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Lectins : Novel Drug Targeting Molecules

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Lectins are carbohydrate-binding oligomeric proteins or glycoproteins of non-immune origin. Their occurrence is not restricted to plant sources but is ubiquitous and are found in animal cells also. These molecules bind reversibly with specific sugars and precipitate polysaccharides, glycoproteins and glycolipids bearing specific sugars, thus acting as cell recognizers. Their presence on tumor cells is being widely exploited for recognizing the specificity of tumor cells towards a possible means of targetting them. In addition, the presence of specific lectins on microorganisms and host tissues is being investigated for targeting drugs towards them. This review discusses the role of lectins in their-site-specific recognition of tissues and for targeted drug delivery.

Lectins are uni or polyvalent carbohydrate-binding oligomeric or glycoproteins of nonimmune origin. They have been isolated from a wide variety of natural sources including plant seeds and roots, fungi, bacteria algae, body fluid of invertebrates, lower vertebrates and from mammalian cell membranes. They bind reversibly with specific sugars and are capable of precipitating polysaccharides, glycoproteins and glycolipids bearing specific sugars, thus acting as cell recognizers. Because of this property, they exhibit many biologically significant activities such as the ability to agglutinate red blood cells, lymphocytes, fibroblasts, spermatozoa, yeast, fungal, bacterial and plant cells[1-3]. The agglutination is a result of interaction of surface sugars and sugar binding sites on lectin molecules. These interactions are usually non-covalent, involving hydrogen bonding, hydrophobic and van der Waal's forces[4]. Also, lectins on cell surfaces mediate cell-cell interactions by combining with complementary carbohydrates of the same or different types, located on the surfaces of apposing cells. Other mechanisms by which cells may interact include, bridge formation by soluble glycoproteins that bind to cell surface lectins or the interaction of lectins with carbohydrates of insoluble components of extra cellular matrix that promote cell adhesion. Some mechanisms that are involved in interaction of lectins at the cellular level are illustrated in Fig.1 Due to these behaviours, lectins play an important role in cell recognition[5].

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Lectins have various specificities that are associated with their ability to interact with acetylaminocarbohydrates, aminocarbohydrates, sialic acid, hexoses, pentoses and other carbohydrates. Such a property of lectins has led to their use in diverse fields of clinical interest, such as, typing of blood cells, carriers of chemotherapeutic agents, as mitogens, fractionation of animal cells and as epidemiology and taxonomic markers of specific microoganisims[6]. They have also been used for detection of toxins in food and pharmaceuticals[7-9]. Few other clinical applications of lectins include, their use in bacterial typing and bone marrow transplantation[3], in studying the variation in glycid composition of human urothelial membrane with cell differentiation[10], functional study of CD4 cells[11], recognizing capillary endothelial cells and their processes during angiogenesis,[12], prevention of cancer metastasis[13] and protection of neonates against environmental antigens[14].

CRITICAL CONSIDERATIONS IN LECTIN RECOGNITION

Cell recognition is akin to the fundamental concept of lock and key complimentarity[15]. Almost all cells carry

carbohydrates on their surfaces in the form of glycoproteins and polysaccharides. These carbohydrates have been reported to possess the ability for encoding biological information[16-19]. The vast diversity in structure of carbohydrates arises due to the information which is encoded in the position and anomeric configuration of the glycosidic units and in the occurrence of side chains. Theoretically, four different monosaccharides can form 35,560 distinct tetrasaccharides, whereas, four different amino acids or neucleotides can form only 24 tetrameric structures[20]. Additional structural diversifications may also occur due to covalent bonding of different functional groups viz., sulphate, phosphate and acetyl to the sugars. This great diversity of carbohydrate structures associated with soluble and surface-bound glycoconjugates has the potential to modify the activities of proteins to which they are attached. Thus, they serve as markers of cell differentiation, development, disease characterization and drug targeting[21-26].

The methods used to ascertain the lectin dependence of a cell-cell interaction include, inhibition or enhancement of the particular event by using specific sugars, glycoconjugates, chemical or enzymatic modification of cell surface carbohydrates or by using lectin resistant mutants. However, the contribution of other types of carbohydrate-binding protein (glycosyltransferases) needs to be ruled out[27]. Also, lectins may contain non-carbohydrate ligand sites. Hence, the dependence of a cell-cell interaction event on such sites should also be critically evaluated[28]. Therefore, location of the lectin and ability of the purified lectin and ligand, as well as of the antibodies to the lectin and to the ligand, to specifically block the interaction between cells should be proved.

Therefore, the role of carbohydrates is not as simple as it seems to be. For instance, although, the bacterial lectins of type 1 fimbriae are classified in general as "mannose-specific," these lectins on different genera may exhibit differences in "fine sugar specificities." For example, by measuring the inhibitory activity of linear and branched oligosaccharides and glycosides of D-mannose on the agglutination of yeast cells, Firon *et al.*[29] found that while within the *Salmonella* species or *E.-coli* strains the combining sites were similar, they differed among the two species. Logan[30] though found adherence of *H. pylori* to be an important virulence factor in induction of pro-inflammatory response, he could not correlate haemagglutination and the extent or pattern of adherence to the gastric epithelium. These findings suggest that an understanding of "fine sugar specificities" is a must for understanding the lectin-cell recognition phenomena. In fact, such a phenomena may also occur due to a sugar independent mechanism[31].

EXPRESSION OF LECTINS IN NORMAL AND TUMOR CELLS

In order to understand the role of lectins at the molecular level it is important to have an insight into their expression by normal and tumorigenic cells. Many different normal tissues have been found to contain heamagglutinating activity that could be inhibited by specific carbohydrates because of the presence of lectin-like molecules on the cell surface[32-37].

Endogenous lectins have been demonstrated to be involved in adhesion to various types of cells. For example, lectin-2 which is produced by embryonic chick muscle cells, reacts with glycosaminoglycans associated with the cells surface or extracelluar matrix and chicken hepatocytes posses an N-acetylglucosamine-specific lectin[38] which mediates their adhesion to gels derivatized with this sugar. This adhesion is reported to be blocked by free sugar or antilectins antibodies[39]. Similarly, the endogenous asialoglycoprotein-binding lectin of rat hepatocytes has been found to mediate the adhesion of hepatocytes to polystyrene culture dishes coated with desialylated ceruloplasmin[40]. The localization of a galactoside-specific lectin found in extra-embryonic endoderm cells of chick embryo[41,42] and the inhibition of cell aggregation by purified lectin or cells pretreated with β-galactosidase, suggests that the lectin and cell surface galactose-containing glycoconjugates are complementary partners in the formation of adhesive bonds. A β-galactoside specific lectin isolated from rabbit bone marrow, which agglutinates rabbit erythroblasts, has been demonstrated to be inhibited not only by galactose-containing glycoconjugates but also by fab fragments of antilectin anatibodies, indicating that the lectin directly bridges cell surface glycoconjugates[43]. Another model of cell-cell adhesion involving interactions of surface lectins with carbohydrate sequences on surface of neighbouring cells[44] was demonstrated when a membrane bound lectin purified from BHK cells was found to agglutinate these cells more readily than the ricin-resistant mutants expressing less galactose residue from their cell surface membrane[45,46].

N-acetylgalactosamine and galactose-specific membrane lectins have been reported to be expressed by rat liver cells, including hepatocytes, kupffer cells and endothelial cells[47,48]. These lectins mediate adhesion of desialylated erythrocytes or lymphocytes *in vitro*[49]. The presence of lectin like molecules on the surface of lymphocytes has been proposed to be involved in the recirculation of lymphocytes from the blood stream into lymphoid organs by specific binding of the lymphocytes to endothelial cells in postcapillary venules[50,51]. A few other studies pertaining to lymphocytes demonstrated, the inhibition of their adhesion to high endothelial venule sections by fucoidin[51] and inhibition of their heamagglutinin by various sulfated polysaccharides including fucoidin[52]. Human B andT cells have been reported to bind mannose terminated glycoconjugates[53] and α-rhamnosylated serum albumin[50], respectively. The cell surface lectins of lymphocytes have also been found to be directly involved in the binding of lymphocytes to lymph node venules[54].

The role of lectins and cell surface glycoproteins has also been implicated in adhesion of several other organelles of biological interest. Lectins have been shown to be involved with the murine lymphocyte "homing receptor" Mel 14,[55,56] and with the human leukocyte adhesion molecule ELAM-1[57]. A potential adhesion structure of platelets and endothelial cells, GMP-140, has been found to be rapidly translocated to the cell surface after cellular activation. This granule membrane protein shares sequence similarity with ELAM-1 and a homing receptor and participates in adhesion of neutrophils to activated endothelium and to stimulated platelets. Such a function is expected to recruit both platelets and neutrophils to sites of injury as well as modulate the function of each cell type by other[58,59].

A series of developmentally regulated cell surface glycoconjugates like lactoseries glycoconjugates have been found to be expressed in the cytoplasm and surface of small diameter dorsal root ganglion (DRG) neurons and their central terminals in laminae I and II of the dorsal horn[60]. The DRG neurons with central terminals in laminae III and IV express globoseries glycoconjugates[61]. Hathaway and Shur[27] have reviewed the role of β-1,4-galactosy-ltransferases which act as receptor in a variety of cellular interactions during fertilization, intercellular adhesion, cell migration and growth control.

The importance of cell surface carbohydrates in cancer cell adhesion and metastasis has been established[35,62-67] implying that the endogenous lectins of various organs may be involved in tumor cell arrest, organ colonization and metastasis development[68-70].

Although, the presence of a galactoside specific heamagglutinating activity in neoplastic cells was first demonstrated in murine neuroblastoma cell extracts[37] a carbohydrate binding protein specific for mannose containing glycoproteins was found to inhibit rosette formation by rabbit erythrocytes on the teratocarcinoma cells[71]. The cultured tumor cells were suggested to contain lectin like molecules on their cell surface on the basis of the ability of desialylated derivative of fetuinasialofetuin to induce aggregation of the tumor cells in the absence of calcium ions.

Meromsky *et al.*[72] found that the glycopeptides prepared from asialofetuin were effective inhibitors of aggregation, suggesting that the intact molecule which is polyvalent, contains several oligosaccharide side chains that can act as a bridge between lectin molecules present on surface of adjacent cells. However, direct binding of fluorescently labeled asialofetuin to the surface of tumor cells has also been demonstrated by Raz and Lotan[73]. Asialofetuin has been found to contain several terminal non reducing galactose residues that are masked by sialic acid residues in the native fetuin molecule[74,75]. Since, asialofetuin was found to be more potent that fetuin in inducing aggregation of different tumor cells and different murine and human tumour cells were found to contain soluble lectin-like activity detectable by heamagglutination and inhibitable by galactosidases, it was proposed that these cells express a galactoside specific cell surface lectin[73].

The peanut lectin (PNA) has been reported to bind avidly to the terminal sequence of the disaccharide β-D-Gall —>3α-D-GA1Nac. This disaccharide is the immunodeterminant group of the Thomsen-Friedenreich (T) antigen which has been found to be present in an exposed form on a number of human and animal adenocarcinomas. The PNa was found to exhibit a high *in vitro* binding affinity for TA3/Ha tumor cells and epiglycan (a glycoprotein shed by TA3/Ha cells). Tissue biodistribution studies after IV injection of ^{125}I-PNA into TA3/Ha tumor-bearing mice showed tumor:blood ratios of 7:1 and 55:1 at 24 and 48 hours and muscle:blood ratios of 33:1 and 77:1 indicating high tumor uptake and blood clearance of the labeled PNA[76].

Studies on antilectin antibody binding to sublines, variants or clones of murine B16, K-1735 melanoma, or UV-2237 fibrosarcoma revealed that those exhibiting a higher metastatic potential expressed more lectin molecules on their surface[77]. The finding that preincubation of B16 melanoma or UV-2237 fibrosarcoma cells with the antilectin monoclonal antibodies inhibited lung metastasis after intravenous injection into the tail vein of syngeneic mice suggests that tumor cell surface lectins might mediate intercellular adhesive interactions relevant for metastasis[72]. The sugar moieties of cell surface glycoproteins have also been known to change upon malignant transformation[78] and such change have been correlated with the metastatic properties of transformed cells.[64,79] Studies using inhibitors of protein glycosylation[80] have shown that malignant cells with modified oligosaccharides on their cell surface glycoconjugates lose their ability to colonize certain target organs[81-85]. Similarly, glycosylation mutants selected on the basis of their lectin resistance have been shown to have different metastatic abilities[86].

The change in the oligosaccharide structures of cell surface glycoconjugates are related to the capacity of a cell to be recognized by endogenous membrane lectins of the same or other cell. This may either result in an increased ability of the cell to adhere to endothelial cells expressing the relevant endogenous membrane lectins, to form self aggregates, to induce an immune response, to be trapped by a specific organ, or non malignant cells may become tumorigenic, if the modification impairs the defense mechanism involving recognition of the unmodified structure.

POTENTIAL OF LECTINS IN DRUG TARGETING

Attributes of the 'spacer':

The need for targeting drugs specifically to the diseases tissues or microorganisms is well recognized. Use of liposomes and microparticles to achieve this goal is usually unsuccessful owing to the difficulty they have in accessing tumors and due to their repaid phagocytosis by the reticuloendothelial system. Natural macromolecular drug carriers such as dextran[87], human serum albumin[88] and tumor specific antibodies[89] though possess advantages in terms of tumor specificity, they pose problems of limited body distribution and immunogenecity. Hence, there is a need to use soluble macromolecular drug carriers substituted with carbohydrate residues as they can traverse compartmental barriers in the body and thus gain access to a greater number of cell types and are mostly not subject to rapid clearance by the reticuloendothelial cells.

However, due attention should be paid to the following aspects while attempting conjugation of drug with carriers. These include, long life span of the carrier in the body fluid, retainment of drug's pharmacological activity upon conjugation, enzymatic or pH-sensitive cleavage of the conjugated 'spacer' in order to release the free drug and toxicity of the spacer. For example, daunorubicin or adriamyin directly bound to a carrier via their amino group are inactive[90]. Conversely, when they are linked to a carrier through an appropriate spacer leading to a drug arm carrier, they can be selectively released as free, active drug[91]. The spacer can be an appropriate peptide cleavable by proteases of lysosomes or tumor[90] or can be a compound such as cis-acotinic acid which gives an acid-labile spacer-drug conjugate capable of releasing the drug in the lysosomes[92], endosomes[93] and certain tumors[94] where the pH is low. A conjugate containing benzylthiocarbamoyl-aspartyl daunorubicin has been reported to be stable at neutral pH and releases the free drug when exposed to pH below 5[94] N-(2-hydroxypropyl) methacrylamide copolymers modified by including residues, such as galactose are capable of targeting the polymer efficiently to hepatocytes[95] and rat IgG[96].

Tissue targeting through lectin recognition:

It is known that lectin recognition is akin to lock and key complimentarity. Hence, drugs or diagnostic agents and carriers which recognize determinants present on normal or diseases endothelium provide a natural means for targeting such tissues. Also, membrane lectins of certain cells are capable of inducing the internalization of their ligands[97,98] and hence, glycoconjugates specifically recognized by these lectins can be used as carriers of metabolite inhibitors and toxic drugs. This process involves the following effects *in vivo:* (i) rapid endothelial envelopment of the carrier; (ii) sequestration of the carrier and protection of the entrapped agent from rapid blood clearance: and (iii) rapid carrier transport across the vascular endothelium into the interstitium. Advantages of this approach include, localization of drug to the desired tissues and low effective concentrations which results in considerable dose reduction. Not only diseased tissues, but also microorganisms are known to express specific

lectins on their surfaces. We have recently reviewed the various sources, activities and applications of lectins[99].

A palmitic acid derivative of purified wheat germ agglutinin (WGA), palmitoyl WGA (1:1) complex) when incorporated into liposomes, was found to cause agglutination of red blood cells at a concentration eight fold lower than that of the native lectin. Furthermore, enhanced binding of liposome-bound WGA to mouse spleen cells suggests the potential role of liposome bound lectins in targeting them to different organs.[100] Roche et al., prepared a compound by linking gelonin (a toxic plant protein which inhibits protein synthesis in a cell free system) to a neoglycoprotein bearing β-glucose through a disulphide bridge and reported this conjugate to be 100 times more toxic than free gelonin for 3LL lewis lung carcinoma cells in culture[101]. Methotrexate bound to a neoglycoprotein bearing α-fucose has been found to be 10 times more toxic for L1210 leukemia cells than that bound to sugar free serum albumin[102]. Fu dr bound to neoglycoproteins bearing β-glucose inhibits the growth of human colon carcinoma, whereas, that bound to a neoglycoprotein bearing α-mannose does not. Similarly, daunomycin bound to glycosylated N-2-hydroxypropyl methacrylamide copolymer is more effective than that bound to non-glycosylated hydrophilic polymer[103].

The involvement of glycoprotein 3 in the binding of sperm to zona pellusida layer and that of sialyl Le (x), sialyl Le (a), sulphatides and other less well defined sugar structures in leukocyte-endothelial cell interaction, has been envisaged to have clinically important application[104]. Lectins capable of binding to sperms and/or pathogenic microorganisms have been studied for contraception, prophylaxis and therapy of sexually transmitted diseases[105]. Recently, binding of human sperm to various lectin-coated agarose microbeads has been attempted and correlated to the binding with biological zona pellusida[106]. Also, variations in expression of carbohydrate moieties during capacitation and acrosome reaction of human sperm has been studied using lectins[107]. These would provide a convenient means of testing sperm-zone pellusida binding ability.

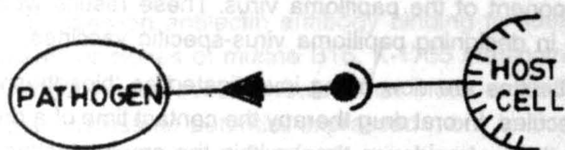
Zhou *et al.*[108] using HPV16L1 protein glycosylation in CV-1 and HaCa T-cells found that while majority of L1 protein was localized in the cell nucleus, glycosylated L1 was retained (neither exported nor translocated to cell membrane or nucleus) in the endoplasmic reticulum, suggesting that glycosylated L1 is not an important component of the papilloma virus. These results would help in designing papilloma virus-specific vaccines.

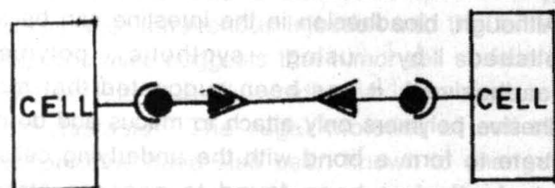
Lectins are now being investigated as 'bioadhesive' molecules. In oral drug therapy the contact time of a drug formulation (residence time) within the small intestine is too short (approximately 3 h) to allow its complete absorption. This is also effected by the presence of food etc. Although, bioadhesion in the intestine can be accomplished by using synthetic polymers (mucoadhesives), it has been suggested that most bioadhesive polymers only attach to mucus and do not penetrate to form a bond with the underlying cells[26]. Tomato lectin has been found to possess strong bioadhesive property *in vitro*[109,110] but no significant difference in the transit time of tomato lectin and an inert polymer (poly vinyl pyrrolidone), *in vivo,* suggests interactions of the lectin with intestinal mucus, limiting its use as an intestinal bioadhesive[111]. However, recently tomato lectinconjugated nanoparticles (500 nm) have been shown to be internalized through the villous tissue, probably due to the presence of N-acetylglucosamine residues on the epithelial surface of the rat gastrointestinal tract[112].

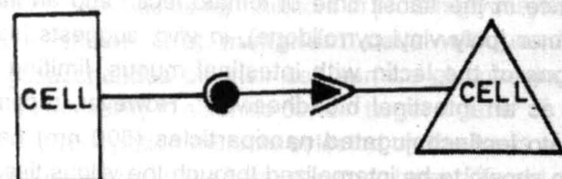
Aggregates of nasal lymphoid tissue (NALT) located at the base of the nasal cavity are believed to be sites of induction of mucosal immune responses to airborne antigens. The epithelium overlying these nasal tissues contain M cells which are specialized for the transcytosis of immunogens. It has been found that lectins recognizing α-linked glucose exclusively label the nasal follicle-associated epithelium of hamsters[113]. the M-cell selective lectin specifically targets the follicle-associated epithelium and are efficiently endocytosed, suggesting a possible route for targeted delivery of immunogens through the nasal route.

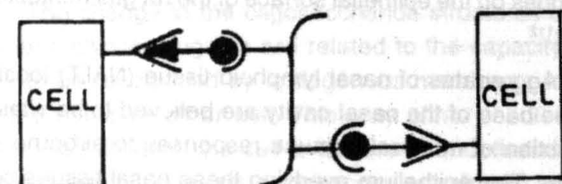
Eleonore *et al.*[114] utilizing oral administration of *Yersinia pseudotuberculosis*, found a 103 KD surface protein (invasin) of the organism attached covalently to model particles to be significantly take up by MDCK cells, Caco-2 cells which do not express receptors for invasin did not show enhanced transport. This suggests 'bioinvasion' by lectins to be a new tool for oral drug delivery by receptor mediated endocytosis.

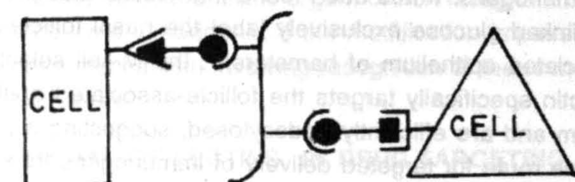
Selective targeting of malignant cells is necessary for implementing gene therapy strategies to combat cancer. Targeting can be achieved by transductional or transcriptional approaches. Batra et al.[115] has shown that by











Surface lectins;

Sugars;

Soluble lectin;

Soluble Glycoproteins

exploiting the differences in the molecules or receptors expressed on the cell surface of malignant and normal cells, gene transfer can be accomplished by using lectin-targeted molecular conjugate vectors for targeting cancer cells for the purpose of gene therapy. Wadhawa and Rice[116] have recently reviewed different types of glycotargeting agents and the lectins which have been successfully targeted to treat both model and human diseases.

Lectin-coated liposomes have been envisaged to possess increased affinity towards erythrocytes bearing multiantennary glycophorin molecules[117]. On this line, Ulex Europaeus Agglutinin I (UEA I) conjugated to N-glutaryl-phosphotidyl ethanolamine and incorporated into liposomes has been shown to be transported through the Payer's patches whereas, Wheat Germ Agglutinin (WGA) is not. This suggests specific affinity of mouse M cells towards fucosylated glycoconjugates and not towards sialic acid[118]. Similarly, a high proportion of biodegradable, poly (DL-lactide-co-glycoside) microspheres has been found to be transcytosed by the M cells[119]. Lectins from *Solanum tuberosum* and *Helix pomatia* which are specific for N-acetyl D-glucosamine and N-acetyl D-galactosamine respectively, have recently been shown to significantly bind to ocular tissues after 10 second contact period, thus indicating their potential use in targeting conjugated drugs to the corneal and conjuctival surface[120].

CONCLUSIONS

The sugar specificity of lectins has led to a better understanding of the function of the subcellular mechanisms in diverse fields of biological interest such as pathological markers of diseases, metastasis of tissues and for controlling a variety of infections. The emergence of pathogens resistant to conventional antimicrobial agents has made it essential to identify new strategies for the prevention and treatment of infectious diseases. The research on lectins has shown that adhesion of microorganisms is the first step in the initiation of many infections. Thus, the present research on lectins focuses on the interference of adhesion of microorganisms to the host cell/tissue for preventing infection in which lectins are implicated. The expression of specific lectins on the cells of microorganisms or diseased tissues has been shown to offer a natural means of targeting drugs towards them.

Designing a targeted drug delivery system that operates on the principle of lectin recognition will not only

provide a means of reducing the dose and developing a more efficacious dosage form but will also be comparatively safe because the lectins are natural components of the cellular system and are biodegradable.

Despite the widespread evidence that specific sugars block lectin-mediated microbial adhesion *in vitro* and *in vivo*, there are problems not only in producing the specific antiadhesive sugars, but also because of the adverse reactions these saccharides may have on different physiological systems. However, with better understanding of the specificity of microbial adhesins and atomic structure of their combining sites, this antiadhesion "sweet therapy" is expected to provide an effective means of preventing and treating infections diseases at the molecular level in the future.

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