Post N Med 2016; XXIX(2): 110-112

*Jadwiga Fabijańska-Mitek, Katarzyna Koza

Three new blood group systems

Trzy nowe układy grupowe krwi

Department of Immunohaematology, Centre of Postgraduate Medical Education, Warsaw
Head of Department: Jadwiga Fabijańska-Mitek, PhD, Associate Professor

Keywords

ISBT blood group systems classification, Forssman blood group system, Vel blood group system, CD59 blood group system

Słowa kluczowe

klasyfikacja układów grupowych ISBT, układ grupowy Forssman, układ grupowy Vel, układ grupowy CD59

Summary

In the past four years, five different blood group systems have been defined and introduced to the general ISBT classification as following numbers from 31st to 35th. Two of these blood group systems: Lan and Junior were previously described in the "Progress in Medicine" (2012; XXV(7)) as a review paper. Now we present next three new blood group systems: Forssman, Vel and CD59. Antigen Forssman was described in 1911 on red blood cells of dogs and sheep and for over one hundred years we thought that occurs only on other mammals but not on human and primate RBCs. The investigation of an anomalous ABO subgroup, named A_{pae} in two English families led to the discovery of Forssman glycolipid. Next, its gene was described as the active allele in A_{pae} individuals and inactive in almost all people. The FORS1 antigen is similar to A antigen but is independent of ABO. The Vel was known from 1952 as a high frequency antigen. Now authors discovered its gene *SMIM1* and SMIM1 protein carrying Vel determinants. CD59 is a well-known protein which protects RBCs from complement activity and haemolysis. Antibodies detected in the plasma of transfused CD59-deficient child were shown to be specific for CD59. Her parents were heterozygous for recessive *CD59null* allele. Only seven cases of inherited CD59 deficiency have been published so far and four *CD59null* alleles were described.

Streszczenie

W ciągu ostatnich czterech lat zdefiniowano pięć nowych układów grupowych i wprowadzono je do ogólnej klasyfikacji ISBT (Międzynarodowe Towarzystwo Przetaczania Krwi) jako kolejne numery od 31 do 35. Dwa z tych układów grupowych: Lan i Junior zostały poprzednio opisane w „Postępach Nauk Medycznych" (2012, XXV(7)) w pracy poglądowej. Obecnie przedstawiamy następne z nowych układów grupowych: Forssman, Vel i CD59. Antygen Forssman został opisany w 1911 roku na krwinkach czerwonych psów i owiec i przez 100 lat myśleliśmy, że występuje tylko na krwinkach czerwonych innych ssaków, ale nie u ludzi i naczelnych. Badania nietypowej podgrupy ABO, nazwanej A_{pae} w dwóch angielskich rodzinach doprowadziły do odkrycia glikolipidu Forssmana. Następnie opisano jego gen jako aktywny allel u osób A_{pae} oraz nieaktywny u prawie wszystkich ludzi. Antygen FORS1 jest podobny do antygenu A, ale niezależny od ABO. Vel był znany od 1952 roku jako antygen o bardzo dużej częstości występowania. Obecnie autorzy odkryli jego gen *SMIM1* i białko SMIM1, które jest nośnikiem determinant Vel. CD59 jest dobrze poznanym białkiem, które chroni krwinki czerwone przed działaniem dopełniacza i hemolizą. U dziecka z całkowitym niedoborem CD59 wykryto po transfuzjach przeciwciała, które miały swoistość anty-CD59. Rodzice okazali się heterozygotami i posiadali recesywny allel *CD59null*. Dotąd opublikowano tylko siedem takich przypadków z wrodzonym niedoborem CD59 i opisano cztery allele *CD59null.*

Address/adres:

*Jadwiga Fabijańska-Mitek
Department of Immunohaematology
Centre of Postgraduate Medical Education
ul. Marymoncka 99/103, 01-813 Warszawa
tel. +48 (22) 569-38-20
fax +48 (22) 569-38-29
immunohematologia@cmkp.edu.pl

INTRODUCTION

Starting from the famous discovery of blood groups, precisely the first blood group system ABO by Karl Landsteiner in 1900-1901, until 2011 30 blood group systems were described, including approximately 300 red blood cells (RBCs) antigens (1). The classification and nomenclature of RBCs antigens are supervised by the International Society of Blood Transfusion – ISBT. In the group system there must be at least one antigen, which means that there must be persons producing antibodies against that antigen, absent in them. The biochemical structure of the antigen, the way of inheritance and gene sequence, as well as the antithetic allele must be described. Usually, the biological role of

the antigen or the membrane structure connected with it are studied. In 2012 we described three new group systems in "Progress in Medicine" (2); on one of them, named earlier P, much new information regarding biochemical structure and the way of inheritance was obtained in 2011, and its name was changed into P1PK; publications on two other, at that time new, systems: Lan and Junior were issued in January 2012. Earlier, two common antigens: Lan i Jr^a were known. Their lack, detected in few persons, resulted in alloantibodies production after transfusion and pregnancy, which provided very serious clinical problem, connected with the lack of donors without these antigens. In 2012 the genetic basis was described, meaning the alleles and phenotypes with and without these antigens, as well as their biochemical structure and the function of proteins carrying these antigens. In this way, the criteria of creating of the new group system were fulfilled (3, 4); they took places 32 and 33. In the same year, the group system Forssman was introduced into classification, followed by Vel system in 2013 and CD59 system in 2015 (5). In the case of the Vel system, the situation was similar to Lan and Jr^a, which means, that common antigen Vel was previously known, however the antithetic allele, coding the phenotype Vel negative, the biochemical structure and carrying protein were not known. Characterization of this items enabled the description of the group system. The circumstances of discovery of Forssman and CD59 systems were different and quite surprising. We will describe these three new group systems.

Forssman group system

ISBT 031, symbol: FORS, antigens number: 1, gene: *GBGT1* on chromosome 9 (1, 6).

Antigen is biochemically similar to human group system antigens ABO, P1PK, H, Lewis, I, GLOB. They are all carbohydrates and their specificity depends on the type of the last sugar in glycoprotein or glycolipid chain in red blood cell membrane. It was described in 1911 by Forssman. Since then, the antigen, named after its discoverer, was considered typical for many mammals, excluding primates and human. It was described in dogs, sheep, horses, guinea pigs and mice. Gradually, the antigen structure, the way of inheritance and biological role were discovered. The gene codes protein of the enzyme incorporating N-acetylgalactosamine into appropriate precursor carbohydrate chain. The antigen acts as the receptor for various bacteria. In human, lack of Forssman antigen leads to the creation of natural heterophile antibodies, named Forssman antibodies, which may be the part of the immune response to some infections. At the same time, people have the A antigen, in which the last sugar, N-acetylgalactosamine is the same as in Forssman antigen.

In 1987 in Great Britain, a new subgroup A was described in three families, and it was named A_{pae}. It was thought to be another weak variant of antigen A, after A_2, A_3, A_x, A_m and others. At that time, to determine ABO antigens, human, in other words, policlonal diagnostic sera were commonly used. Sera with anti-A specificity were giving weak reactions with red blood cells of people from the families mentioned above. The lectin ("antibodies" of plants and invertebrates) from *Helix pomatia* with the known anti-A specificity was additionally used, and positive reaction was observed. With the use of human sera, antibodies adsorption and elution was performed, and the reactions were also positive. Then, the name A_{pae} was introduced, from *H. pomatia* and adsorption/elution. When in the '90s monoclonal reagents became widely used in the serological tests, it turned out that none of them reacts with the A_{pae} red blood cells.

At the end of the first decade of the XXI century the studies concerning A_{pae} were resumed. The latest techniques for evaluation of proteins, DNA and RNA, serology and flow cytometry were introduced. It turned out that persons with A_{pae} have glycolipid with the biochemical structure corresponding with the Forssman antigen in animals. It was stated that in this case N-acetylgalactosamine is transported by the enzyme α Fs synthetase and incorporated into the precursor, antigen P, while in the case of group A the enzyme transporting N-acetylgalactosamine is glycosyltransferase, and the precursor chain has the specificity of antigen H. Successive studies detected the gene coding α Fs synthetase in A_{pae} persons. The *GBGT1* gene discovered in these people was different from the allele present in another persons and encoded an arginine to glutamine change at residue 296 (Arg296Gln), which is connected with single nucleotide polymorphism 887 G > A. In this way, inactive protein gains the Forssman synthetase activity. Successive genetic studies revealed that A_{pae} persons had known *O* alleles in the *ABO* gene.

Red blood cells from persons known previously as A_{pae} were incubated with various human sera, and the eluates were prepared. Their reactions in agglutination tests (gel microcolumn technique) were evaluated, and it was found that they were not reacting with any red blood cells from O, A and B donors, whereas the reactions with A_{pae} red blood cells, as well as dogs and sheep erythrocytes were very strong.

Knowing the placement and the structure of the gene, its inactive and antithetic active allele, the enzyme product, substrate and the final product constituting antigen, inducing the immune response as anti-Fs antibodies formation, it was possible to create a new, unexpected in human, Forssman system. It is been proven that the name A_{pae}, used since 1987, was wrong and it has no connection with the group A; the antigen was named FORS-1.

Vel group system

ISBT 034, symbol: VEL, antigens number: 1, gene: *SMIM1* on chromosome 1.

Vel antigen was previously known as the common antigen, present on red blood cells of 99% of peo-

ple (1, 7). Its expression is diverse, and is weaker on erythrocytes of the newborns, in comparison to adults. In 1952 first person without this antigen, producing anti-Vel antibodies was described. Subsequently, Vel-negative persons were detected on average one per 4000 people in Europe, however in Norway and Sweden one per 1500-1700 persons. Anti-Vel antibodies are usually IgM and IgG, and can cause heavy haemolytic posttransfusion reactions and rarely the haemolytic disease of the foetus/newborn. On the basis of family studies and testing of twins from Sweden family it was found that the lack of Vel antigen is inherited recessively. With the use of genetic methods, including MicroMatrix, *SMIM1* gene, containing four exons, was described, coding the SMIM1 protein. The allele present in Vel-negative persons lacks 17 bp in exon 3 (8). Vel antigen carrier, SMIM1 protein constitutes the transmembrane chain, penetrating cell membrane one time, with the extracellular part containing 50 amino acids, probably forming dimmers. The role of this protein remains unknown. Studies with the use of fish *Danio rerio* (zebrafish) and its protein smim1 show that this protein may be connected with erythropoiesis process, utilizing of the iron reserve and heamoglobin synthesis (9). Presence of Vel+ and Vel- phenotypes, characterization of the gene and antithetic allele, as well as description of the protein structure and its antigenic features allowed ISBT to create the new Vel group system.

CD59 group system

ISBT 035, symbol: CD59.1, antigens number: 1, gene: *CD59* on chromosome 11.

CD59 is the surface cluster of differentiation molecule, well known glycoprotein, recognized by monoclonal antibodies. It acts as the molecule protecting cells, including red blood cells, from uncontrolled complement activation. Because of this function it is named HRF (Homologous Restriction Factor), MIRL (Membrane Inhibitor of Reactive Lysis), MACIF (Membrane Attack Complex Inhibitory Factor). CD59 molecules are attached to the cell membrane via glycosylphosphatidylinositol anchor (GPI). Inherited deficit of GPI, connected with the mutation in smaller or bigger haematopoietic cells clone, leads to the production of red blood cells deprived of CD59. It is the cause of the haemolysis connected with complement activation and severe disease – paroxysmal nocturnal haemoglobinuria (PNH). The evaluation with the use of flow cytometry of the population of red blood cells with CD59 deficit is an important element of diagnostics in this disease (10).

Until now, CD59 was not considered as a group antigen, for the first criterion of such classification was not fulfilled, which means that anti-CD59 antibodies were not detected in human. First such case was presented on ISBT congress in 2013 and described in details in 2014 (11, 12). It was the case of the Turkish girl, in which, at the age of two, complete lack of CD59 on red blood cells was detected. As a result of blood transfusion, the girl produced antibodies against common antigen, which means that her serum reacted with red blood cells of all donors. The basis of the anti-CD59 specificity evaluation were tests with the use of various recombined antigens and surface molecules, and the assessment of their ability to inhibit the activity of antibodies. Only CD59 molecules were able to suppress this activity, and the direct antiglobulin test in sensitive gel column technique with the use of this proteins was negative. Weak reactions with red blood cells from PNH patients were confirmatory, which was documented with the use of flow cytometry. CD59 gene sequenced and its three recessive alleles *CD59null* were discovered. They differ in single nucleotide polymorphism. Until now, seven cases of inherited lack of CD59 were described: one in Japan (*123delC*/*361delG*), five unrelated homozygous Jews from North Africa (*266G > A* substitution) and one homozygous Turkish child (*146delA*). In his way, the criteria of creating the new group system CD59 with one antigen were met.

BIBLIOGRAPHY

1. Daniels G: Human blood groups. 3rd ed. Wiley-Blackwell & Sons, Ltd. 2013.
2. Fabijańska-Mitek J, Gieleżyńska A, Koza K: Nowe układy grupowe krwi. Post Nauk Med 2012; 25: 576-582.
3. Helias V, Saison C, Ballif BA: ABCB6 is dispensable for erythropoiesis and specifies the new blood group system Langereis. Nat Genet 2012; 44: 170-173.
4. Saison C, Helias V, Ballif BA et al.: Null alleles of ABGC2 encoding the breast cancer resistance protein define the new blood group system Junior. Nat Genet 2012; 44: 174-179.
5. Storry JR: Five new blood group systems – what next? ISBT Science Series 2014; 9: 136-140.
6. Svensson L, Hult AK, Stamps R et al.: Forssman expression on human erythrocytes: biochemical and genetic evidence of a new histo-blood group system. Blood 2013; 121(8): 1459-1468.
7. Reid ME, Lomas-Francis Ch: The blood group antygen. Facts book. 2nd ed. Elsevier, Philadelphia 2004: 503-504.
8. Storry JR, Joud M, Kronborg Christophersen M et al.: Hemozygosity for a null allele of SMIM1 defines the Vel-negative blood group phenotype. Nat Genet 2013; 45: 537-541.
9. Cvejic A, Haer-Wigman L, Stephens JC et al.: SMIM1 underlines the Vel blood group and influence red blood cell traits. Nat Genet 2013; 45: 542-545.
10. Borowitz MJ, Craig FE, DiGiuseppe JA et al.: Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. Cytometry Part B 2010; 78B: 211-230.
11. Storry JR, Kronborg Christophersen M, Thuresson B et al.: Integrative genomics identifies SMIM1 as a locus of a novel erythrocyte membrane protein and the Vel blood group system. Vox Sang 2013; 105 (suppl. 1): 29.
12. Anliker M, von Zabern I, Hochsmann B et al.: A new blood group antigen is defined by anti-CD59, detected in a CD59-deficient patent. Transfusion 2014; 54: 1817-1822.

received/otrzymano: 04.01.2016
accepted/zaakceptowano: 29.01.2016