ROLE OF ANTIGEN DETERMINANTS A AND B OF AB0 BLOOD GROUP SYSTEM IN HUMAN DISEASE DEVELOPMENT (MINI REVIEW)

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Abstract
ABO blood group system discovery was an important step in development of such areas as transplantation and transfusion medicine. At the same time understanding of fundamental role of antigenic determinants in physiological functions maintenance and pathological conditions development remained unexplained for a long time. Today it is known that A and B antigens are widely represented not only on erythrocytes membrane but also on other cells and tissues: platelets, epithelial tissue, oral and spermal fluids. Earlier authors studied metabolic and coagulation profiles, as well as blood cells composition in clinically healthy individuals on more than 180,000 donations, thus revealing group-specific features for each blood group. The review provides synthesis of association of such pathological conditions as coronary heart disease, thromboembolic complications, tumors of various localizations, inflammatory and destructive oral diseases, psychiatric and some infectious diseases with the presence or absence of antigenic determinants A and B. 0 (I) blood group carriers are more resistant to development of diseases, excepting H. pylori-associated gastrointestinal diseases. Carriers of “antigenic” blood groups A (II), B (III), AB (IV) are more susceptible to infections, cardiovascular diseases, and oncological diseases. The data presented may contribute to a personalized patient approach formation, based on antigen-associated biological variability of various signs in norm and pathology.

Keywords
blood groups • AB0 antigen system • human diseases • H. pylori • malaria • schistosomiasis • coronary heart disease • stomach cancer • esophageal cancer • breast cancer • oral cavity diseases

Introduction
Nowadays studying molecular markers revealing predisposition to certain diseases that could indicate pathological process development possibility is of great importance. In this regard, AB0 system antigens are of special interest. AB0 blood group system was one of the first to be discovered by K. Landsteiner and his students in 1901, for this discovery he was awarded the Nobel Prize in 1930. AB0 system antigens chemical structure is presented with molecules of glycoproteins fixed on erythrocyte cytoplasmic membrane surface. The difference between blood group antigens consists in different terminal oligosaccharide chain glycans [1, 2]. Antigens of AB0 system are presented not only on erythrocyte membrane surface, but also in secretory epithelium of salivary glands, gastrointestinal organs, sex glands and respiratory system. The soluble form of these antigens can be found in oral fluid, semen and other biological secrets [3]. Numerous information is currently available on blood group antigens presenting the carbohydrate component (AB0, Lewis, Secretor) and their relationship to infectious and cancer disease. Existing data enables approaches of personalized medicine in terms of diagnostics and treatment of diseases based on molecular predisposition factors [4, 5]. Earlier authors studied specific features of carbohydrate, protein, and lipid metabolism, blood cell composition [5, 6] and coagulation profile depending on AB0 blood group system on more than 180,000 clinically healthy persons’ donations [7]. Association between blood group type and anemia, hemophilia, pregnancy-related pathology, fetal hypotrophy was observed [8, 9]. This review summarizes research results over the past decade aimed at determining the relationship between blood group affiliation by AB0 system and probability of infectious and somatic diseases.
Infectious Diseases

Glycans play an important role as recognition molecules, explaining a likely relationship between infectious diseases and blood group affiliation. Many vertebrate species retained functional gene responsible for A and B antigens expression. Most humans, on the other hand, are genotype 0 (I) carriers, so that glycosyltransferases completing A and B antigens synthesis formation are inactivated in these persons. AB0 genes polymorphism is associated with evolutionary adaptation as a protection mechanism against interspecific and intraspecific infections, since antibodies are produced against foreign A and B antigens that enter the body with pathogenic microflora. Mimicking pathogenic adhesive glycotopes with other glycans is another possible protective mechanism. While binding sites of infective agents to epithelium surface may support their colonization, AB0 antigens secreted into biological fluids may serve as “bait” receptors for pathogenic microflora and thus have a protective function [4].

Despite evolutionary patterns, gastrointestinal diseases associated with Helicobacter pylori are the most susceptible in persons with “zero” blood type, that is confirmed in meta-analysis of Z. Chakrani et al. [10]. One of the reasons is the absence of glycosyltransferase enzyme, catalyzing attachment of terminal monosaccharides to L-fucose of substance H, a common precursor for antigens A and B. In 0(I) blood group carriers transformation of substance H into Le-b antigen is inherent. High level of this antigen in the stomach and duodenum mucous membrane increases susceptibility to H.pylori infection because it serves as an additional receptor for this microorganism [11].

For the majority of infectious diseases susceptibility of “antigenic” blood groups carriers is higher in comparison with carriers of “zero” group. In particular, meta-analysis by A. Degarege et al. [12], who studied peculiarities of malaria course depending on blood group affiliation, showed that persons with A(II), B(III) and AB(IV) blood groups have higher chances of developing P. falciparum malaria [13-16] infection. When comparing placental infection prevalence it was noted that in comparison with 0(I) blood group probability of active course of P. falciparum malaria is higher in women with “antigenic” blood groups [17-19]. According to R. E. Tiongco meta-analysis, who studied schistosomiasis, people with antigenic determinants A and B on the membrane surface of erythrocytes are more susceptible to schistosomiasis than people with 0(I) blood group, and there is no dependence between the type of schistosome and ethnicity [20].

Non-communicable Diseases

Correlation between AB0 system blood group affiliation and coronary heart disease risk development was established. According to Z. Chen et al. [21, 22], individuals with 0(I) blood group have the lowest risk, and individuals with A(II) blood group – the highest one. Carbohydrate components of antigens A and B are expressed on platelet glycoprotein receptors - GP IIa and IIIa, as well as on GP Ib/IIa complex, playing a key role in thrombosis process. GP Ib / IIa receptor complex ensures platelet aggregation by binding fibrinogen, fibronectin and von Willebrandt factor. GP IIa, as part of GP Ia / IIa complex, binds platelets to collagen in damaged endothelium sites. Thus, AB0 antigens are able to modify platelet glycoprotein receptors structure and play a certain role in thrombosis, that explains risk of cardiovascular diseases development [23].

It was found that the incidence of thromboembolic complications in various diseases is associated with blood group affiliation, incidence in “antigenic” blood groups is 30% higher compared to 0 (I) group carriers [24]. This interrelation can also be explained by antigen-mediated change of von Willebrandt factor levels and factor VIII in plasma [6], the lowest content of which is observed in “zero” blood group carriers. Antigens A and B carriers have an elevated content of these factors, contributing to an increased risk of thrombosis, also explaining risk of myocardial ischemia. Difference in presented coagulation factors level is caused by the fact that some of von Willebrandt factor sites are subjected to structural modifications by means of AB0 antigens. Three O-glycans are known to directly bind with antigenic determinants, leading to posttranslational changes in these molecules [25].

It is interesting to note that coagulation profile difference is reflected far beyond coagulation system. For example, correlation between von Willebrandt factor and factor VIII levels and vascular dementia and cognitive impairment development was shown. 0 (I) blood group carriers are less susceptible to age-related cognitive changes and therefore have longer life expectancy. Another intriguing mechanism may include antiangiogenic properties of von Willebrandt factor, explaining a more complete brain vascularization in individuals with group 0 (I), due to the lower content of von
Willebrand factors and factor VIII compared to individuals with blood group A(II), B(III) or AB(IV) [26].

In addition to relation between somatic diseases and blood group affiliation, there are also associations with mental disorders. According to S. Pisk et al. meta-analysis [27], mental disorders development in general is typical for AB(IV) blood group carriers. As for certain diseases, depressive disorders are more common in A(II) blood type carriers, and the risk of schizophrenia and bipolar affective disorder is higher in 0(I) blood type carriers [28]. According to some studies, more frequent occurrence of bipolar affective disorder in individuals with 0(I) blood group is associated with changes in dopamine-β-hydroxylase enzyme activity, that is involved in dopamine- noradrenaline transformation, increased in bipolar affective disorder, and decreased in depression. 0(I) blood group carriers are also more susceptible to schizophrenic disorders, probably due to excessive dopamine activity [29].

Cancer

Stomach cancer ranks fifth among the most frequently diagnosed malignant tumors and is the third most important cause of death worldwide [30], so establishing relationship between blood group and this type of cancer is of great diagnostic importance. Currently, it has been determined that A(II) and AB(IV) blood groups have the largest number of patients with stomach cancer [31]. It follows that a certain cause of death worldwide is of great diagnostic importance. Currently, it has been determined that A(II) and AB(IV) blood groups have the largest number of patients with stomach cancer [31]. It follows that a certain role is played by antigen A, affecting systemic inflammatory reactions, intercellular adhesion, membrane signal transmission, as well as immune surveillance of malignant cells. It is assumed that persons positive for this antigen have lower free hydrochloric acid production, which plays the role of antibacterial protection, compared to those who do not carry this antigen [32]. Also, in A(II) and AB(IV) blood groups carriers there is a decrease in type 1 intercellular adhesion molecule soluble form production as compared to 0(I) and B(III) blood groups, which negatively affects immune system antitumor protection [33]. The lowest risk of esophageal cancer is typical for persons with 0(I) blood group, and the highest risk is in persons with B(III) blood group [34].

Over one million new cases of breast cancer are diagnosed annually [35]. According to S.Y. Miao et al. meta-analysis [36], the highest risk of breast cancer is observed in women with A (II) blood group. One of the reasons is the fact that normal breast tissue constantly expresses blood group antigens of the same type, while in the areas of benign neoplasia a more diverse pattern of antigen expression is observed. They play an important role in malignant progression and tumor cells spread [37].

Oral Diseases

Inflammatory and destructive diseases of oral cavity are equally important in general morbidity structure. Differential secretion of blood group AB0 antigens in tissues may be a factor influencing development of oral cavity systemic diseases and depends on patient secretory status. AB0 system antigens expression is influenced by differentiation and maturation of cells in stratified squamous epithelium of oral cavity. Basal layer cells express precursors of carbohydrate chains of A and B antigens, while antigens themselves are more often found in spinous layer. In oral tissues A and B-glycosyltransferase and their substrates presence determines expression of A and B antigens [38].

Correlation of inflammatory-destructive diseases with blood group affiliation has not been yet established, obtained results are contradictory and there are no meta-analyses. We cite studies by a number of authors on this problem. According to G.P. Pai et al. [39], whose study included 750 individuals, the highest percentage of healthy volunteers was found among 0(I) blood group carriers, while most patients with moderate to severe gingivitis were of blood group A(II) and B(III). A similar situation is observed in individuals who have been diagnosed with periodontitis. This pattern may be due to the fact that antigens A and B are receptors for fixation of infective agents, thereby contributing to periodontal disease development. According to D.Mostafa et al. [40], whose study involved 1126 patients with generalized chronic periodontitis, in contrast, individuals with 0(I) blood group are at increased risk regardless of severity compared to other blood groups. 0(I) blood group carriers and persons of A(II), B(III), AB(IV), who do not have antigens A and B in their oral fluids, are more susceptible to inflammatory and destructive oral diseases. Low IgA in the oral fluid should also be considered, which may compromise their ability to maintain oral antibiotic protection [41].

Conclusion

Considering blood groups as an evolutionary heritage, we can conclude that 0 (I) blood group carriers, whose erythrocyte membrane contains no AB0 antigens in comparison with other “antigenic” variants of this system, have a certain advantage in relation to general risk of neoplasm development, cardiovascular diseases, thromboembolic complications, and some other life-threatening infections. Over the past decades, various researchers have assessed whether congenital biological determinant, that is AB0 antigens affiliation, has clinical significance beyond its use in transfusion and transplantation medicine.
Currently, there is sufficient data available to demonstrate the role of ABO antigens in various systemic diseases pathogenesis, including cancer, infectious, cardiovascular and a number of other diseases. The data presented justifies necessity to take into account blood group affiliation when diagnosing various diseases, planning treatment or assessing prognosis. It may be reasonable to include blood group affiliation into scales for determining risk of cardiovascular diseases, coagulation disorders, gastrointestinal diseases.

Determining ABO group affiliation has become a routine laboratory study, but prospect of using this data in context of personalized medicine is still underestimated.

**Conflict of Interest Statement**

The study was not sponsored; the authors state that there is no conflict of interest.

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