The OK blood group system: a review

E.A. Smart and J.R. Storry

History

The very high-incidence RBC antigen Ok[a] was first described by Morel and Hamilton[1] in 1979, after the detection of clinically significant antibodies in the serum of a Japanese woman (Mrs. S.Ko.G.) who had been admitted to the hospital with severe gastrointestinal bleeding. On the basis of extensive serologic tests, it was shown that the antibody was distinct from other antibodies to high-incidence or "public" antigens. The antibody was named anti-Ok[a] and the antigen Ok[a] after the name of the patient who lacked the antigen and developed the antibody. The patient had a history of previous blood transfusions but had not been pregnant. The patient and her family were from a small island in the Inland Sea off the coast of Honshu in Japan. Family studies showed that Ok[a] is inherited. The proband's parents were consanguineous (cousins), and two siblings typed Ok(a–) and one sibling typed Ok(a+). Apart from the two siblings, no other Ok(a–) individuals were found when testing blood samples from more than 400 people living on the same island. No Ok(a–) samples were found when testing blood samples from a further 870 Japanese individuals, 1378 Mexican-Americans, 9053 Caucasians, 261 Asians, 911 Blacks, and 1570 blood donors of undesignated ethnicity. Anti-Ok[a] was not detected in the serum of Mrs. S.Ko.G.'s compatible sister although she had five children, two of whom tested Ok(a+).

The Ok(a–) phenotype is extremely rare. To date, it has been identified in eight families in Japan.[2] However, two other variants have been identified: anti-Ok[a] was identified in the plasma of a woman of Iranian background. Her RBCs gave variable reactivity with a panel of anti-Ok[a], indicating that her phenotype was different from that of previously identified Ok(a–) individuals.[3] Second, an antibody in the plasma of a prenatal Hispanic woman reacted with all RBCs except for three samples of Ok(a–) RBCs. However, her RBCs were reactive with all anti-Ok[a] tested, again indicating a variant phenotype.[4] In both cases, molecular analysis revealed point mutations in the gene that were different from Ok[a] (discussed in more detail later), and both have been assigned provisional numbers by the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology.

Nomenclature

There are three RBC antigens in the OK blood group system (ISBT 024), Ok[a] (OK1), and the provisionally assigned antigens OK2 and OK3. The antigens are located on CD147 encoded by the gene *BSG* on chromosome 19p13.[3] (Tables 1 and 2).[5,6]

Table 1. The OK blood group system

ISBT No.	System name	System symbol	Gene name	Chromosomal location	CD number
024	OK	OK	*BSG*	19p13.3	CD147

Table 2. Blood group antigens within the OK system

Antigen number	OK1	OK2*	OK3*
Antigen name	Ok[a]	OKGV	OKVM

*Provisionally assigned by the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology (2010 meeting report in preparation).

Genetics and Inheritance

In the original family studies[1] two siblings were Ok(a–), and one was Ok(a+), showing that Ok is an inherited characteristic on the basis of the serologic tests. Further studies by Williams et al.,[7] reported in 1988, showed that the Ok determinant is controlled by a single gene *OK* and that the *OK* locus is on chromosome 19, in the region 19pter-p13.2. Using the monoclonal antibody TRA-1-85, which they showed was specific for the Ok-bearing glycoprotein, these authors identified that Ok[a] was carried not only on human RBCs but also on leukocytes and on many immortalized human cell lines of different tissue origin. Spring et al.[6] later demonstrated that Ok[a] antigen was carried on the M6 leukocyte activation antigen (now known as basigin; other synonyms EMMPRIN, CD147, TCSF) and identified the point mutation responsible for the Ok(a–) phenotype (see below). Using immunohistochemical and Western blotting techniques, the Ok glycoprotein was identified on a wide range of tissues.

Molecular Basis

The gene encoding basigin (*BSG*) consists of eight exons and encodes a type I single-pass transmembrane glycoprotein of 269 amino acids. The leader sequence of 21 amino acids is cleaved from the mature membrane-bound protein, which consists of a glycosylated amino-terminal extracellular domain of 187 amino acids that is arranged into two Ig-like subunits and a transmembrane/cytoplasmic domain of 40 amino acids. Sequencing of cDNA extracted from three Ok(a–) individuals showed a unique missense mutation 274 G>A in exon 3, which encodes a Glu92Lys substitution in the amino-terminal Ig-like subunit of the glycoprotein.[6] This substitution was shown by transfection studies in murine NS-0 cells to be solely responsible for the Ok(a–) phenotype. A silent mutation in exon 4 (384T>C) was also identified.

The OK:-2 phenotype described in 2003 was shown to arise from a nucleotide substitution in exon 2 of *BSG*: 176G>T, which encoded the amino acid change Gly59Val.[3] This mutation was found only in the proposita, together with two additional silent single-nucleotide exchanges; 195C>T (Asp65) and 234G>C (Ser78). Interestingly, an additional silent transition, 327T>C (Ala108), was identified in one of the control samples sequenced in this study. Crew and her colleagues also determined the molecular basis of the OK:-3 phenotype; sequence analysis of *BSG* revealed another mutation very close by in exon 2, 178G>A, causing a Val60Met change in basigin.[4]

Biochemistry

As mentioned above, the OK blood group antigens are located on basigin (CD147), which is an immunoglobulin superfamily glycoprotein having an apparent molecular weight on SDS-PAGE of 35,000 to 68,000. It is widely distributed in human tissues and is present on leukocytes and RBCs. Spring and colleagues used the monoclonal antibody MA103 to immunopurify the OK glycoprotein.[6] MA103 defines an epitope on the OK glycoprotein but reacts with Ok(a–) RBCs. They found that the *N*-terminal 30 amino acids were identical to those of the M6 glycoprotein and went on to confirm that M6 was the carrier protein for the Ok^a antigen. M6 glycoprotein was also known as the M6 leukocyte activation antigen, basigin (BSG), or the extracellular matrix metalloproteinase inducer, EMMPRIN.[8]

Extensive studies have been performed on the tissue distribution and the role of CD147 in functions such as cell adhesion and tumor invasion. Basigin induces the production of matrix metalloproteinases in normal fibroblasts as well as in tumor cells. It also induces expression of vascular endothelial growth factor and hyaluronan and thus stimulates angiogenesis in tumor tissue.[9] Basigin has been shown to regulate lymphocyte responsiveness, monocarboxylate transporter expression, and spermatogenesis, and more recently research has revealed its role as a signaling receptor for the extracellular cyclophilin family of proteins.[10] It has also been reported that basigin facilitates HIV-1 infection by an interaction with the virus-associated cyclophilin A on the target cell.[11]

Antibodies in the System

The first reported anti-Ok^a (Mrs. S.Ko.G.) was detected in a patient who had a history of previous blood transfusions, but no history of pregnancy. The anti-Ok^a was determined to be an IgG antibody using the 0.01 M DTT test (which differentiates between IgM and IgG antibodies) and was also shown to be monospecific. The titer was 128 using the antiglobulin technique, and the antibody was reactive against both cord and adult RBCs. One other example of anti-Ok^a has been found in Japan.[2]

Both OK2 and OK3 antigens were identified by the presence of an anti-Ok^a-like specificity in the plasma of both probands, although further examples have not been described.

Despite the paucity of human polyclonal antibodies to antigens on CD147, there are monoclonal antibodies that detect the protein. The monoclonal anti-Ok^a TRA-1-185 is an IgG1 monoclonal antibody that reacts by the antiglobulin test with all RBC samples tested except Ok(a–) RBCs. TRA-1-185 was prepared using spleen cells from a mouse immunized with a human teratocarcinoma cell line.

The monoclonal antibody MA103[12] and a number of other monoclonal antibodies[2] have been produced; these antibodies recognize an epitope on the OK glycoprotein and react with CD147 but do not have Ok^a specificity.

Both human anti-Ok^a and the monoclonal antibody TRA-1-85 react with RBCs that have been pretreated with AET, chymotrypsin, neuraminidase, papain, pronase, and trypsin.[13]

Examples of human Ok^a antibodies are rare. Three novel monoclonal Ok^a antibodies have been generated that may be useful reagents in the laboratory for typing patients' RBCs and for screening donors to find the very rare Ok(a–) blood.[14]

Clinical Significance

The first example of anti-Ok^a was clearly shown to be of clinical significance. RBC survival studies showed that when 10 mL of Ok(a+) whole blood labeled with ^{51}Cr was injected into the patient, only 10 percent of the Ok(a+) RBCs survived 3 hours later. The percentage of donor RBCs surviving was reduced to 2 percent at 6 hours.[1] In addition, a human macrophage assay gave values that correlated with antibodies known to cause significant shortening of RBC survival.

There have been no reports of anti-Ok^a causing hemolytic transfusion reactions or hemolytic disease of the fetus and newborn, perhaps not surprising given the rarity of the phenotype.

Summary

The OK blood group system is rarely encountered in transfusion medicine because of the high incidence of its three antigens and the sparse examples of the corresponding antibodies. The carrier protein basigin, however, is widely distributed throughout the body and is functionally very important as a signaling molecule in a variety of normal and pathogenic processes.

References

1. Morel PA, Hamilton HB. Ok^a: an erythrocytic antigen of high frequency. Vox Sang 1979;36:182–5.
2. Daniels G. Human blood groups. 2nd ed. Oxford, UK: Blackwell Scientific, 2002.
3. Karamatic Crew V, Daniels G, Poole J. A new variant in the Ok blood group system. Transfus Med 2003;13(Suppl 1):32.

4. Karamatic Crew V, Thomas R, Gillen B, Poole J, and Daniels G. A novel variant in the Ok blood group system. Transfus Med 2006;16(Suppl 1):41.
5. Kaname T, Miyauchi T, Kuwano A, Matsuda Y, Muramatsu T, Kajii T. Mapping basigin (BSG), a member of the immunoglobulin superfamily, to 19p13.3. Cytogenet Cell Genet 1993;64:195–7.
6. Spring FA, Holmes CH, Simpson KL, et al. The Ok^a blood group antigen is a marker for the M6 leukocyte activation antigen, the human homolog of OX-47 antigen, basigin and neurothelin, an immunoglobulin superfamily molecule that is widely expressed in human cells and tissues. Eur J Immunol 1997;27:891–7.
7. Williams BP, Daniels GL, Pym B, et al. Biochemical and genetic analysis of the Ok^a blood group antigen. Immunogenetics 1988;27:322–9.
8. Biswas C, Zhang Y, DeCastro R, et al. The human tumor cell-derived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily. Cancer Res 1995;55:434–9.
9. Nabeshima K, Iwasaki H, Koga K, Hojo H, Suzumiya J, Kikuchi M. Emmprin (basigin/CD147): matrix metalloproteinase modulator and multifunctional cell recognition molecule that plays a critical role in cancer progression. Pathol Int 2006;56:359–67.
10. Yurchenko V, Constant S, Bukrinsky M. Dealing with the family: CD147 interactions with cyclophilins. Immunology 2006;117:301–9.
11. Pushkarsky T, Zybarth G, Dubrovsky L, et al. CD147 facilitates HIV-1 infection by interacting with virus-associated cyclophilin A. Proc Natl Acad Sci U S A 2001;98:6360–5.
12. Mattes MJ, Cairncross JG, Old LJ, Lloyd KO. Monoclonal antibodies to three widely distributed human cell surface antigens. Hybridoma 1983;2:253–64.
13. Reid ME, Lomas-Francis C. The blood group antigen factsbook. 2nd ed. San Diego, CA: Academic Press, 2003.
14. Tian MH, Halverson GR. Characterization of three novel monoclonal anti-Ok^a. Immunohematology 2009;25:174–8.

Elizabeth A. Smart, Dip. Med. Tech. SA (Blood Transfusion), Durban, South Africa, and Jill R. Storry, PhD, FIBMS (corresponding author), Clinical Immunology and Transfusion Medicine, Regional and University Laboratories, Klinikgatan 21, SE-22185, Lund, Sweden.