

Chapter

ABO Blood Group Antigens as a Model of Studying Protein-Protein Interactions

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Abstract

This work presents a research of intermolecular interactions on the example of the antigen antibody interactions of the ABO system. This model could be successfully used in the future due to the lack of knowledge in the area of the ABO antigen's behavior as a biomolecule and the integration of these structures into chain of metabolic processes in a human being. Using computer PASS system ("in silico" research), we describe the possible biological effects of pyruvate, lactate, and antigen determinants A and B. Glycoproteins A and B are very perspective to study as biological active connectors due to the wide range of their biological effects. The obtained knowledge proves that ABO antigen, as well as other glycoprotein conjugates, could play an important role in intercellular adhesion and signal transmission, which could be used in perspective in personalized medicine, target therapy, and evaluation of lab results in clinical practice.

Keywords: ABO blood groups, protein-protein interaction, computer modeling, biological activity

1. Introduction

Erythrocytes are the most common blood cells in the human body. They present on their surface a huge number of different receptors and antigens, which explain their multiple biological functions. Since 1900, when Carl Landsteiner first found red blood cell antigens and named them ABO blood group system, a big step forward was made by scientists in this direction. Up to now, over 35 blood groups are registered in the International Society of Blood Transfusion. Some of them as ABO blood groups, MNS, Rh, Lutheran, Kell, Lewis, and Duffy are well studied and found their place in clinical practice, but others as Ok, Scianna, Colton, and Knops are on their way to be fully understood. The genes of the blood groups are mainly autosomal with the exception of XG, XK, and MIC2 genes as they are presented on X and Y chromosomes.

The biochemical structure of blood group antigens differs a lot; they can either be proteins (Rh, Kell) or glycoproteins and glycolipids (ABO) [1].

ABO blood group system consists of three alleles, dominant A and B, and recessive O, and it is controlled by a gene located on chromosome 9 (9q34.2).

These genes (A and B) code different glycosyltransferases: glycosyltransferase A which adds N-acetylgalactosamine and glycosyltransferase B which adds D-galactose to H-substance. O allele is inactive and does not encode an enzyme, so that H substance remains unmodified with a fucose moiety. Combinations of these three alleles give us four different blood groups O (I), A (II), B (III), and AB (IV) [2].

It is notable that ABO antigens are expressed not only on the surface of erythrocyte, but they can also be found in a variety of tissues and cells, such as the endothelium of blood vessels, neurons, epithelium, platelets, etc.

In recent years, the amount of research on protein-small molecule (metabolite) interactions has increased significantly. However, the study of these interactions, according to the 2011 Wiley Online Library, is lagging far behind other types of interactions, such as protein-protein, protein-DNA, and protein-RNA, in terms of publications. Only in 2009 the first publications about protein-metabolite interactions appeared.

From a biochemical point of view, most biological systems work by fulfilling their diverse functions by proteins. Due to the revolutionary progress in the study of genomics and proteomics, a more accurate idea of the amount of proteins synthesized in the body has now been formed, but there is a weak idea of which proteins nonspecifically interact with metabolites [3].

It has been established that intermolecular interactions play a crucial role in almost all major biological processes, such as cell regulation, biosynthesis and biodegradation, signal transmission, transcription and translation processes, the formation of oligomers and multimolecular complexes, packaging of viruses, and the immune response, are protein-ligand interactions [4]. The polyfunctionality of proteins is due to their ability to change the conformation of a molecule when interacting with ligands. Proteins can interact with almost all types of molecules: from small compounds—water, metal ions, carbohydrates, fatty acids, and cell membrane phospholipids—to high molecular weight proteins and nucleic acids. Disruption of protein interactions underlies some diseases [5].

This fact provides a key argument that biological and clinical significance of blood groups in general and ABO especially extends far beyond our expectations and needs to be clarified.

2. Computer modeling of antigen determinants A and B

2.1 Antigen A and its predicted biological activity

It is almost impossible to evaluate the specific properties of the terminal fragments of antigenic structures in an experiment, but with the method of computer simulation, one can predict the biological effects of substances.

Glycosylation of protein molecules significantly affects their ability to contact with other molecules, which is important for understanding the mechanisms of intermolecular interactions, signaling, and adhesion at the cellular and molecular levels. The group-specific antigens of the blood ABO system are formed by the glycosylation of transmembrane proteins presented on the surface of red blood cells.

A-Antigen terminal monosaccharide N-acetylgalactosamine contains in the position C2 NHCOCH₃ group, and B-antigen terminal monosaccharide D-galactose, in position C2, contains OH group. Functional groups confer variability in the structure of antigens and provide specificity for binding ligands. The presence in the structure of the N-acetylgalactosamine acetyl group leads to the disappearance of the positive charge.

N-Acetylgalactosamine is an amino sugar found in almost all glycoproteins. The immediate precursor of N-acetylgalactosamine is fructose-6-phosphate. Amino sugar is further acetylated with acetyl-CoA.

Monosaccharides can take part in all reactions which are typical for hydroxyl-containing compounds: they form esters and ethers, acetals and ketals, undergo substitution and elimination reactions. An important property of monosaccharides is their ability to form glycosides due to hydroxyl at the first carbon atom. Elucidation of the potential biological activity of antigens, determined by the structural characteristic of the antigenic determinants of the ABO system, is an important task.

We used a program for computer modeling called PASS. Prediction of Activity Spectra for Substances (PASS) is a program designed for computer modeling created by a group of Russian scientists. This tool is based on the dependence between chemical formula of a random substance and its functional activity. Chemical formula is described using Multilevel Neighborhoods of Atom (MNA) descriptors, the combination of which is unique for each substance. The user gets the list of probable activities based on the program's self-educating "training set," which aggregates data on active compounds from databases, publications, and patents, marked with Pa (probability to be active) and Pi (probability to be inactive), placed in the order from the maximum Pa to the minimum one. The program uses the Bayesian approach with some modifications for calculating the Pa and Pi (for more detailed information, see [6, 7]). In our study we chose effects with Pa > 0.5. Total number of biological activities in the database is 4130, 501 of them are pharmacological effects, 3295 are molecular mechanisms of action, 57 are toxic effects, 199 are mediated metabolic actions, and 29 are influences on gene expression.

We have identified a significant number of previously unknown properties and mechanisms of action for the antigenic determinant antigen A, namely, 99 out of 501 possible pharmacological effects, 304 out of 3295 possible molecular mechanisms of action, 17 out of 57 adverse and toxic effects, 12 of 199 metabolic-related activities, 2 of 29 effects regulating the expression of genes, and 5 of 49 effects associated with the transport of substances. We chose biological activities with a probability of Pa greater than 0.5. The PASS program allowed us to establish that the antigenic determinant of antigen A exhibits the following pharmacological effects (**Table 1**).

It is predicted that the antigenic determinant of antigen A exhibits antibacterial, immunostimulating, antifungal, antiviral, and pharmacological effects, as well as antibiotic properties.

Pharmacological effect	Pa	Pi	Pa – Pi
Membrane permeability agonist	0.840	0.006	0.834
Antibacterial	0.707	0.005	0.702
Immunostimulating	0.697	0.07	0.690
Antineoplastic	0.654	0.016	0.638
Antifungal	0.632	0.013	0.619
Antiviral	0.620	0.011	0.609
Angiogenesis stimulator	0.577	0.012	0.565
Vasoprotector	0.552	0.045	0.507

Table 1.
 Predicted pharmacological effects of antigen A.

ABO phenotypic analysis of blood groups is often used to detect the degree of susceptibility of a person to infectious diseases. In the literature, there are data in which it is noted that the interaction of certain parasites and bacteria with human cells depends on the presence of certain blood groups [8].

Thus, antigen A exhibits high adhesive activity against lactic acid bacteria. Some of the antigens affect the humoral and cellular response [9].

For the oligosaccharide of the antigen A, the antineoplastic effect on the cancer of various etiologies and localization is predicted: gastric and lung cancer, sarcoma, leukemia, and cancer of the brain and ovaries. Numerous studies have shown an association between ABO blood groups and the risk of developing various types of cancer [10].

With a high degree of probability, the antigen A is able to regulate angiogenesis and has a potential vasoprotective effect, as well as an effect of inhibitor of membrane permeability and integrity. The formation of new blood vessels in the organ or tissue is activated only when the damaged tissues are regenerated. Some factors, depending on the dose, can be both inducers of angiogenesis and inhibitors [11]. Many predicted effects of the antigenic determinant of antigen A are realized through the molecular mechanisms of its action (**Table 2**).

It is predicted that the oligosaccharide of the antigen A can act as an agonist of nerve growth factor, tumor necrosis factor, hyaluronic acid, α -interferon, interleukin-2, and tissue kallikrein inhibitor. The stimulating effect of the oligosaccharide antigen A on the activity of caspases 3, 8, and 9, participants in the apoptosis process, is predicted. As it is known, all caspases are synthesized in an inactive form and are activated when necessary by initiating caspases in the process of partial proteolysis. Probably, the antigenic determinant A, by activating caspases, can trigger a signal chain of programmed cell death.

Analyzing molecular mechanisms of action of antigenic determinants A, we paid attention to the inhibitory effect, to a number of carbohydrate metabolism enzymes, complex lipid metabolism, and protein biosynthesis process.

Molecular mechanism of action	Pa	Pi	Pa – Pi
Inhibitor of CDP-glycerol phosphotransferase	0.837	0.006	0.931
A-glucosidase inhibitor	0.826	0.001	0.825
Analogue of insulin	0.755	0.003	0.552
Antagonist of membrane integrity	0.731	0.009	0.713
Lactase inhibitor	0.718	0.007	0.711
Nerve growth factor agonist	0.715	0.007	0.708
Inhibitor ceramide glycosyltransferase	0.713	0.010	0.703
Aspartyl transferase inhibitor	0.708	0.007	0.701
Hyaluronic acid agonist	0.701	0.002	0.699
B-glucuronidase inhibitor	0.661	0.005	0.656
Caspase stimulator	0.646	0.005	0.641
N-acetylglucosamine transferase inhibitor	0.636	0.003	0.633
Glycerol monooxidase inhibitor	0.628	0.025	0.603
A-interferon agonist	0.595	0.019	0.576
TNF agonist	0.550	0.019	0.531
IL-2 agonist	0.517	0.011	0.503

Table 2.
Predicted molecular mechanisms of action of antigen A.

Oligosaccharide antigen A may inhibit the activity of enzymes involved in the metabolism of simple carbohydrates, such as α -glucosidase, β -glucuronidase, and β -galactosidase, and in the exchange of complex carbohydrates, predominantly heteropolysaccharides— α -N-acetyl-glucosaminidase, dolichol glycosyltransferase, and GDP-mannose-6-dehydrogenase, which creates the possibility of inhibiting the metabolism of the components of the extracellular matrix of connective tissue—glycoproteins and proteoglycans. Dolichol glycosyltransferase plays a leading role in the glycosylation of membrane proteins.

It is predicted that the oligosaccharide of the antigen A can be an agonist of hyaluronic acid. Hyaluronic acid belongs to the innate immunity system and is involved in tissue regeneration, as evidenced by the likely manifestation of the pharmacological effects of tetrasaccharide A, as immunostimulating and vasoprotective.

Also, we predicted possible toxic effects (**Table 3**).

The effect of carbohydrate determinants of antigen A on the metabolism of complex lipids is predicted, and the molecular mechanism of action is inhibition of the activity of CDP-glycerol glycerophosphotransferase, ceramide glycosyltransferases, ganglioside galactosyltransferases, and galactosylglucosylceramidase, involved in the synthesis of phospho- and glycolipids, necessary for the construction of cell membrane structures. Glycolipids play an important role in making cell-to-cell contacts; some serve as a kind of receptor for a number of bacterial toxins.

The possibility of an inhibitory effect on a gene expressing telomerase was predicted. About 85% of cancer cells acquire unlimited replicative potential due to the reactivation of a specific telomerase enzyme [12].

After analyzing the data obtained by computer prediction, we can conclude that the immunochemical specificity of the antigenic determinant of antigen A is realized by the characteristic and diverse biological activity and toxicity.

2.2 Antigen B and its biological activity

The antigenic determinant of antigen B contains terminal D-galactose, at position C2 where it has a hydroxyl group.

D-Galactose itself can enter into the reactions of alkylation, acylation, reduction, and oxidation. Analysis of the data of the probable biological activities of the antigenic determinant of antigen B showed 106 out of 501 possible pharmacological effects, 311 of the 3295 probable molecular mechanisms of action, 16 of 57 adverse and toxic effects, 15 of 199 metabolically mediated actions, 3 of 29 effects regulating gene expression, and 6 of 49 effects associated with transport of substances. We chose biological activities with a probability of Pa greater than 0.5. The pharmacological effects of the antigenic determinant of antigen B are shown in **Table 4**.

Toxic effects	Pa	Pi	Pa – Pi
Hypokalemia	0.744	0.033	0.711
Nephrotoxicity	0.734	0.018	0.716
General toxicity	0.691	0.038	0.653
Bronchoconstrictor	0.647	0.035	0.612
Cardiotoxicity	0.644	0.031	0.613
Hepatotoxicity	0.611	0.051	0.560
Embryotoxic	0.504	0.012	0.492

Table 3.
Possible toxic effects of antigen A.

Pharmacological mechanism	Pa	Pi	Pa – Pi
Agonist of membrane permeability	0.863	0.005	0.858
Antibacterial	0.688	0.05	0.683
Immunostimulatory	0.668	0.008	0.660
Antineoplastic	0.630	0.021	0.609
Antifungal	0.622	0.014	0.608
Vasoprotector	0.599	0.042	0.557
Angiogenesis activator	0.591	0.010	0.581
Antiviral	0.583	0.014	0.569
Antibiotic	0.524	0.005	0.519

Table 4.
Predicted pharmacological effects of antigen B.

Many effects and mechanisms of action are common for both antigen A and antigen B, but they are characterized by different degrees of probability of manifestation (Pa value). It is predicted that the antigen B is able to exhibit antibacterial, antiviral, antifungal, and pharmacological effects. According to the literature, group-specific antigens A and B can play a direct role in the susceptibility of the infection, acting as receptors or co-receptors for microorganisms, parasites, and viruses (**Table 5**).

In the study, Kato shows that carbohydrates can act not only as receptors for various microbes but also function as a barrier to infection [13].

Numerous molecular mechanisms of the action of antigen B tetrasaccharide have been predicted, in particular the inhibitory effect on the activity of a number of enzymes involved in the metabolism and stimulating effects on various bioregulators.

Molecular mechanism of action	Pa	Pi	Pa – Pi
Inhibitor of CDP-glycerol phosphotransferase	0.806	0.008	0.798
A-glucosidase inhibitor	0.799	0.001	0.798
Antagonist of membrane integrity	0.764	0.010	0.754
Agonist of hyaluronic acid	0.720	0.001	0.719
Nerve growth factor agonist	0.701	0.009	0.709
Insulin agonist	0.699	0.004	0.695
Antagonist of interferon	0.603	0.017	0.586
Inhibitor of glycerol oxidase	0.638	0.023	0.615
Caspase 8 activator	0.625	0.007	0.618
TNF regulator	0.570	0.014	0.556
B-galactosidase inhibitor	0.558	0.003	0.555
IL-2 agonist	0.526	0.018	0.508
Caspase 3 activator	0.514	0.014	0.500
Glycosyltransferase inhibitor	0.512	0.004	0.508
Inhibitor of protein synthesis	0.509	0.007	0.502

Table 5.
Predicted molecular mechanisms of action of antigen B.

The stimulating effect of oligosaccharide B on the activity of caspases 3 and 8 is predicted; it can act as an agonist of hyaluronic acid, nerve growth factor, interleukin-2, and interferon antagonist. It has been established that galactooligosaccharides selectively increase the content of useful intestinal microbes, as well as C-reactive protein and interleukins [14].

The probable effect of oligosaccharide B on the expression of the telomerase gene (Pa 0.785) and the transport of electrons in mitochondria (Ra 0.504) is shown. Oligosaccharide B is highly likely to be a substrate for cytochrome P-450 2J2 (Pa 0.980), glutathione-S-transferase (0.907), and cyclooxygenase (Pa 0.759).

Using PASS we also identified possible toxic effects (**Table 6**).

The PASS program revealed that the antigenic determinant of antigen B can exhibit a variety of biological effects and molecular mechanisms of action that regulate various physiological and metabolic processes in the body.

The role of carbohydrates as key biological ligands is well known. This is due to the high degree of isomerism, possible within individual carbohydrate units, in a variety of ways to combine monosaccharides, among themselves, different variations of substituents (acetyl, sulfate) and flexibility of carbohydrate chains.

With the development of computational methods for studying protein-ligand interactions, it became possible to determine the type of bonds and the most important positions of atoms “C” in monosaccharides for the formation of an antigen-antibody complex. Using the molecular docking method, Stanca-Kaposta with a group of scientists found that hydrogen bonds and hydrophobic and van der Waals interactions are involved in the formation of an antigen-antibody association [15]. Monosaccharides of antigens can act as acceptors of hydrogen, and amino acid residues of paratope antibodies can serve as hydrogen donors. Most commonly, hydrogen bonds form atoms “C” at positions 3 and 5 in terminal galactose (antigen B) and atoms “C” at position 5 in N-acetylgalactosamine (antigen A). Accessibility of the nitrogen atom in the GalNAc epitope to participate in the formation hydrogen bonds are hampered by the presence of an acetyl group. The “C” atoms in position 6 are involved in hydrophobic and van der Waals interactions, both in galactose and in N-acetylgalactosamine [16].

In studies by J. Milland, it was found that in the N-acetylated version of the epitope of antigen A, the interaction of the acetyl group of the epitope with the tyrosine 35 of the immunoglobulin heavy chain precludes further penetration of the antigen into the antibody’s binding site. In contrast, the Gal epitope of antigen B penetrates deeper into the antibody’s binding site, and the second galactose antigenic determinant participates in hydrophobic interactions with tryptophan at position 36 of the immunoglobulin heavy chain [17]. ABO antigens, like other glycoconjugates, are important intercellular adhesion mediators and participants in signal transduction. Due to the diversity of biological effects manifested, oligosaccharides A and B are evaluated from a new perspective side as biologically active compounds and not only blood group antigens that protect blood cells [18].

Toxic effects	Pa	Pi	Pa – Pi
Hypokalemia	0.763	0.030	0.733
Nephrotoxicity	0.709	0.022	0.687
Bronchoconstrictor	0.703	0.026	0.677
Cardiotoxicity	0.687	0.023	0.664
General toxicity	0.667	0.043	0.624
Hepatotoxicity	0.590	0.057	0.533

Table 6.
Possible toxic effects of antigen B.

Computer modeling exists as a way of combining the microscopic world of molecules and experimental results, which helps to confirm our understanding of metabolic processes and propose new directions for research. For many of the predicted types of activity of compounds in the available literature, experimental evidence has not been found, since these organic compounds are difficult for conformational analysis. Computational methodology makes it possible to obtain structures of compounds at the atomic level and information about activity with an accuracy equivalent to or greater than can be obtained in an experiment. The prognostic and interpretative program PASS has helped to better present the mechanisms of action of the studied metabolites and carbohydrate determinants of antigens A and B in relation to the main body systems.

3. ABO system as a marker of metabolic state

We selected 3678 healthy people with no chronic somatic and dental diseases, as well as latent socially significant viral infections (hepatitis B and C, HIV). Then, we performed a complex biochemical testing of blood with 40 parameters, complete blood count with 21 parameters, and hemostasiograms with 8 parameters. Studies of concentration of total protein; albumin; immunoglobulins A, G, and M; urea; creatinine; uric acid; total and direct bilirubin; C-reactive protein; alanine aminotransferase; aspartate aminotransferase; gamma-glutamyltranspeptidase; creatine kinase and creatine kinase-MB fraction; total cholesterol content; triglycerides; high-density lipoprotein and low-density lipoprotein; lipase activity; the coefficient of atherogenicity; glucose concentration; lactate dehydrogenase; alpha-amylase; alkaline phosphatase activity; and magnesium, calcium, phosphorus, and iron levels were carried out on an automatic biochemical analyzer “Hitachi-902” and “Integra 800” (“Roche,” Japan) with the help of a commercial reagent kit from the company “Roche” (Germany). Intra-laboratory quality control when performing studies was carried out using control serum Precinorm and Precipath (Roche, Germany).

Complete blood count was performed using an automated hematology analyzer Sysmex KX-21 (Roche, Japan) using a commercial set of reagents produced by Roche (Germany). We measured distribution curves for the size of erythrocytes, leukocytes, and platelets, as well as analytical results for 18 parameters: the number of erythrocytes, leukocytes, and platelets; the content of hemoglobin and hematocrit; the average volume of erythrocytes and platelets; the average content and average concentration of hemoglobin in the erythrocyte; the width of the distribution of erythrocytes and platelets by volume; the relative and absolute content of neutrophils, medium cells, and lymphocytes; and the ratio of large platelets. The morphological study of blood cells was performed using a Zeiss light microscope using a unified method. The erythrocyte sedimentation rate was determined using a Panchenkov unified micromethod. The functionality of platelets was assessed by the method of visual detection of the start time of aggregation with different inducers (ADP, with a universal aggregation inducer (UIF), collagen).

Statistical processing of the results was carried out using the statistical package SPSS 12.0 and Microsoft Excel 2007. The statistical characteristics were used: arithmetic average (M), standard arithmetic average error (m), median (Me), max, min, and 95% interval. Indicators of skewness and steepness reflect the asymmetry of distribution; normality tests were evaluated using the Kolmogorov-Smirnov test with the Lilyfors and Shapiro-Wilkie corrections. We used the nonparametric Mann-Whitney U test with the amendment of Bonferroni as an alternative to the Student's t-test. Taking into account the deviation from normality of various values of dispersions, a nonparametric analogue of dispersive analysis was used—the

Kruskal-Wallis analysis. To study the correlation of blood parameters, Spearman's correlation analysis was used.

The data we obtained supplemented information about the connection of certain diseases with blood groups (**Table 7**).

On the basis of the study of the metabolism in the O (I)—AB (IV) blood groups, we determined the trends characterizing their biological variability and identified the parameters associated with a specific blood group (**Table 8**).

According to the specifics of these indicators, we attributed the owners of AV (IV) blood groups to the protein type, since they have the highest protein availability and they are less likely to get ill. It is known that A (II) carriers of the second blood group suffer from a wide range of diseases, including infectious diseases. They have an immunological memory of old and fresh contacts with bacterial and viral agents. The level of lipids can be conditionally attributed to the lipid type. In the presence of the first blood group, a high level of specific and nonspecific protection factors is characteristic. For them, a preferential connection with somatic pathology has been identified. Owners of the third blood group are characterized by sufficient good health. They have the highest level of albumin, cholesterol [19].

The identified features of the metabolic profile in individuals with different blood groups are the rationale for the individualization of standards for each person. In the future, every citizen should have his own health passport.

In accordance with the results obtained, in persons with O (I) blood group, a lower number of erythrocytes are noted with a relatively small volume of cells.

Blood group	Possibility of pathological process development	Authors
O (I)	Peptic ulcer disease	U. Altuhov (1983); G. Drannik,
	Stomach cancer	G. Dizik (1990)
	Hip joint dysplasia	A. Tananyan (2001);
	Myasthenia	S. Garmonov et al. (2006)
	Mutation (F7)	Wang Qing-yun (2007);
	Women papillomavirus infection	Bogdanov N.N. (2015)
	Acute inflammatory processes in women reproductive system	B. Bjorkholmet al (2001)
	Sympathetic ophthalmia	M. Aspholm-Hurtig et al. (2006)
	Laryngeal cancer	I. Taboridze (1991)
	HCV	B. Gehte (1996)
	Risk factor for ovarian reserve	T. Subbotina (2012)
	Hemophilic patients with anemia	E. Shevchenko (2010)
	Rare bleeding disorders	L. Arkhipova (2012)
	Rare intraductal papillary mucinous neoplasm	T. Jin et al. (2016)
	Rare case of malaria	X. Li et al. (2016)
	Rare hepatocellular carcinoma	J. Deng (2016)
	Rare postpartum blood loss	U. Kosyakova
		F. Gilmiarova
		L. Spieza (2018)
		K. Poruk (2018)
	A. Degarege (2018)	
	F. Liu (2018)	
	M. Kahr (2018)	
	Chronic prostatitis with benign prostatic hyperplasia	Shatohin M., Konoplya A., Dolgareva C. A., (2011)
	Bladder cancer	Mayskov I., (2013)
	Urolithiasis	Gusein-zade, R., (2013)
	The increased spontaneous platelet aggregation	Gergesova E., (2011)
	CHD	Biswas S., Ghoshal P.K., Halder B., Mandal N. (2013)

Blood group	Possibility of pathological process development	Authors
A (II)	Coronary artery disease	Z. Chen et al. (2016)
	Rheumatic diseases	E. Suslova (2012)
	CHD	E. Meshalkin (1981)
	Bronchial asthma	M. Freidin et al. (2006)
	Allergies	M. Rafalovich et al. (1982)
	Cholecystitis, cholelithiasis	E. Chichenko, U. Koshel (1975)
	Diabetes mellitus	B. Geht et al. (1995)
	Meningococcal infection	G. Dizik et al. (1986)
	Secondary purulent meningitis	A. Veselov, N. Malushkina (1988)
	Leiden mutation (F5)	
	Prothrombin mutation (F2)	U. Rudometov et al. (1981)
	Platelet receptors mutation (GpIa, GpIIa)	I. Danilov (2010)
	Thromboembolism	R. Vitkovskiy
	HIV	E. Gergesova (2011)
	The combined prevalence of HIV and hepatitis C	G. Liunbruno (2013)
	Hepatitis B	S. Vasan (2016)
	Preeclampsia and fetal hypotrophy	F. Gilmiyarova, V.Radomskaya et al. (2007)
	Iron deficiency anemia	
	Onychomycosis	Shatohin M., Konoplya A. (2011)
	Chronic generalized periodontitis	Shatohin M., Konoplya A. (2011)
	<i>Helicobacter pylori</i> antibodies in oral fluid	Yanchenko M. (2011)
	Chronic prostatitis	Bektasova M., Kapcov V. (2014)
	The combination of chronic prostatitis with benign prostatic hyperplasia	Suslova E., Vasilyeva L. (2012)
	Breast cancer	Gavrilyuk V. (2011)
	Tuberculosis	Doyle B., Quigley J. et al. (2014)
	Atherosclerosis with complications	Rizzato C., Campa D. et al. (2013)
	Appendicular peritonitis in children	Sadreddini M., Rasmi Y. et al. (2011)
	Hemolytic disease of the newborn with A-blood group mothers	B. Mroczek et al. (2018)
	Pancreatic cancer	D. Stakisaitis (2018)
	Gastroesophageal reflux disease	A. Erden
	Asthma	
	Bladder cancer	
Mediterranean fever		
B (III)	Pneumonia	Averbah M. (1985)
	Postoperative infection	Dizik G. (1990)
	Osteochondrosis with radicular syndrome	Subbotina T. (2012)
	Sciatica	Shevchenko E. (2010)
	MGTFR mutation	K. Jamamuru (2012)
	Chronic inflammatory processes in women reproductive system	Shatohin M., Konoplya A. (2011)
	Damage of the coronary artery associated with Kawasaki disease	Suslova E., Vasilyeva L. (2013)
	Chronic prostatitis	Subbotina T., Petuhova A. (2012)
	The combination of chronic obstructive bronchitis with coronary heart disease	Stolbova E., Bane B. (2009)
	Thrombosis	Mortazavi H., Lotfi G. (2015)
	Brain neoplasms	Ramamoorthy B., Varghese S.S. (2015)
	Gingivitis	T. T. Lao et al. (2014)
	Periodontal disease	
HBV		
AB (IV)	Acute respiratory viral infection	L. Grebenshikov (2001),
	Sore throat	S. Garmonov et al. (2006)
	Chronic tonsillitis	Sheng Liming (2013)
	Sinusitis	
	Nasopharynx cancer	

Table 7.
Possibility of pathological process development in ABO blood groups.

ABO blood group				
Characteristic	O (I)	A (II)	B (III)	AB (IV)
Protein	N	N	–	+++
Albumin	–	----	+++	++
α1	+++	N	--	N
α2	+++	N	--	–
β-Globulin	+++	N	--	–
γ-Globulin	+++	----	--	–
IgA	+++	-----	----	N
IgG	N	+++	----	N
IgM	N	+++	----	N
Thymol turbidity test	N	+++	–	-----
CRP	+++	N	-----	--
Urea	+++	N	N	-----
Uric acid	-----	+	N	++
Creatinine	N	N	N	N
Bilirubin	+	–	+	-----
ALT	N	N	++	++
AST	-----	–	++++	N
GGT	++++	----	N	--
Cholesterol	+	----	+++	--
TAG	+++	++++	–	-----
HDL	--	--	N	N
LDL	--	–	--	++
Lipase	–	–	++	-----
Glucose	----	--	++	--
Lactate dehydrogenase	+++	N	+++	-----
Amylase	+++	N	---	++

Table 8. Metabolic characteristic of ABO blood groups (N stands for average results for general population; “+” and “–”—the degree of deviation compared to general population).

The level of hemoglobin in the blood is the lowest, while the saturation of each erythrocyte with hemoglobin is maximum, which ensures full blood transport of gases. A (II) of the second blood group is characterized by the lowest hematocrit value, the average hemoglobin content in one erythrocyte, the average platelet volume, and the maximum indicator of the number of leukocytes, neutrophils, and lymphocytes. Carriers of B (III) blood group showed the largest volume of platelets and the maximum of the average concentration of hemoglobin in one erythrocyte. In persons with AB (IV) blood group, the highest absolute and relative content of lymphocytes, which are the basis of cellular and humoral immunity, is noted. Tendency to lymphocytosis, a higher level of the spectrum of immunoglobulins is an indicator of the intensity of specific resistance and sufficient compensatory reserve in patients with AB (IV) blood group (**Figure 1**).

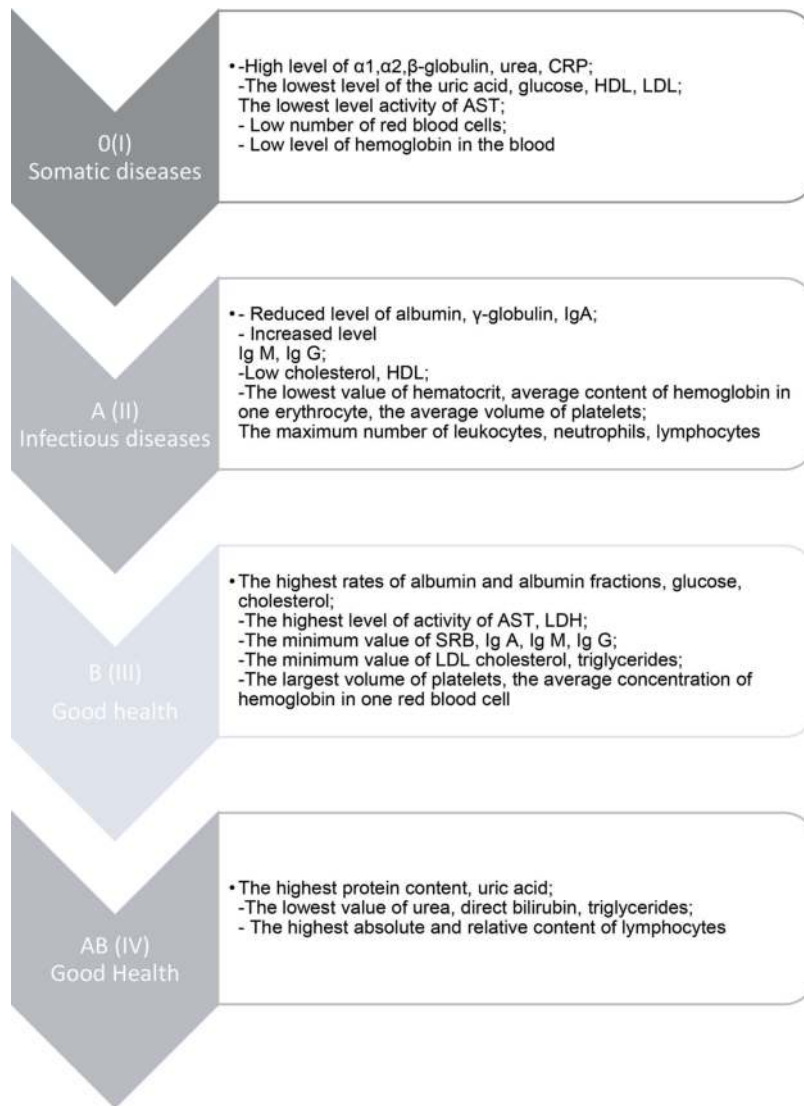


Figure 1.
Biological diversity associated with ABO blood groups.

4. Conclusions

The results obtained *in silico* by computer prediction with PASS program show that antigens A and B influence on intermolecular processes, protein-protein interaction, maintain balance by regulating protein, carbohydrate, lipid metabolism, antioxidant processes, and tissue respiration quite differently which can be explained with their structure and conformational features.

The series of experiments clearly showed biodiversity in metabolic state of different ABO groups which allow us to create metabolic passport for each blood group summarizing the key data [19].

We found out that the carriers of O (I) blood group suffer from somatic diseases more recently than the other blood group carriers, while the carriers of A blood group are predisposed for infectious diseases, and the carriers B (III) and AB (IV) blood groups are more likely to show metabolic stability.

To summarize, methods of molecular modeling and forecasting allow us to broaden the fundamental knowledge about the molecules' properties and to

successfully predict new possible biological effects, as well as molecular mechanisms for its realization in complex interactions of ligands and their targets.

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Conflict of interest

The authors state that they have no conflicts of interest.

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