

Figure 2: Lectins in the immune system and relevant carbohydrate ligands (examples). Immune cells express lectin receptors such as S-type lectins (galectins), C-type lectins (e.g. collectins, selectins, lymphocyte lectins), or I-type lectins (siglecs). These lectins recognize glycan structures present on either pathogens or host cells. Exemplary glycan structures recognized by galectins, C-type lectins, and siglecs are shown. CRD = Carbohydrate-recognition domain; S-CRD = S-type lectin CRD; C-CRD = C-type lectin CRD; I-CRD = I-type lectin CRD; TM = Transmembrane region

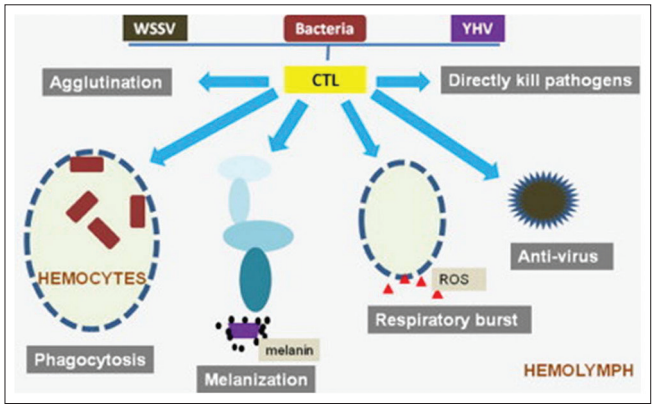

Figure 4: The functions of shrimp C-type lectins (CTLs). CTLs show considerable diversity in shrimp and have multiple functions. As pathogen receptors, shrimp CTLs are involved in phagocytosis, melanization (Junkunlo *et al*., 2011), respiratory burst (Alpuche *et al*., 2005), agglutination (and) and anti-viral response (and). A shrimp CTL also has antimicrobial activity (Sun *et al*., 2008)

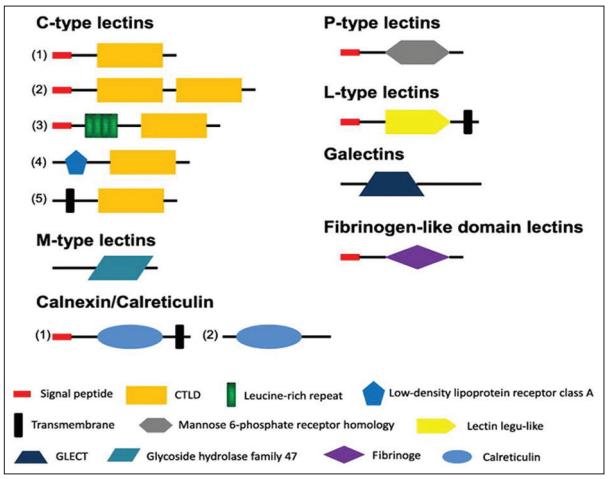

Figure 3: Domain architectures of shrimp lectins. Five subgroups of C-type lectins (CTLs) were found in shrimp: (1) a CTLD-containing lectin (C- type lectin like domain; (2) dual CTLDs-containing lectins (C-type lectin like Domain); (3) leucine-rich repeats-containing; (4) low-density lipoprotein (LDL) receptor class A-containing CTL; (5) transmembrane-containing CTL the M-type lectins. For the lectin like calnexin family: (1) Calnexin and (2) calreticulin. P-type lectins, L-type lectins, fibrinogen-domain like lectins

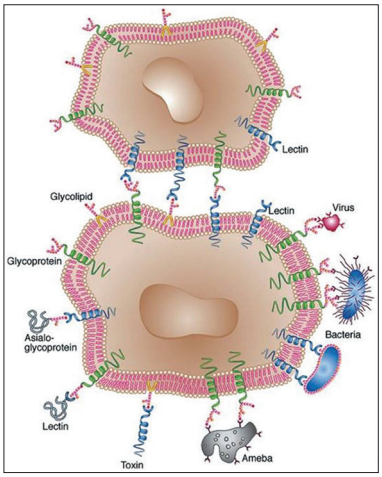

Figure 5: Specificity of cell surface carbohydrates towards various biomolecules

- Cell-extracellular matrix interactions
- Gamete fertilization
- Embryonic development
- Cell growth, cell differentiation
- Cell signaling
- Cell adhesion and migration
- Apoptosis
- Immunomodulation and inflammation
- Host-pathogen interactions
- Glycoprotein folding and routing
- Mitogenic induction and
- Homeostasis.

Advantages	Disadvantages
Stability	Promote growth of harmful bacteria in gut
Active action in small concentration	Disrupt protein and carbohydrate
Commercial availability	Mal-absorption
	Mass food poisoning, hemolytic anemia, jaundice (Maxican fava beans)

APPLICATIONS

Lectins have varied role in human

- In carcinoma and metastasis
- Odontogenic cysts and tumors
- Microbiology
- Food and human reaction
- Inflammation[7]
- Use in medicine and medicine research
- Use as a biochemical tool
- Lectins - toxins or therapeutics.

In dysplasia

Malignant tumors of the oral cavity represent a major public health concern, especially in view of the increasing incidence and prevalence rates observed along the last few years1. Parkin *et al*. (1999) estimated about 210,000 new cases per year worldwide. Some studies have shown that the process of malignancy is associated with a variety of changes in cell surface carbohydrate expression, not to mention the role played by carbohydrates in determining the metastatic capabilities of neoplastic cells.[4-8] Few studies have suggested that membrane bound carbohydrates may be essential for cellular differentiation and malignant transformation. In epithelium, lectins are detected on the basal cells and spinous cells. This sequential distribution of lectins was observed to be more disturbed with increasing grade of epithelial dysplasia.[7] Nangia-Makker *et al*. (2002) had reported that developing cancer cells use the functional groups of carbohydrate molecules to avoid being recognized by immune cells.[9] During metastasis formation, carbohydrates are involved in interactions between tumor cells, between tumor cells and the extracellular membrane, or between tumor cells and endothelial cells.[4] However, due to the structural complexity of carbohydrates and the scarce knowledge currently available in the field of glycobiology, a better understanding of this mechanism is not yet possible.[6,9,10]

Lectins in tumor markers

These are polyvalent proteins of nonimmune origin. Glycoproteins and glycolipids are the proteins present on the cell surface of squamous cells, which acts as antigens. These markers help in immunohistochemical (IHC) studies on skin or oral mucosa of human tissue.[7]

Role of lectin in oral cancer and metastasis

Squamous cell carcinomas (SCCs) of the oral cavity are the most common cancers among men and the third most common among women.[1] Nearly, half of them have lymph node (LN) metastasis at the time of diagnosis and half the remaining develop LN disease later on. Among the various factors that influence prognosis, LN involvement is probably the most important one. The size of the primary tumor, invasion of muscle or bone, and histological grade influence the development of LN metastasis. Large tumors have higher frequency of LN metastasis, and tumors with skin or bone involvement have higher chance of node involvement; but, not infrequently, small tumors with no apparent deep invasion develop LN metastasis. Verrucous carcinomas are known to produce LN metastasis rarely, whereas it is very common for poorly differentiated SCCs. However, at present, there are no methods which can identify the invasive and metastatic potential of oral cancers. It has been suggested that the cell membrane is involved when a malignant cell shifts from a state of local growth to metastatic growth.[8-12] Tumor metastasis and invasion may be mediated by carbohydrates on the surfaces of these cells. Alterations in the cell surface carbohydrates have been found to severely affect the metastatic potential of experimental tumors.[12-18] Plant lectins, because of their specific carbohydrate binding properties, have been used extensively as probes to study the surface architecture of normal and transformed cells. Differences in cell surface carbohydrate expression can be detected using lectins and such differences have been shown to be of prognostic significance.[18-23]

Nangia-Makker *et al*. (2002) reported that developing cancer cells use the functional groups of carbohydrate molecules to avoid being recognized by immune cells. During metastasis formation, carbohydrates are involved in interactions between tumor cells, between tumor cells and the extracellular membrane, or between tumor cells and endothelial cells. However, due to the structural complexity of carbohydrates and the scarce knowledge currently available in the field of glycobiology, a better understanding of this mechanism is not yet possible. Among animal lectins, galectins stand out because they

have a permanent sequence of about 130 amino acids for the recognition of carbohydrates, in addition to a high affinity for beta-galactosides present in both normal and tumor cells. As a result of this lectin-cell interaction property, galectins are involved in several biological processes, such as cell cycle control, immune response, cell adhesion, apoptosis, and metastasis.[23-25]

Galectin 3 can present both nuclear and cytoplasmic IHC staining. Cytoplasmic staining is associated with the antiapoptotic function of this lectin, thus promoting tumor progression; however, when expressed in the nucleus, the apoptotic function of Galectin 3 is lost. Gillenwater *et al*. analysed the expression of Galectins 1 and 3 in 35 cases of primary SCC of the head and neck and found that Galectin 1 was usually expressed in the basal layer of adjacent normal tissue, stroma and at the periphery of invasive tumor islands. Galectin 3, in turn, was found in superficial mucosal layers and adjacent to keratin pearls in areas of invasion. The authors concluded that galectins are expressed in the tumor cell surface, where they may participate in cellular interactions, and that the expression pattern of galectins appears to be associated with tumor grade, suggesting a role of galectins as biological markers in SCCs of the head and neck.[23-28]

The risk of LN metastasis is of prime consideration in deciding the treatment policy for an oral cancer patient presenting with clinically negative neck. If there is low risk of LN metastasis localized treatment like excision or brachytherapy can be opted for, whereas a patient with a high risk needs prohylactic neck dissection or irradiation. A clinician usually relies on various clinico-pathological factors like histological subtype, primary tumor size and presence of local invasion for this, considering them as "tests".[29-35] Understandably both sensitivity and specificity of the test are important here since it is important to avoid unnecessary treatment and yet not miss out treatment for those whom it is necessary. Tumor metastasis and invasion may be mediated by carbohydrates on the surfaces of these cells. A direct correlation between sialylation and metastatic capacity has been observed in several tumor cell lines.[29-36] Alterations in the cell surface carbohydrates have been found to severely affect the metastatic potential of experimental tumors. Specific glycosylation defects are known to result in loss of metastatic potential. The involvement of carbohydrates in metastasis formation would imply that tumor cells with different metastatic potential possess distinct qualitative or quantitative differences in their glycosylation of membrane glycoconjugates.[30] A correlation between the amount of cell surface sialic acid and metastatic potential was found by Yogeswaran *et al*. Relation of Ulex europaeus agglutinin (UEA-1) binding to disease-free interval and survival in breast cancer was reported by Fenlon *et al*.[28]

To sum-up we can suggest that cell membrane characteristics, particularly the density of sugar residues is of importance in determining LN metastatic potential of oral cancers. The prediction of LN metastasis can be made more accurately if lectin binding characteristics are taken into consideration along with the usual clinical and histological parameters. There is a need for further research in this area, particularly with regard to the role of immune responses, lectin binding pattern and cell membrane characteristics.[37-39]

CONCLUSION

Role of lectin in research is on steady rise based on their ability to bind with specific glucoconjugates. Although lectins have been marketed as potential toxins, there is now extensive literature reporting the activity of lectins in a number of different tissues and processes. Lectins are unique and naturally occurring cytochemical and histochemical tool, which in near future will further emphasize their values as potential diagnostic reagents for the clinicians. A relatively high number of studies have been conducted to investigate the role of lectins as biomarkers of oral cavity tumors, covering a variety of lesions and lectins. In our review, studies assessing SCCs and peanut agglutinin and UEA-1 lectins were the most frequent ones, as well as studies focusing on one specific lectin and one lesion. Further analyses of lectins as biomarkers should be undertaken to improve our understanding of the processes involved in malignant tumor formation.

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