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GLYCOPINION MINI-REVIEW

Importance of lectins for the prevention of bacterial infections and cancer metastases

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Adhesion of bacteria and of metastasizing tumour cells have much in common, especially the participation of lectins in this process. In the future it might be possible to inhibit the metastatic process and bacterial adhesion by blocking with lectins specific for appropriate (oligo) saccharides or glycoconjugates. Initial clinical trials are very promising.

Keywords: lectins; cancer metastases; bacterial infections

Introduction

In 1888 H. Stillmark first reported that castor bean extracts were able to agglutinate erythrocytes from different animal species [1]. The seed extracts were found to contain haemagglutinating proteins, defined as agglutinins, haemagglutinins, or more recently as lectins, a term given by Boyd in 1954 [2]. The term lectin (Latin legere, to select) was based on the observation that certain seed extracts (e.g. from *Phaseolus limensis, Ricinus communis*) could discriminate among human blood groups [3–5]. Lectins are ubiquitous (glyco) proteins which exhibit a specific and reversible carbohydrate binding activity. They combine reversibly and noncovalently, with mono- or oligosaccharides, both simple or complex whether free in solution or on cell surfaces. Binding may involve several forces, mostly hydrophobic and hydrogen bonds; only rarely electrostatic forces are involved since most carbohydrates are devoid of electrical charge. The specificity of a lectin is defined in terms of the monosaccharide(s) or simple oligosaccharide which inhibits the lectin-induced cell agglutination or precipitation reaction. Such specific inhibitors are commonly effective at concentrations in the millimolar range or lower. Lectins with a similar specificity towards monosaccharides may differ in their affinity to disaccharides, oligosaccharides, or glycoproteins. Although lectins are similar to antibodies in their ability to agglutinate cells, they differ in that lectins are not products of the immune system, their structures are diverse, and their specificity is restricted to carbohydrates [6–8].

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During the last decade many lectins have been detected in plants, animals and microorganisms [4, 6, 7, 9]. In the course of investigations lectins have been shown to be useful for various scientific purposes including detection and identification of blood groups and microorganisms, mitogenic stimulation of immune cells, detection of carbohydrates in solutions, on macromolecules and cells, (glyco)-protein purification and cell fractionation [4, 10]. Furthermore, they could be shown to be involved in specific adhesion of symbiotic and pathogenic microorganisms to host tissue, in specific adhesion of tumour cells to organ cells in metastatic spread, and in certain interactions within the cellular immune system [9, 11, 12].

Carbohydrate-binding proteins (lectins) on bacterial cells

Aspects of host-parasite interactions encompass a wide range of phenomena from the adhesion to epithelial surfaces to interactions with cells of the immune system. Since the 1950s it has been known that the adherence of gram-negative bacteria to eukaryotic cells is specifically inhibited by mannose and methyl-alpha-D-mannoside [7, 13, 14]. In 1978 it was suggested that bacteria possess surface lectins which serve as adhesins binding microorganisms to mannose residues on human cells [13]. Since then, both gram-positive and gram-negative bacteria have been found to express specific lectins on their surfaces. Several different carbohydrates are known which may serve as sites of attachment for those lectins [4, 7]. These carbohydrates are all characteristic constituents of cell surface glycolipids or glycoproteins and at low concentrations they inhibit bacterial

adherence to host cells [7, 15–17]. Lectins are organized on bacterial surfaces in either fimbrial or nonfimbrial structures [4, 7].

Fimbriae (Latin word for fibres) were first described in 1955 by Duguid *et al.* as nonflaggelar bacterial appendages [18], in 1965 Brinton introduced the term *pili* (Latin word for hair) for these surface organelles [19]. Fimbriae are assembled as hollow fibres by the polymerization-of monomeric subunits composed entirely of protein [19]. On the basis of their carbohydrate specificity several types of fimbrial lectins have been distinguished. These have been divided into two main groups: those which react specifically with D-mannose-containing glycoproteins or glycolipids (mannose-sensitive fimbriae) and those reacting specifically with saccharides other than D-mannose (mannose-resistant fimbriae). In the subsequent course of investigation it was demonstrated that type 1 fimbriae of enterobacteriacae behave as typical lectins which bind bacteria to epithelial cells [4, 7]. The isolated fimbriae were shown to agglutinate erythrocytes as well as other mannose-containing cells (e.g. yeast cells) and the agglutination was inhibited specifically by mannose.

The interaction between mucosal surfaces and microbes depends upon the specificity of microbial surface lectins. Some of the receptors are present on glycoproteins, such as mannose which is recognized by type 1 fimbriae, while others occur on glycolipids like the Gal-β (1–4) Gal moiety, which is present on the globoseries of glycolipids recognized by the majority of pyelonephritic *Escherichia coli* [17, 20]. Because Gal-β (1–4) Gal is a determinant of human blood group P, the fimbrial lectins of these bacteria have been designated 'P fimbriae'. As expected, P-fimbriated bacteria fail to agglutinate erythyrocytes from individuals who lack the P determinant [7, 17]. More interestingly, such individuals appear to be less susceptible than the general population to urinary tract infections with P-fimbriated bacteria [7].

Recent work has demonstrated that bacterial lectins may recognize the receptor on internal as well as on terminal positions [16]. However, chemical groups distal as well as proximal to the oligosaccharide receptor site in the glycolipid/glycoprotein may in some cases enhance the binding and in others sterically interfere with receptor binding [21]. Membranes from different tissues apparently differ in their composition as well as distribution and topochemistry of surface carbohydrates. Accordingly, two lectins recognizing different epitopes on the same oligosaccharide may have a markedly different tissue tropism. Previously it has become evident that bacteria interact with components of the extracellular matrix as well as with membrane receptors. Apart from non-specific attachment mechanisms (e.g. electrostatic forces, lipophilic or hydro-philic interactions) more or less specific binding to fibronectin, vitronectin, laminin and collagen are common properties of gram-positive and gram-negative bacteria [4, 7].

Lectin-mediated adhesion to various tissues

To demonstrate lectin dependent mechanisms of bacterial adhesion, cryotome sections were incubated with micro-organisms suspended in a phosphate buffered saline (PBS) and in PBS-glycoconjuted solutions. Sections of human lung and kidney both supported adherence of *S. saprophyticus* and *P. aeruginosa*. Adherence of *S. pneumoniae* was only demonstrable to lung and meninges. These experimental observations are compatible with clinical experience of *P. aeruginosa* and *S. saprophyticus* infections which involve the respiratory and urinary tracts, and pneumococcal infections which primarily affect the respiratory tract and meninges. Receptor-mediated organotropism of infectious agents may be assumed by these findings and have been confirmed in studies with BALB/c-mouse tissue sections. PBS-solution of lectin-specific glycoconjugates (NeuAc for *P. aeruginosa*; GlcNAc for *S. pneumoniae*; GlcNAc and GalNAc for *S. saprophyticus*) completely inhibited microbial adhesion to tissue sections of lung, kidney, liver, spleen, brain and meninges while non-specific glycoconjugates did not show any inhibitory effect [22, 23]. To quantitate specific microbial adhesion and its inhibition by lectin-blocking glycoconjugates, human uroepithelial cells (UEC) were incubated with *S. saprophyticus*. The total numbers of adherent bacteria to 100 UEC was determined and the mean value was calculated for S. saprophyticus strain S1 (23.2 per UEC) and strain S35 (23.4 per UEC), respectively. Preincubation of bacterial suspensions with lectin-specific glycoconjugates significantly decreased staphylococcal adherence to UEC (81% decrease for strain S1, 87% decrease for strain S35). Non-specific glyco-conjugates did not inhibit the adherence process. Analogous experiments have been performed with other micro-organisms (e.g. *Klebsiella* strains) and yielded comparable results [23, 24].

In vivo, intratracheal administration of *S. pneumoniae* to BALB/c-mice resulted to a diffuse infection of the lung. However, intratracheal lavage with microbial lectin-specific carbohydrate solution inhibited streptococcal adhesion to pulmonary cells. Quantitative *in vivo* analysis with *P. aeruginosa* also supported the initial findings. Lungs, kidneys and livers of BALB/c-mice were heavily colonized with bacteria after intravenous inoculation. However, specific carbohydrate (*N*-acetylneuraminic acid) treatment of the mice significantly reduced *P. aeruginosa* organ colonization [22, 25].

To demonstrate the importance of blood group antigens (carbohydrate receptors) and microbial surface lectins for the initiation of infectious diseases, *S. saprophyticus* induced urinary tract infections (UTIs) were investigated. The medical records of patients with 'significant' growth ($>10^4$ colony forming units per ml) of *S. saprophyticus* in midstream urine samples were studied and can be summarized as follows:

(1) *S. saprophyticus*-induced UTIs seemed to be age and sex dependent, since they were almost exclusively found among female patients (94.5%) not older than 40 years (76.4%).

(2) Acute cysto-urethritis was the predominant clinical correlate of UTIs by *S. saprophyticus*.

(3) Pre-existing diseases were not obligatory for symptomatic *S. saprophyticus* UTIs [26].

This study further suggested that UTIs by *S. saprophyticus* can be positively correlated with the patient's blood group. Thus, the A/AB phenotypes of the ABO blood group system could be determined in 94.6% of patients with *S. saprophyticus*-induced UTIs. This percentage is considerably different from the regular distribution of the A/AB blood group phenotypes among Western European inhabitants (48.2%) and obviously correlates with the GalNAc lectin-specificity of *S. saprophyticus*-isolates from UTIs (as proved in haemagglutination tests), since GalNAc represents the terminal carbohydrate moiety and the most important antigenic determinant of the blood group A [26, 27]. Accordingly, antigenic determinants of blood group A seem to be of special importance for urinary tract colonization by *S. saprophyticus* with GalNAc-specific surface lectins. Isolation of lectins from microorganisms recognizing blood group antigens and assessment of their immunogenicity might provide new approaches to the prevention of colonization and subsequent infection.

These experimental investigations encouraged clinical trials in humans to test the efficacy of local administration of microbial lectin blocking carbohydrates for the inhibition of specific adhesion in *P. aeruginosa*-induced *otitis externa diffusa*. Based on the fact that the lectin-specificity of *P. aeruginosa*-isolates is limited to Gal, Man and NeuAc and that this pathogen is found in more than 60% of patients suffering from *otitis externa diffusa acuta* a double blind trial was performed comparing the efficacy and tolerability of a defined carbohydrate solution (5% Gal, 5% Man, 1% NeuAc) with a standard aminoglycoside (gentamicin) therapy [28]. The results of this clinical trial can be summarized as follows: the average length of treatment, the grading of pain, swelling and excretion of moisture into the external auditory canal as well as relapse rates were identical in both (gentamicin and carbohydrate-treated) groups. Thus, experimental blocking of lectin-mediated *P. aeruginosa* adhesion eradicated these pathogens from the external auditory canal of patients suffering from *otitis externa diffusa acuta* and its therapeutic benefit was comparable to standard aminoglycoside treatment [28]. This study, for the first time, integrated basic results from lectin research into practical clinical application.

Throughout these investigations a positive correlation was found for *P. aeruginosa*-induced *otitis externa diffusa* and the ABO blood group system of the patients. Analogous to *S. saprophyticus*-mediated urinary tract infection a prospective randomized clinical trial proved a highly significant correlation between *P. aeruginosa*-induced *otitis externa diffusa* and patients' blood group A. Altogether 133 patients were enrolled in this study presenting blood group A: 74.4%; AB: 9.3% O: 16.3%; B: 0 [29] which is considerably different from the regular distribution in Germany (A: 41.8%; AB: 64%; O: 37.0%; B: 14.8%). These results are in favour of the hypotheses that: 1) *P. aeruginosa* adhere to the outer ear canal epithelium by receptor-ligand (lectin) interactions; and 2) that individuals presenting with blood group A apparently display a genetic disposition for this form of *otitis externa*.

Lectinophagocytosis: mechanism in phagocytosis of bacteria

The phagocytic process initiated by lectin-carbohydrate interactions between integral components of the cell surface (lectinophagocytosis) can easily be distinguished from another mechanism which requires serum opsonins as bridging molecules (opsonophagocytosis). Recent investigations on the chemiluminescence response (correlating to the phagocytic activity) of human polymorphonuclear leukocytes (PMNL) and monocytes suggest that opsono-phagocytosis is a considerably more effective process than lectinophagocytosis [30]. To obtain evidence on lectino-phagocytosis of *S. saprophyticus* (besides other pathogens) by human PMNL and monocytes, chemiluminescence assays were performed in the presence of lectin-specific and non-specific glycoconjugates. Contrary to PMNL stimulation which was shown to be mediated by microbial lectins this activating mechanism proved to be negligible for monocytes. Pretreatment of non-opsonized *S. saprophyticus* (and other microorganisms) with microbial lectin specific glycoconjugate did not interfere with the chemiluminescence response. However, pretreatment of monocytes with Man significantly inhibited the phagocytic activity of the cells. Non-specific glycoconjugates did not interfere with the chemiluminescence activity. Contrary to PMNL, lectinophagocytosis of human monocytes apparently is the result of specific interactions between phagocyte membrane lectins and microbial surface carbohydrates [30].

Conclusion

The specific adhesion and tissue tropism of many infectious agents can, at least in part, be explained by their recognition of defined epithelial receptors. Adherence of bacteria to epithelial surfaces may be considered to be a prerequisite for colonization and infection of numerous tissues. Specific microbial adhesion is obviously mediated by lectins interacting with complementary carbohydrate receptors and may be inhibited by lectin blocking or destruction. Initial laboratory studies and clinical trials are very promising.

Lectins: adhesion molecules for tumour cells in metastasis

The succesful formation of metastases depends, at least in part, on the ability of tumour cells to express a certain repertoire of adhesive behaviour. Such adhesive diversity enables tumour cells to detach from the primary tumour, move through the normal tissue, enter the vascular system, re-attach at sites distant from the primary tumour and again exit from the vascular system into normal tissue [31, 32].

One of the most stimulating challenges in tumour biology is the investigation of molecules mediating a adhesion-related events.

Recently, it has been shown that cell- associated glycoconjugates are involved in the metastatic spread of tumour cells. In particular cell surface glycoproteins may be regarded as principal candidates for the involvement in tumour cell spread since they are generally oriented towards the exterior of the cells and thus ideally suited to mediate the interaction of metastatic cells with their environment [14, 33, 34]. Various hypotheses have been advanced to explain adhesive phenomena [35, 36] and in general a nonspecific trapping of tumour cells may be distinguished from a specific ligand-receptor type of interaction (lectin-receptor interaction).

After the discovery of vertebrate lectins (liver lectins = hepatic binding protein) by Ashwell and Morell [9] it was postulated that organ-characteristic lectins may act as acceptors of malignant tumour cells in the metastatic process by interacting with cryptic carbohydrates on the surface of metastatic tumour cells [35, 37–39]. In view of the galactosyl specificity of the liver lectins it has been suggested that lectin blocking with competitive receptor-bearing glycoconjugates as well as by authoantibodies and down-regulation of membrane lectins in certain liver diseases may inhibit the metastic spread into the liver [38, 40]. Recent *in vitro* and *in vivo* experiments proved these postulations and demonstrated that the homing of tumour cells into the liver can be significantly inhibited by non-immunogenic galactans and galactose in different murine model systems [37, 38].

Considerably increased serum asialoglycoprotein levels are observed in certain liver diseases (cirrhosis, acute/chronic hepatitis) [41]. This phenomenon was shown to arise from alterations of the liver cell membrane whose surface lectins recognize and eliminate serum asialoglycoproteins [9]. It has been claimed that asialoglycoproteins of the tumour cell surface may carry cell characteristic carbohydrates and it has further been postulated that these structures are apparently responsible for the arrest of metastasizing tumour cells [37–39]. Since the liver contains lectins which appear to be diminished in function or quantity in certain liver diseases, this phenomenon was investigated experimentally. Histochemical studies with Gal-containing (neo) glycoproteins proved that in experimental cirrhosis and hepatitis the specific lectin-mediated adhesion of labelled marker molecules was greatly diminished or completely missing. Accordingly, the loss or dysfunction of organ characteristic liver lectins can directly be correlated with high serum levels of asialoglycoproteins and reduced metastasis formation in the liver of experimental mice [40].

Recently, the development of the liver metastases in more than 1500 cancer patients has been monitored [42] and it was found that in liver diseases such a cirrhosis, chronic hepatitis and fatty infiltration the incidence of liver metastases was significantly reduced as compared to that in cancer patients with otherwise normal livers. These data were confirmed by Uetsuji *et al.* [43] who found that colorectal carcinoma metastasizes into the normal but not into the injured liver, especially the cirrhotic liver.

Adhesion and inhibition experiments with pulmonary cells of BALB/c-mouse origin and syngeneic sarcoma L-1 cells indicated that L-fucose specific lectin-like molecules presumably situated on pulmonary cells are (at least partly) responsible for the specificity of this cellular interaction. Addition of specific carbohydrates or glycoconjugates (fucose and fucoidan, respectively) to the incubation medium evidently inhibited the *in vitro* adhesion process as quantitated using radiolabelled tumour cells [44]. Non-receptor carrying glycoconjugates did not affect cellular interaction. *In vivo*, repeated administration of fucoidan or fucose (but not of non-specific glycoconjugates) significantly inhibited the settling of metastatic sarcoma L-1 cells in the lungs of BALB/c-mice [44].

Conclusion

Adhesion and inhibition experiments with parenchymal cells and tumour cells has indicated that lectins mediate specific cellular interactions. Both *in vitro* and *in vivo* the adhesion of tumour cells to parenchymal cells could be inhibited by lectin-blocking glycoconjugates while non-specific glycoconjugates did not interfere with the adhesion process. Accordingly, when organ-characteristic lectins were blocked with competitive receptor analogues, tumour colonization of liver and lung could be significantly reduced.

Therapeutical liver lectin blocking in colorectal carcinoma patients

Experimental evidence that liver lectin blocking with the receptor analogue galactose as well as liver lectin loss or dysfunction in certain liver diseases inhibit metastatic tumour spread into this organ encouraged the initiation of prospective randomized studies with patients suffering from colorectal carcinoma. The aim of these clinical trials is the prevention of (surgically induced) liver metastases by perioperative blocking of liver lectins with infusions of galactose. The perioperative period of such treatment was chosen because tumour cell kinetics and time dependent manifestation of liver metastases after radical surgical treatment of colorectal carcinoma suggested tumour cell release and spread during surgery, at least for some of the patients. According to protocol (which was based on the guidelines for standard clinical routine in surgical oncology), patients were preoperatively checked for distant metastases and randomized into this study, when no evidence was found for metastatic tumour spread. Patients randomized into the therapy group were perioperatively treated with galactose-infusions whereas patients of the control group were given standard infusion therapy. Galactose-infusion (1.6 g Gal per kg body weight per 24 h) for patients of the therapy-group was preoperatively started (1-2 h before surgical treatment) and continued until the third day postoperatively (1200 pm). Because of the rapid uptake of serum galactose by liver lectins and subsequent metabolism by the liver, a continuous infusion was found to be necessary to saturate these lectins and the metabolic capacity of the liver, guaranteeing detectable serum

levels in treated patients. Since no serum galactose can be measured in healthy human individuals and colorectal carcinoma patients receiving standard infusion therapy, adequate blocking of liver lectins was assumed for patients of the therapy group when serum galactose was detectable.

So far, no relevant side effects of this infusion therapy have been observed, especially no alterations of serum glucose levels or ophthalmological symptons. Some minor side effects comprised fatigue, headache, gastrointestinal symptoms and vomiting but they could not be separated from usual perioperative disorders.

In the Cologne project 192 patients with colorectal carcinoma entered this prospective randomized study until May 1994. After giving their informed consent, patients were randomly divided into control group ($n = 96$) and therapy group ($n = 96$) receiving perioperative galactose infusions. All patients underwent standard oncological therapy depending on tumour localization and (patho)- biology and were comparable concerning age, sex, staging of tumour and duration of operation.

With respect to the limited mean time of patient follow up (32 months; however, a 12 months follow up after patients' recruitment phase – which was terminated in May 1994 – was fixed in the original protocol of this study) only a preliminary evaluation of this study is possible at the moment. The most interesting information so far relates to the number of liver metastases in the control group ($n = 7$) and galactose-treated therapy-group ($n = 3$). Although no conclusion on statistical significance can be drawn from these data so far, a positive trend can be anticipated. So far no obvious difference could be detected between control and therapy group with respect to occurrence of other metastases (e.g. lung, bone, peritoneum), tumour relapse rate and patient survival.

Conclusion

For the first time, basic lectinological knowledge has been applied in clinical trials to prevent metastatic liver colonization by hepatic lectin blocking with a receptor analogue carbohydrate in colorectal cancer patients. Since initial prospective randomized clinical studies are very promising, a multicentre trial is currently under investigation to substantiate these data.

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