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Review

Antigen structure and genetic basis of histo-blood groups A, B and O: their changes associated with human cancer [1]

Sen-itiroh Hakomori [a, b]

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Abstract

Three areas of research involved in blood group (or histo-blood group) ABO antigens and their genes, developed by our research group, are reviewed: (1) *Antigen structures.* The structural basis of A and H, A_1 and A_2, i and I antigens expressed in erythrocyte membranes. Major carriers of A and H determinants in erythrocytes are type 2 chain poly-LacNAc, short vs. long and unbranched vs. branched structures termed A^a, A^b, A^c, A^d and H_1, H_2, H_3, H_4. Regular A (A_1) and weak A (A_2) were identified respectively as repetitive A (type 3 chain A) and A-associated H. A_1- and A_2-specific type 3 chain A and H, type 1 chain (representing Lewis blood group antigens), and type 4 chain (globo-series antigen; an extremely minor component in erythrocytes) are all glycosphingolipids. A and H determinants in fetal and newborn erythrocytes are carried by unbranched poly-

LacNAc, whereas these determinants in adult erythrocytes are carried by branched poly-LacNAc. (2) *ABO genes*. A few cDNAs encoding A enzyme (UDP-GalNAc: H-a-GalNAc transferase) were cloned based on the amino acid sequence of purified A enzyme and their structures were compared with those of homologous cDNA from blood cells of B and O individuals (genotype *BB*, *OO*). Four nucleotide substitutions and four corresponding amino acid sequences essential for expression of A^1 allele and *B* allele, and differences between A and B enzymes, were identified. Amino acids 266 and 268, i.e. Leu and Gly for A enzyme vs. Met and Ala for B enzyme, were dominant in determining A vs. B activity (presumably recognizing UDP-GalNAc vs. UDP-Gal). The A^2 allele was characterized by deletion of the termination codon, extending nucleotides up to 1128 and thus encoding 21 extra amino acids at the C terminus, which may affect (diminish) the dominant function of amino acids 266 and 268. Typical *O* allele (O^1) is characterized by deletion of nucleotide 261 G, causing frame shift and encoding of an entirely different, short polypeptide, due to appearance of early termination codon at nucleotide 354. Structures of other *O* alleles (O^{1v}, O^2) and other weak *A* alleles (A^3, A^{el}) are also described. The genomic structure of ABO genes consists of seven exons which span â^¼19 kb of genomic DNA on chromosome 9, band q34. Most of the coding sequence is located in exon 7. Analysis of the 5â€² upstream region revealed the presence of the binding site for transcription factors and enhancer element. (3) *Antigens and genes in cancer*. A and B phenotypes aberrantly expressed in various types of human cancer, and their genetic basis, have been studied. One widely-occurring change observed in a large variety of human cancers is deletion of A or B epitope, associated with accumulation of their precursor H (Le^y, Le^b), which causes enhanced malignancy. A less-commonly observed change is expression of incompatible A, identified as real type 1 chain A, in tumors of O or B individuals. A possible molecular genetic mechanism leading to such phenotypic changes is discussed.

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[1] Blood group phenotypes A, B, O and Lewis (Le) are shown without italics. Their alleles are shown with italics: *A*, *B*, *O*, *Le*, *le*. Similarly, phenotypes of A and O variants (subtypes) A_1, A_2, A_3, A_x, O_1, O_2, $O_{1\ variant}$ ($O_{1\ v}$) and O_{el} are shown without italics and with numbers subscripted. Their alleles are shown with italics and with numbers superscripted: A^1, A^2, A^3, A^x, O^1, O^2, $O^{1\ variant}$ ($O^{1\ v}$), O^{el}. Blood group A-active glycosphingolipids, separated by thin-layer chromatography, are named A^a, A^b, A^c or A^d according to their order of chromatographic migration. Similarly, blood group H-active glycosphingolipids, according to their order of migration on thin-layer chromatography, are named H_1, H_2, H_3, or H_4. Structure of purified A- or B-active glycosphingolipid components are respectively defined in Table 2. However, each unpurified fraction contains not only the GSL component defined in Table 2, but also some other structures, e.g. â€˜A^c fractionâ€™ contains A^c glycolipid as shown in Table 2 and repetitive A (type 3 chain A) structure as shown in Table 3. A^a, A^b, A^c and A^d are GSLs having 6, 8, 12 or 14 sugar residues. These terms are used in order to distinguish regular A phenotype (A_1) from weak A phenotypes (A_2, A_3, etc.). H_1, H_2, H_3 or H_4, according to their order of chromatographic migration, corresponds respectively to GSLs having 5, 7, 10 or 12 sugar residues (S. Hakomori, Semin. Hematol. 18 (1981) 39â€“62). Blood group A, B and H determinants are carried by different, specific â€˜carrier typeâ€™ structures, i.e. type 1, type 2, type 3 associated with A-glycosphingolipid, type 3 associated with O-linked Ser or Thr in mucin-type domain and type 4 (globo-series structure). Specific monoclonal antibodies can distinguish ABH epitopes carried by different carrier carbohydrates (H. Clausen, S. Hakomori, Vox Sang. 56 (1989) 1â€“20). For carrier type structures, see Table 1.

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Glycosyltransferase structural biology and its role in the design of catalysts for glycosylation, gyroscopic frame clearly reflects the object, opening new horizons.
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