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BIOLOGICAL FUNCTIONS OF CARBOHYDRATE ABH BLOOD GROUP DETERMINANTS

Victoria Sarafian[1], H. Taskov[2], and A. Popov[3]

'Departament of Biology, Medical University of Plovdiv, Plovdiv, Bulgaria, [2]Laboratory of Molecular and Cell Biology, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria, [3]Departament of Pathology, Medical Institute, Sofia, Bulgaria

SUMMARY

• *The ABH blood group determinants are carbohydrates found in different human cells and tissues. The modulation in their expression in the course of ontogenesis, as well as the studies on their subcellular localization, impose a discussion on the role of ABH antigens as molecules participating in cell interactions, contact inhibition, adhesion and metastases. It is supposed that they are also involved in cellular differentiation during human embryogenesis. The described association between blood groups and disease and the de novo acquisition of blood group determinants support the idea that ABH antigens are related to pathological processes. The modulation in blood group antigen expression observed in several tumors demands a clarification of their diagnostic and prognostic value as tumor-associated markers.*

INTRODUCTION

• The ABH blood group determinants are oligosaccharides bound to different human glycolipids and glycoproteins. Although they are discovered in the very beginning of the century (K.Landsteiner, 1901) and their biochemistry is already well defined, the biological functions of blood group antigens (BGA) are still obscure. Only the role of red blood cell antigens in blood typing, haemotransfusions and organs transplantations is specified for the present.

The recent interest in carbohydrate molecules, and in BGA in particular, impose a discussion on the participation of these structures in cell interactions (1). It is supposed that ABH antigens play an essential role in the differentiation of normal cell (2,3). There is evidence supporting the contribution of BGA to cell membrane rigidity and to cell's interaction with its surrounding (1). It is also believed that AB H determinants are involved in intercellular contacts. The molecules engaged in these processes have common biochemical structure with BGA, so that it is quite possible ABH antigens to participate in the complex cell interactions (2,4-6).

The cytological expression of BGA is a dynamic phenomenon. Each cell can easily change its glycosilation (6). The alterations in ABH antigen expression accompanying cell growth and maturation are especially important. The interactions between glycoconjugates taking part in the regulation of cell growth are not clear enough. Two possible mechanisms are discussed: contact inhibition or interaction with cell surface receptor proteins (7). The gradual elongation and arborization of BGA observed in the course of cell differentiation is modified in anaplastic cells (8). It is believed that

antigenic modulation in tumor cells could reflect the degree of their malignancy (9,10). The hypothesis for the paraembry onal character of tumor cells gives reasons a correlation between EGA expression and oncogenesis to be searched (11). The possibilities B G A to be included in the list of the stage-dependent and oncofoetal antigens and to be regarded as diagnostic and prognostic markers for the clinical outcome of malignant diseases are also discussed (12). These suggestions could be supported by the relationship between the decreased number of EGA determinants and the loss of contact inhibition discovered in vitro (2). This in turn could facilitate tumor invasion and metastases.

GENETICS AMD BIOCHEMISTRY OF ABH BGA

• The molecules determining the erythrocyte EG-specificity are glycosphingolipids, while EGA in epithelial cells are water-soluble glycoproteins (8). Both types of macromolecules contain a common oligosaccharide chain, but the antigenic specificity is defined by the so called immunodominant sugar residues: L-fucose (determining H-specificity), N-acetyl-galactosamin (A) and D-galactose (B) (13). Their sequential addition to one of the six precursor backbone chains leads to the formation of ABH BGA (Fig. 1) (14).

The synthesis and expression of ABH BGA are regulated by three independent gene loci: ABH

Chain type	Sugar residues
1	..... βGal1 → 3βGlcNAc1 → R
2	..... βGal1 → 4βGlcNAc1 → R
3	..... βGal1 → 3βGlcNAc1 → R
4	..... βGal1 → 3βGlcNAc1 → R
5	..... βGal1 → 3βGlc1 → R
6	..... βGal1 → 4βGlc1 → R

Figure 1. Precursor chains for the biosynthesis of ABH BGA

situated in chromosome 9p34, Hh and Sese - in chromosome 19 (8). It is known that the transferase enzymes but not the ABH antigens themselves are the primary gene products (8). BGA genes encode three glycosyltransferases: (i) 1-2-fucosyltransferase responsible for the synthesis of antigen H; (ii) N-acetyl-galactosylransferase responsible for the synthesis of antigen A, and (iii) D-galactosylransferase responsible for the synthesis of antigen B (13-16). Because of the multistep biosynthesis the loss in the enzymes results in the disappearance of the antigen it is responsible for.

According to the model of Oriol et al. (17) the genes Hh and Sese are closely linked and located in chromosome 19. They encode two-1-2-fucosyl-transferases with different biochemical activity and tissue localization (18). It is supposed that some epistatic interactions leading to variations in ABH antigen expression intensity cannot be neglected either (19).

CELLULAR AMD TISSUE EXPRESSION OF ABH BGA

• Phylogenetic studies indicate that BGA have first occurred in tissues, but not on red blood cells (20). ABH antigens are discovered in ectodermal and endodermal epithelial cells of lower mammals whose erythrocytes are entirely lacking BGA. Even the baboons expressing ABH antigens in their vascular endothelium are negative for red blood cell ABH antigens. Erythrocytes are in fact evolutionary the latest cells that have acquired ABH BGA. Only the humans and some primates possess red blood cell ABH antigens (20,21).

The scanning electron microscopy on human erythrocytes reveal that the number and density of antigenic determinants is different in the particular red blood cell subgroups, as well as on the convex and concave part of the cell (22). The flow cytometric analyses reveal the presence of nonsymetric (non-Gaucian) distribution of A-epitopes among the erythrocyte population of every single person (23). It is supposed that this heterogeneity is due to intrinsing differences in the quantity of antigen A or to variations in glycosyltransferase activity. The exact reason for these variations is not yet known.

The tissue expression of ABH BGA depends on the combined influence of the genetic determination, the embryological origin and the cell differentiation (Fig.2) (24).

In the tissues and organs with ectodermal origin BGA are discovered in cells of basal and spinous epidermal layers, in the hair follicles, oral mucosa, and lobular and ductal zones of the mammary gland (25,26). In the endodermal derivates, ABH antigens are found in stomach, bile duct and bladder epithelial cells (12,25). From the mesodermal derivates only the endometrium expresses BGA in accordance with the secretory status of the uterus.

There are some cells that do not express ABH antigens during human ontogenesis. Such are the osteocytes, myocytes, thymocytes, thyroid epithelial cells, splenocytes and hepatocytes (25,26). It is not clear whether these cells do not possess or have lost the ability to produce BGA. -

BGA AMD ASSOCIATION WITH DISEASE

• The association between the ABH BGA phenotype and the genetic predisposition towards some diseases is still a debatable issue. Aird at al (27) were the first to announce the positive correlation between the higher frequency of antigen A and the stomach carcinoma. Higher morbidity rate of pancreatic carcinoma is recorded in patients with A blood group as compared to B and O (28). Some researchers report prevalence of A blood group-bearing women suffering from breast cancer (29), while others do not establish such correlation (30).

The information concerning the leukaemia morbidity is quite controversial. Patients with B and AB phenotypes predominate in acute leukemia, but pantients with lymphocytic leukaemia are more common in O blood group individuals (31). American investigators notify of higher frequency of Hodgkin's disease in B blood group patients (32), while English researchers do not find any dependence (33). Australian scientists reportlower frequency of A_x phenotypes and higher of A_2 in leukemic patients (34).

There are no definite conclusions about the blood groups-disease links, as well as satisfactory explanation of the correlations observed by some authors. It is possible that populational variations in blood group phenotype distribution, and/or biochemical changes are to be concerned. It may well be that

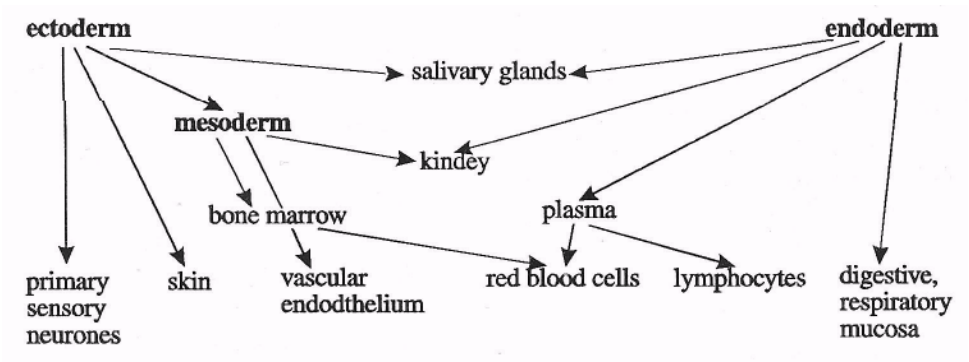

Figure 2. Genetic control of the tissue expression of ABH BGA.

individuals possessing a particular allele to have higher predisposition to some diseases. For example, people with allele A_2 are more susceptible to leukaemia as compared to those not possessing it (34). An enzyme defect in EGA biosynthesis could be a possible explanation. It is not clear whether the changes in the frequency of ABH antigens are the reason or the result for development of pathologic processes.

BGA ACQUIRED DE HOVO

• In infectious and malignant diseases an acquisition of BGA-like substances is observed. Usually "demasking" of the so called "crypt" antigens (built of carbohydrate residues mainly) takes place. When the last sugar residue is removed from the backbone chain, the last but one is exposed, thus leading to the appearance of a new antigen. Crypt antigen demasking is usually a result of glycosylytic degradation on membrane oligosaccharides caused by bacterial enzymes. A similar phenomenon is often observed in gut and lung infections. In the course of intestinal inflammatory diseases, the so called "acquired B status" is manifested in some patients having Aj genotype (35,36). It is supposed that a membrane absorption of B antigen-like substances by E. coli 086 and P. vulgaris on A and O blood group cells is concerned.

ABH BGA AMD CELL INTERACTIONS

• The presence of specific oligosaccharide antigens on cell membranes and in extracellular matrices during embryogenesis and cell differentiation impose a discussion on the possibility such carbohydrate antigens to play the role of "recognition" structures for several proteins (37).

The immunodominant sugar of the stage-dependent embryonic antigen SSEA-1 found on the cell surface of 8 days old mice embryos is composed of the monofucosylated isomer, known as antigen Lewis^x. SSEA-1 participates in the earliest processes of embryonic cell adhesion (18,38, see also the paper of Marani reviwed CD 15, this issue of Biomed Rev, pages 1-9). The variations in the duration of SSEA-1 antigen expression prompt that it could serve as a ligand for receptors engaged in this process. The studies on SSEA-1, lymphocyte antigens and on BGA suggest that ABH antigens on human leucocytes act as ligands for cell adhesion molecules (18). These data put forward the questions for the biological functions of the oligosaccharide repertoire. The first carbohydrate antigens discovered are characterized on the molecular level as ligands for E-selectin involved in inflammation (18). The biological specificity is manifested by cytokine regulated expression of carbohydrate-linking proteins on endothelial cell membranes. It is already accepted that biological specificity could originate from the binding of a particular protein to oligosaccharide structures that are not unique but a part of the cell type-specific repertoire (38).

The experiments aimed at clarifying the molecular basis of mammalian fertilization show that a BGA-like specific oligosaccharide is situated in mouse zona pellucida, i.e. glycoprotein-3 that is responsible for the sperm binding (39). On the other hand, oc-D-galactosyltranferase with molecular weight similar to that of the zona pellucida glycoprotein-3 is found on sperms (40). It is assumed that different adhesion mechanisms facilitate the con tact between egg and sperm. Obviously carbohydrate structures play an important role in this process.

Studies on the function of epidermal growth factor receptor (EGF-R) reveal that ABH antigens are related to this protein and they could possibly participate in the EGF binding, as well as in the signal cascade triggered by the EGF itself (41).

The glycolipids and the glycoproteins bound to BGA oligosaccharide chains are situated on the extracellular part of the cell membrane. The participation of membrane-bound sugar residues in the adhesion of different cell types in the vascular system is a well known phenomenon. P- and E-selectins meditate the adhesion of endothelial cells to leukocytes. The presence of ABH BGA on platelet adhesion glycoproteins focuses on the role of B GA in the recognition between platelets and endothelial cells, as well as on the association between blood groups and cardiovascular pathology (9). It is established that people with blood group A show a

higher risk of thrombosis and cardiac diseases (42). Thus, the supposed EGA-influenced modulation of cell adhesion mechanisms is an issue demanding further research in cardiovascular medicine.

The investigations on the subcellular localization of EGA further contribute to the clarification of their participation in cell interactions. Immunoelectron microscopic studies on human foetal thymus reveal the presence of EGA A in the zones of desmosomal contacts, as well as antigen clustering on lymphocyte membranes in close proximity to epithelial cells and macrophages (unpublished results).

The experiments with lectins having EGA specificity demonstrate that ABH antigens could be regarded as recognition sites for the stimulation of Ca^{2+} and Cl' ion transports (4). The activation of ion transport through the cell membrane is often linked with the proliferative and mitogenic effect of some lectins and growth factors. Any modifications in ABH antigen structure could possibly lead to changes in cell proliferation. They in turn could either favour or hamper the interactions between cells, growth factors, and endogenous lectins.

It is suspected that BGA could function as signal molecules in cell interactions (43). The information exchange between neighbouring cells is extremely important for their proliferation and differentiation both in vitro and in vivo (43).

ABH BGA AND CELL DIFFEREMTIATIOM

M The informative function of cell membrane carbohydrates has probably evolved later on as multicellular organisms developed. Koscielak (44) considers that BGA undergo changes connected with cell differentiation and maturation. Cell migration is known to be a common event in the course of the embryogenesis of all vertebrates. Obviously the cells participating in this process possess inert BGA preventing their interaction with lectins, adhesion and aggregation factors. Once settled in their new surrounding, the cells gradually differentiate and acquire novel specific and active membrane determinants.

Some authors describe the expression of ABH BGA in embryonic mesenchyme cells even before their transformation into endothelial ones (unpublished results). They believe that the presence of BGA in the still undifferentiated mesenchyme could be regarded as an early immunocytologic marker for potential endothelial differentiation.

Another fact confirming the thesis for the role of BGA in cell differentiation is the increasing gradient of ABH antigen accumulation towards the corneous layer in both embryonic and adult normal epidermis (3,26).

Examining erythrocytes of foetuses, newborns and healthy adults, Watanabe and Hakomori (45) establish large amounts of antigen H in adult cells (45). The foetal and newborn erythrocytes entirely lack the antigen or it is in minimal quantities. Lots of precursor chains are discovered in prenatal cells. The postnatal changes in the agglutinability of human red blood cells is now explained with the arborization of oligosaccharide chains, a process parallel to cell differentiation. The lower agglutination activity of foetal erythrocytes could be due to the lack of branched A and B antigens which could be accepted as markers of differentiation.

ABH BGA AMD TUMORS

M The investigations on BGA expression in the course of human ontogenesis and oncogenesis give grounds to some authors to consider BGA as "stage-dependent, oncofoetal or tumor-associated antigens" (1,2,46). Szulman's studies show that there is a stage-dependency in the tissue expression of ABH antigens (47). It is most obvious in the distal colon where BGA are present up to the 10-14-th weeks of gestation; afteron they disappear and miss during the whole postnatal life. They reappear when malignant transformation in the same region begins (3,47,48). It is supposed that contiguous processes of repression and derepression of the glycosyltransferase genes occurs. According to Manzo's hypothesis for the paraembryonal character of malignant cells (11), tumor cells acquire the ability to express embryonic features and traits. It is likely that the expression of BGA, typical of the prenatal period, to be

sion of EGA, typical of the prenatal period, to be one of these characteristics.

Four different types of changes in BGA expression are recorded in tumor cells: (i) antigen loss; (ii) enhanced synthesis or neoexpression; (iii) BGA expression incompatible with the blood group of the person, and (iv) changes in the cellular localization of ABH antigens, from cell surface to cytoplasm (1,2,12,48).

The neoplasms of breast, urinary bladder and prostatic gland are characterized with antigen loss (3,12,48). Some researchers do not find any correlation between the antigen deletion and the clinical course of the disease. Others claim that the higher the antigen loss, the worse the patient's prognosis (bladder and lung carcinomas especially) (2). It is supposed that BGA deletion disturbs cell's "orientation" in its microenvironment. If so, the hampered contact inhibition enforces the cells to begin invading and metastazing (1).

Enhanced BGA synthesis is observed in stomach tumors and primary hepatocellular carcinomas (25,48). The foetal and adult normal hepatocytes lack BGA, but the malignant ones can express ABH antigens. This could be possibly due to derepression of glycosyltransferase genes. Itis notknown whether this genetic alteration is a cause or a consequence of neoplastic transformation.

The tissue expression of incompatible BGA is explained with defective antigen biosynthesis.The insufficient glycosyltransferase activity can result in misproduction of oligosaccharide chains. There also could be normal enzyme activity but lack of precursor molecules that in turn leads to antigen loss. Another possible explanation could be presence of normal BGA synthesis accompanied by enhanced glycosylytic degradation.

The changes in the cellular localization of BGA in tumor cells could reflect the deletion of molecules participating in cell contacts. So, an increased invasive and metastatic potential is observed. The scanty and contradictory parallel studies on BGA expression in the primary tumors and in their metastases put forward the discussion on the decreased intensity of antigen expression in the primary tumor as a reflection of initial anaplasia (2).

COMCLUSION

Carbohydrate structures, and BGA in particular, focus the current interest of many scientists because of the modulations in their expression. Although complex immunobiological functions need further elucidation, recent knowledge in glycoimmunology suggests that ABH BGA are involved in cell differentiation, cell interactions, oncogenesis, and predisposition to several diseases. The efforts are now aimed at the diagnosis, prognosis and control of the clinical and biological characteristics of these processes through monitoring B GA expression.

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Address for correspondence:
Dr Victoria Sarafian
Department of Medical Biology
Plovdiv Medical University
15a VAprilov Blvd
BG-4000 Plovdiv
BULGARIA