Review

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Glycobiology of Head and Neck Squamous Epithelia and Carcinomas

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Key Words
Lectin-carbohydrate interactions · Squamous epithelium · Head and neck squamous cell carcinoma

Abstract
An impressive variety of regulatory processes including cell adhesion and migration, proliferation, apoptosis and differentiation folding and routing of glycoproteins have been found to be mediated by specific lectin-carbohydrate interactions. This article summarizes the data on glycobiological aspects of differentiation of squamous epithelia in the head and neck region under physiological conditions and in cancer. The possible function of lectins in tumor development and invasiveness is debated. Introduction of labeled endogenous lectins as a tool for the study of functional glycomics at the cellular level in head and neck squamous epithelia and carcinomas enables a complex interpretation of studied data because these lectins are normally occurring in these tissues. The lectinology of Langerhans cells in head and neck squamous epithelia and carcinoma is also mentioned. Finally, the use of the described data in the diagnosis and prospectively in the treatment of head and neck squamous cell carcinoma is shown.

Glycocode

Saccharides represent one of the basic building blocks of living organisms. Mammalian cells have an effective glycosylation machinery that includes glycosyltransferases and glycosidases. The sum activities of these enzymes determine the glycosylation patterns of proteins and lipids. Carbohydrates are able to form oligo-/polymers representing a favorable medium for the storage of biological information. Comparing the theoretical number of distinct oligomers synthesized from the same number of amino acids and monosaccharides, the number of saccharides is significantly higher than the number of peptides. The properties of peptides are primarily dependent on the number and sequences of amino acids. In contrast, carbohydrates might provide broader variations that depend not only on the number and sequences of monomeric units, but also on the position and anomeric configuration (α or β) of the glucosidic units and the occurrence of branch points. Thus, 2 molecules of a single monosaccharide can join to form 11 different disaccharides, whereas 2 single amino acids can form 1 dipeptide. Four different monosaccharides can form 35,560 distinct tetrasaccharides, but 4 different amino acids can form only 24 tetrapeptides. The heterogeneity and branching of oligosac-

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charides might yield a further level of structural and functional diversity compared to peptides and lipids [1].

Carbohydrate can be associated with proteins or lipids and form glycoproteins, glycolipids or glycosaminoglycans. Oligosaccharide chains link to protein by two types of linkage: firstly, through C–1 binding of N-acetylgalactosamine to the hydroxyl of threonine or serine, via a glycosidic bond (O-link chain), or, secondly, through binding of N-acetylglucosamine to the amide side chain of an asparagine (N-link chain). Carbohydrate domains of glycoproteins and glycolipids are synthesized by series of hierarchically organized glycosyltransferases within the endoplasmic reticulum and Golgi apparatus. In addition, glycosidases can remove some carbohydrates and thus modify the carbohydrate portion of the glycoconjugates. Because of this complexity and potential biological importance, some authors use the term glycocode [2, 3].

The importance of cell carbohydrates, especially cell surface carbohydrates, is particularly evident from the finding of variation in their expression during embryonic development and cell differentiation. Numerous data have been accumulated showing that malignant transformation is also associated with various alterations in the expression of cell carbohydrates. This might indicate that carbohydrates play a role in malignant transformation. Moreover, it has been suggested that cell surface carbohydrates might determine the ability of malignant cells to form distant metastases in various anatomical locations [4].

It is not surprising that receptor molecules able to decode information stored in saccharides were developed during phylogeny. These receptor molecules are called lectins (from the Latin *legere*, 'to select' or 'choose'), and they were initially isolated from various plants. Lectins can be defined as proteins (glycoproteins) different from enzymes or immunoglobulins (antibodies) that could also bind carbohydrates. Usually, lectins are oligomeric proteins with several carbohydrate recognition domains per molecule.

Lectins isolated from plants and invertebrates have been used for the detection of distinct saccharidic epitopes for a long time. Many plant lectins are able to aggregate erythrocytes and other cells (agglutinins), and they have distinct biological properties (stimulation of mitotic division, toxins). The lectin molecules were also discovered in higher vertebrates, such as mammals, including humans. Five families of animal lectins (so-called endogenous lectins) are present in these species. They have numerous important intracellular functions (participation in the control of pre-mRNA splicing, proliferation and apoptosis and glycoprotein addressing) and extracellular functions (intercellular interaction, interaction with extracellular matrix, immune recognition of non-self cells) [5].

Glycobiology at the Cellular Level

Labeled plant and invertebrate lectins are widely used to determine the presence of distinct saccharidic epitopes in normal and malignant cells. The animal (endogenous) lectins have also been used as probes for the last several years [6]. Their employment in the monitoring of cell glycophenotype is very important as the positive reaction allows interpretation of the function of observed glycoligands, too, since the lectin probe occurring naturally in the tissue is used. The expression of endogenous lectins is detected by conventional immunocytochemistry. These two methods detected carbohydrate-binding sites (lectin reactivity) by labeled (neo)glycoconjugates containing a distinct saccharidic epitope. This permits to detect endogenous lectin, the carbohydrate ligand reactive for this lectin and the reactivity of this lectin for glycoconjugates in cells and tissues [7].

The normal squamous epithelia enable to interpret very roughly the glycobiological observation in relation to cell differentiation and function because this tissue is morphologically and differentiation-dependently stratified [8]. Moreover, if the typical epithelial architecture is altered (in vitro cultured cells, malignant tumors), the differentiation must be estimated by the detection of well-defined markers. The multiple labeling technology at the single-cell level, where the studied glycobiological parameters were assigned to the defined differentiation marker, seems to be a favorable procedure for this purpose. The fluorescence methods are preferred because multiple fluorescence labelings (e.g. green signal + red signal = yellow signal) are very important to interpret the colocalization of two (or more) detected markers [7].

Squamous Epithelium

The squamous epithelia are usually located on the surface of the body areas affected by mechanical stress (e.g. epidermis, oral and oropharyngeal mucosa, vocal cord of larynx, esophagus, conjunctiva, cornea). They also protect our body against water evaporation, chemical injury and microorganism invasion. Moreover, they produce a wide panel of cytokines and growth factors [9]. The epidermis

as a squamous epithelium prototype is composed of the stratum basale (basal layer), the stratum spinosum (spinous = prickle cell layer), the stratum granulosum (granular layer) and the stratum corneum (cornified layer). However, the detailed histological structure of squamous epithelium is strongly influenced by its location (for example a difference between cornea and epidermis covering the plantar region of the foot). The innermost layer, which is in contact with the basement membrane through hemidesmosomes, is the basal layer. The cells of the spinous layer with abundant intercellular contacts of the desmosome type are located more superficially. The cells of the cornified layer are present over the spinous layer, and the dead cells desquamate [10]. The majority of squamous epithelia are of ectodermal origin (e.g. epidermis, a part of the oral cavity); however, squamous epithelia of endodermal origin are also known (oropharynx, esophagus, larynx). The different developmental origins of the same tissue are good evidence of the influence of the body environment on the tissue appearance and function. Similarly to other tissues, squamous cell epithelia also contain a pool of stem cells, elements responsible for epithelial renewal under physiological conditions and regeneration after injury. These elements are present in distinct locations such as the bulge region of the hair sheath and corneal limbus or in the basal layer of the epithelium [11]. These stem cells are slowly proliferating elements with a nonlimited number of mitotic divisions. The further element is the progenitor cell, the so-called transit amplifying cell, which is quickly cycling but with restricted mitotic potential [11]. Alteration of stem cell function is connected with serious skin/mucosa failure and cancer formation [11–15]. However, despite extensive research in this field, no marker specific for the stem cells is available.

Besides keratinocytes of different stages of differentiation, other elements are present in the epithelium. The melanocytes are of neural crest origin and protect the cells of the basal layer of epidermis against UV light injury [10]. Merkel cells are located in the epidermis of mammals; they form a functional unit with axon terminals and can be characterized as mechanoreceptors. However, their neuroendocrine function is also hypothesized. Although Merkel cells were shown to originate from epithelial cells, recent data demonstrate the neural crest origin of these elements [16, 17]. Langerhans cells (LC) of hematopoietic origin are professional antigen-presenting cells. They colonize squamous epithelia and participate in the immune surveillance against pathogens and cancer cells [18].

Proliferating cells of the basal layer of the squamous epithelium can be distinguished from postmitotic cells of suprabasal layers according to their expression of distinct phenotypic markers. The pattern of cytokeratins is highly specific for both basal and suprabasal compartments. While basal cells express cytokeratins K5 and K14/15, cytokeratins of type K1, K10, K2e and K11 (granular layer) are expressed suprabasally [19]. The cells of the basal layer express integrin receptors employed for their contact with the basement membrane. P-cadherin, a molecule participating in the intercellular contact formation, is also expressed by basal cells only. As basal cells can proliferate, their nuclei are frequently positive for the proliferation marker Ki-67 and proliferating cell nuclear antigen [20]. The highly specific proteins connected with late terminal differentiation such as involucrin are expressed suprabasally and reflect the formation of the cornified envelope in the suprabasal keratinized cells. The suprabasal cells have no migration activity and express proteins participating in the formation of desmosomes [10]. As it is known that the cell differentiation continues from the basal layer to the surface of the epithelium and many cell markers characteristic of a distinct differentiation level are known, the differentiation of epithelial cells can be easily estimated not only in normal epithelia, but also in tumors and under in vitro conditions when the normal architecture of the epithelial sheet is heavily altered.

Glycobiology of Normal Squamous Epithelia

Galectins

Galectins (Gal; former S-lectins) represent a family of minimally 12 endogenous lectins with a conservative carbohydrate recognition domain. They are reactive for β-galactosides, and Gal-3 recognizes also trisaccharides of the histo blood group A and B antigens. Gal are located intracellularly or secreted extracellularly. All representatives of this endogenous lectin family have no hydrophobic domain, which could be included into the cell membrane, and therefore no transmembrane Gal is known. Gal are widely distributed in cells and tissues, and their function is very complex ranging from the participation in pre-mRNA splicing to the cell-extracellular matrix interaction. Ligation of glycoligands located on the cell surface by Gal seems to be biologically highly active, and this mechanism participates in the control of biologically important processes such as cell adhesion, intercellular interactions, proliferation or apoptosis [5]. Gal-1, -3 and -7

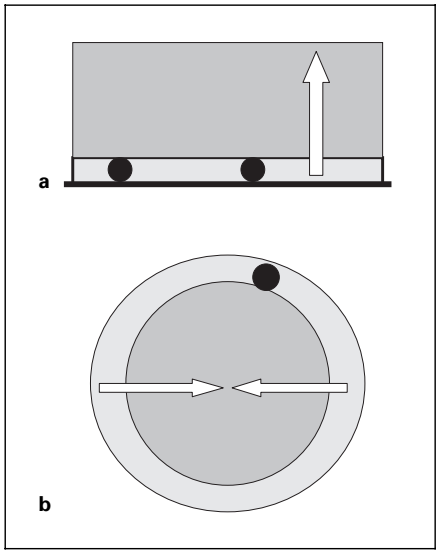

Fig. 1. Schematic presentation of squamous epithelium such as epidermis or oropharyngeal epithelium (**a**) and squamous cell carcinoma (**b**) showing expression of selected markers without pretreatment with neuraminidase. The mitotic cells are presented as black circles, and the arrows indicate the direction of differentiation. **a** Gray: integrin receptors, P-cadherin, α2,6-NeuNAc, α2,3-NeuNAc (epidermis only), Gal-1, glycoligands reactive for Gal-1, Gal-7; black and white mosaic: desmosomal proteins, α2,3-NeuNAc, Gal-1, glycoligands reactive for Gal-1, Gal-3, glycoligands reactive for Gal-3, Gal-7. **b** Gray: desmosomal proteins (in some tumors only), α2,6-NeuNAc, Gal-1, glycoligands for Gal-1; black and white mosaic: desmosomal proteins, α2,3-NeuNAc, Gal-1, glycoligands for Gal-1, Gal-3, glycoligands for Gal-3.

seem to have some relation to squamous epithelia structure and function [21].

Gal-1 and Gal-1-reactive glycoligands are expressed in the cytoplasm of cells of basal and suprabasal layers of all types of squamous epithelia [22]. Keratinocytes prepared from hair follicle sheath exhibited distinct intranuclear binding of Gal-1 colocalizing partially with SC35 splicing factor [23] under in vitro conditions. No similar phenomenon was observed in cultured cells prepared from the interfollicular epidermis [23]. These observations suggest a possibility of differentiation-dependent control of nuclear Gal-1-reactive epitope expression which can participate in pre-mRNA splicing in epithelial cells at the low differentiation grade.

Expression of Gal-7, a lectin specific for this type of epithelial tissue, is detected in both basal and suprabasal layers [24]. Gal-7 participates in the control of the apoptotic pathway in squamous epithelia [25]. Because Gal-7 is overexpressed in UVB-irradiated keratinocytes [26], some role suppressing the risk of malignization of UV-damaged epithelium can be hypothesized.

A significantly different situation is observed concerning Gal-3. This lectin and, similarly, accessible glycoligands reactive for Gal-3 are expressed by suprabasal cells [27, 28]. No expression of proliferation markers such as Ki-67 is observed in cells positive for Gal-3 and its reactive glycoligands [20]. These cells do not express the β_1-chain of the integrin receptor either [29]. The Gal-3-reactive epitope expression is restricted to the intercellular contacts of suprabasal cells [20, 28]. These binding sites precisely colocalize with the desmosomal proteins desmoplakin and desmoglein [20, 28]. The cells recognized by Gal-3 strongly express cytokeratin type 10 [20]. Labeled neoglycoligands with covalently linked defined saccharidic motifs reactive for Gal-3 recognize cells of the suprabasal layers of the studied epithelia. These findings from histological sections are very similar to observations received in colocalization experiments using cultured cells [20]. Gal-3 is produced not only by epithelial cells of the cornea and conjunctiva, but also by leukocytes located in the tear fluid of the inflamed human eye. Gal-3 seems to be able to interact with corneal and conjunctival epithelium [30]. Thus, some role of Gal-3 as agent preventing the adsorption of pathogenic microorganisms to the cell surface by lectin mechanisms can be hypothesized [31].

From the functional point of view, Gal-1 is participating in the inhibition of proliferation and induction of apoptosis [32], and Gal-3 seems to be pro-proliferative and antiapoptotic as was investigated in other cell types than squamous epithelia [33]. Gal-3, Gal-3-reactive glycoligands and binding sites for saccharides reactive for Gal-3 are under differentiation-dependent control, and these markers are present in the nonproliferative cell compartment of squamous epithelia. The different localization of Gal-1 and -3 (including reactive epitopes) in distinct layers of the epithelium indicates the cell-type-specific function of these endogenous lectins in epithelial cells. The intracellular role of Gal-1 such as participation in the splicing of pre-mRNA [23] seems to prevail in squamous epithelium in contrast to Gal-3, where a share of this lectin in the intercellular contacts of suprabasal cells is observed. Gal-7 has some relation to the induction of apoptosis [25]. However, the data about function of this Gal need further specification (fig. 1a).

Dolichos biflorus *Agglutinin*

A plant lectin prepared from *Dolichos biflorus* recognizes α-N-acetylgalactosamine including the histo blood group A epitope. Therefore, one glycoligand recognized

by this lectin is also reactive for Gal-3. In agreement with the expression of Gal-3-reactive glycoligands, this lectin recognizes some suprabasal cells of squamous epithelia. However, part of basal cells, namely in the epidermis, is also positive. These basal cells are negative for expression of the Ki-67 proliferation marker, and expression of β_1-integrin at the site of their contact with the basement membrane is lower than in the *D.-biflorus*-agglutinin (DBA)-negative basal cells [34, 35]. Mitotic cells and interphasic cells with high expression of Ki-67 are never recognized by DBA in vitro. The depression of the Ki-67 signal is connected with perinuclear binding of DBA [20]. The DBA-positive cisternae and granules also contain β_1-integrin and p58 protein, marker of ERGIC (endoplasmic reticulum Golgi intermediate compartment). The loss of the epidermal cell anchor known as an inductor of differentiation significantly elevated DBA binding to these elements [20, 35]. ERGIC is known as the cell compartment where β_1-integrin is accumulated in cellular mutants with affected adhesion [36]. Glycosylation is the common post-translational modification, and it influences protein intracellular addressing. The glycosylation of β_1-integrin with DBA-reactive glycoligand may have some role in the retention of this integrin in ERGIC. Therefore the DBA-positive basal cells can be interpreted as elements at the beginning of the differentiation cascade migrating to the first suprabasal layer of the stratum spinosum (fig. 2).

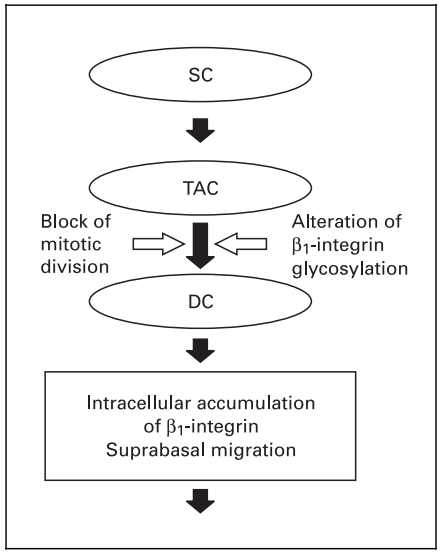

Fig. 2. Proposal of a model demonstrating the role of the glycosylation change of β_1-integrin by the DBA-reactive motif on the movement of early differentiated keratinocytes to the spinous layer. SC = Stem cell; TAC = transit-amplifying cell; DC = differentiated cell.

Sialylation Detected by the Maackia amurensis *Isolectin II and* Sambucus nigra *Lectin*

Representatives of the sialic acid family (mostly N-acetylneuraminic acid, NeuNAc) are usually located in the end position of the oligosaccharidic chain, where they are linked as α2,3-NeuNAc or α2,6-NeuNAc. α2,3-NeuNAc is specifically recognized with *M. amurensis* isolectin II, and *S. nigra* lectin is reactive for α2,6-NeuNAc. While α2,3-NeuNAc expression seems to be more common, α2,6-NeuNAc seems to be regulated oncodevelopmentally, namely in case of enterocytes and colon carcinoma [37]. The situation seems to be similar in squamous epithelia, where α2,6-NeuNAc is detected in cells of the basal layer of the epidermis, cornea and vocal cord containing proliferating cells at a low stage of differentiation. α2,3-NeuNAc is expressed suprabasally or in basal as well as suprabasal layers of the epithelium [29] (fig. 1a). Interestingly, the removal of sialic acids by neuraminidase makes the cells of the basal layer accessible for Gal-3 binding. Since Gal-3 binding to the basal layer of neuraminidase-treated epithelium is sensitive to the lipid extraction, a role of glycolipids expressed by the basal layer as counter-partners for Gal-3 can be hypothesized. The same observation was made in young colonies of cultured epidermal cells [29].

The sialic acids are known as masking agents that prevent binding of many other lectins to the glycoepitope [38]. Data received from the squamous epithelia suggest that α2,6-NeuNAc is a more potent masking agent than α2,3-NeuNAc concerning the binding of Gal-3 and also indicate the differentiation-dependent control of α2,6-sialylation of the basal layer cell surface. As has been mentioned above, Gal-3-binding sites seem to have some role in the intercellular contact of desmosomal type formation. The cells of the basal layer are able to migrate laterally in contrast to suprabasal cells with no migratory activity. Perhaps, the masking of glycoepitope reactive for Gal-3 with α2,6-NeuNAc has some role in the mobility of these elements.

Glycobiology of Head and Neck Carcinomas Derived from the Squamous Epithelia

The tumor represents a clone based on the transformation of one cell, probably caused by severe mutations of the stem cell [39]. There are many data demonstrating some glycobiological abnormalities of tumor cells. These studies support the contention that glycoproteins and car-

bohydrate-binding molecules may play a role in the progression of head and neck squamous cell carcinoma (HNSCC). Although there have been several investigations into the role of protein-protein binding in cell adhesion in HNSCC, little is known about the role of carbohydrate binding in these tumors. Cell-cell and cell-extracellular matrix interactions are critical events in the development of the tumorigenic and metastatic phenotypes. Aberrant expression of cell membrane carbohydrates as well as their receptors (lectins) may affect the tumor cells' ability to interact with molecules of the basement membrane or alter the intercellular interactions; thus, it may facilitate proliferation, invasion and metastasis of tumor cells. It is therefore pertinent to investigate the expression of lectins and their binding sites in HNSCC.

Initially, different plant and invertebrate lectins were used to analyze the carbohydrate status of HNSCC [40, 41]. Later, a main effort has been focused on the investigation of endogenous lectins, including Gal. This review stresses the markers and their role in normal epithelia.

Basal Cell Carcinoma

The glycobiological profile of basal cell carcinoma is very similar to cells of the basal layer of epidermis and mucosa covered with squamous epithelia [28]. These cells are recognized by Gal-1 and express α2,6-NeuNAc and no α2,3-NeuNAc. Pretreatment of sections by neuraminidase makes the tumor cells also accessible for Gal-3, which is not able to interact with basal cell carcinomas in native form. A limited number of cells is also reactive for DBA. The mentioned glycobiological markers colocalize with β_1-integrin in part of the tumor cells [20, 29].

Squamous Cell Carcinoma

HNSCC strongly express Gal-1 and Gal-1-reactive glycoligands in almost all cells [22, 28]. Expression of Gal-3 and Gal-3-binding sites positively correlates with a high differentiation status in HNSCC [22, 28, 42, 43]. The cells, which are recognized by Gal-3, express the desmosomal proteins on their surface [22, 28]. Interestingly, cells of regional lymph node metastases of HNSCC are usually free of Gal-3-reactive glycoligands [28]. First studies on the evaluation of the prognostic value of Gal-3 expression in HNSCC have recently been published (fig. 1b). The lack of Gal-3 expression in node-negative patients with laryngeal carcinoma and translocation of Gal-3 from the nucleus to the cytoplasm in carcinoma of the tongue was associated with a reduced survival of patients [44, 45]. A study on 53 patients with advanced HNSCC revealed that the absence of Gal-3-reactive glycoligand expression was an independent negative prognostic marker in advanced HNSCC. Multivariate statistical analysis showed that only Gal-3-reactive ligand expression retained an independent prognostic significance for both relapse-free and overall survival among various clinicopathological parameters [46]. A significant decrease in Gal-8 expression was observed in squamous cell carcinomas of the larynx compared to normal cases [47].

The differences in the degree of sialylation of glycoconjugates on a tumor cell surface of HNSCC may play an important role in the process of cell malignization and metastasis [48]. The poorly differentiated tumor cells are characterized by α2,6-linked NeuNAc expression, and the differentiated squamous cell carcinoma cells are positive for α2,3-linked-NeuNAc. Similar results were obtained by Wang et al. [49] in squamous cell carcinoma of the uterine cervix and cell lines derived from aggressive types of these tumors (fig. 1b). The removal of α2,6-linked NeuNAc by sialidase makes tumor cells accessible for Gal-3 [29]. Almost all DBA-reactive tumor cells are free of nuclear expression of Ki-67 [20]. The differentiated cells of craniopharyngioma, a tumor developed from Rathke's pouch originating from the embryonic oral cavity also covered with squamous cell epithelium, exhibit the binding of Gal-3 to intercellular contacts among differentiated cells in the late postnatal period [50].

In conclusion, the glycophenotype of cells of basal cell carcinomas is almost identical with that of the basal cell layer of normal epidermis. The cells of squamous cell carcinoma exhibit signs of differentiation. However, the glycobiological pattern of the tissue organization is highly aberrant particularly for Gal-3-binding site expression. Gal-3 seems to be the most useful prognostic marker of the glycobiological parameters investigated so far in HNSCC.

Langerhans Cells

LC are professional antigen-presenting dendritic cells of myeloid lineage occurring in the epidermis and other epithelia (nasal cavity, oral cavity, pharynx) delineating the external as well as internal body surfaces [18, 51]. In contrast to other types of dendritic cells, LC do not express the macrophage tandem repeat 175-kDa mannose receptor, although it is known that this lectin is very important in antigen uptake and presentation. However, LC also recognize mannosides [52]. A new protein called Langerin important for the formation of LC-specific organelles – Birbeck granules – was discovered, and it is also

a C-type lectin recognizing mannosides [53, 54]. LC express Gal-3, although mRNA for this lectin was not detected in these elements; it is produced by keratinocytes. Gal-3 is present in its active form in Birbeck granules, organelles participating in antigen processing [27, 55]. This phenomenon can be explained by the collaboration of keratinocytes with LC in the course of non-self discrimination. Interestingly, the binding reactivity of LC for Gal-3-reactive epitopes and mannosides is dramatically reduced in LC infiltrating HNSCC [54].

Conclusions

The glycobiological approach to the cell biology of squamous epithelia brings new data allowing to better understand the biology of this tissue under physiological as well as pathological conditions. HNSCC is a considerable healthcare problem worldwide. Despite many improvements in the treatment of cancer, remarkable, but generally insufficient progress has been achieved in the overall survival of patients suffering from HNSCC. Recent studies showed an additional support to the importance of cell carbohydrates in the regulation of malignant properties of tumor cells. However, the involved mechanism still remains obscure. With the discovery of endogenous lectins, possible interactions between these lectins and their glycoligands in tumor formation have been extensively explored. It has been demonstrated that the expression pattern of various lectins and their glycoligands is altered in HNSCC. In addition, the level of expression of these markers by cancer cells has been shown to be associated with biological characteristics of tumor (differentiation, metastatic potential) or treatment outcome. Although various aspects of lectin-carbohydrate interactions are far from being completely understood, the increasing number of experimental data confirms their importance in malignant transformation of normal squamous epithelium [56]. Further investigations are needed to throw more light onto the biological significance of endogenous lectins, their interactions with cell carbohydrates and their role in tumor biology. Data of these studies might be employed in more precise carcinoma diagnostics and later, hopefully, in cancer treatment. Firstly, endogenous lectins may become targets for therapy. Quantitative difference in lectin expression between tumor and normal cells could encourage application of specific neoglycoconjugates with the carrier modified by introduction of an active chemotherapeutic drug (fig. 3, lectin A) [57, 58]. A major handicap for the success of this approach is the heterogeneous extent of expression of surface lectins within a population of tumor cells and the possibility of their downregulation, which enables responsive cells to escape the glycobiological attack. Secondly, lectins could be used as therapeuticals in future. Interaction of a tumor cell oligosaccharide with an appropriate lectin might trigger a biosignaling cascade, which results in inhibition of proliferation, activation of apoptosis or might affect cell surface properties by blocking important cell-cell or cell-extracellular matrix interactions (fig. 3, ligation B) [59].

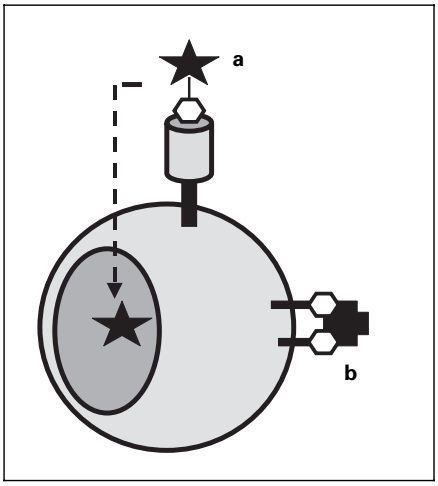

Fig. 3. Possible therapeutic strategies using glycobiological approaches for the treatment of carcinoma cells. Distinct saccharidic motifs can be used for targeting of a chemotherapeutic drug to tumor cells expressing the specific endogenous lectin (A). Ligation of the membrane glycoepitope by lectin added as a therapeutic drug can influence the biological behavior of tumor cells, e.g. induce the G_0 phase of the cell cycle or apoptosis (B).

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