The Ok blood group system: an update

J.R. Storry

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This update of the Ok (OK) blood group system (Smart EA, Storry JR. The OK blood group system: a review. Immunohematology 2010;26:124–6) focuses on new information on the role of basigin (BSG), the carrier molecule of the Ok blood group antigens. No further antigens have been identified since the original review. However, the role of BSG in malaria continues to be explored. Immunohematology 2021;37:18–19.

Summary of the Ok Blood Group Antigens

To date, the Ok blood group system, system 24 in the International Society of Blood Transfusion (ISBT024), comprises three high-prevalence antigens: Ok⁺, OKGV, and OKVM. Only one example of the OKGV⁻ and OKVM⁻ phenotypes has been described, each identified by the presence of a specific antibody to its respective high-prevalence antigen. The Ok(a⁻) phenotype was identified in Japanese people only, and the allele frequency in the gnomAD database is 0.1 percent in the so-called East Asian population. Table 1 shows a summary of information regarding the Ok blood group system antigens.

The Ok antigens are carried on basigin (CD147, extracellular matrix metalloproteinase inducer [EMMPRIN]), a single-pass membrane protein and member of the immunoglobulin (Ig) superfamily. There are two primary isoforms of basigin (BSG); the first (BSG1) is a longer protein of 385 amino acids and three Ig domains, which is found in the retina. The shorter, more widely distributed isoform (BSG2) of 269 amino acids and two Ig domains is found on red blood cells (RBCs) and is commonly referred to as BSG. BSG interacts with a number of proteins in the membrane. It has been shown to bind directly to members of the monocarboxylate transporters and act as a chaperone to the membrane for these proteins. In addition to its interaction with monocarboxylate transporters, BSG forms a lipid raft–associated complex in the membrane with CD44, glucose transporter 1 (GLUT1), and the epidermal growth factor (EGF) receptor. For further details on the function of BSG, the interested reader is referred to the review by Muramatsu.

Role of BSG in Infectious Disease

The role of BSG as an adhesion molecule and its role in the stimulation of tumor growth and invasion were discussed in the original review. BSG was also shown to be an important receptor for a number of pathogens. Pushkarsky et al. showed 20 years ago that BSG facilitated human immunodeficiency virus 1 (HIV-1) infection by interacting with virus-associated cyclophilin A and that the cytoplasmic region of the protein was important for enhancing HIV-1 replication. Measles virus–associated cyclophilin B was shown to bind to BSG on epithelial cells. Although leukocytes are the primary target for the virus, other tissues are known to be infected. Watanabe et al. showed that virion-incorporated cyclophilin B bound to BSG and hypothesized that this interaction could account for symptoms such as pneumonia and diarrhea in measles-infected patients.

Table 1. A summary of information regarding the three known Ok blood group system antigens

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>ISBT allele name</th>
<th>Nucleotide change in BSG</th>
<th>Exon</th>
<th>Predicted amino acid change</th>
<th>Reference</th>
<th>rs number</th>
<th>Identified in</th>
<th>Occurrence in gnomAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>OK:1 or Ok(a⁺)</td>
<td>OK*01.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OK:–1 or Ok(a⁻)</td>
<td>OK*01.–01</td>
<td>c.274G&gt;A</td>
<td>4</td>
<td>p.Glu92Lys</td>
<td>3</td>
<td>rs104894669</td>
<td>Japanese</td>
<td>East Asian 0.1%</td>
</tr>
<tr>
<td>OK:–2 or OKGV⁻</td>
<td>OK*01.–02</td>
<td>c.176G&gt;T</td>
<td>2</td>
<td>p.Gly59Val</td>
<td>1</td>
<td>rs1023817527</td>
<td>Iranian</td>
<td>No data</td>
</tr>
<tr>
<td>OK:–3 or OKVM⁻</td>
<td>OK*01.–03</td>
<td>c.178G&gt;A</td>
<td>2</td>
<td>p.Val60Met</td>
<td>2</td>
<td>rs2229662</td>
<td>Hispanic</td>
<td>European 0.005%</td>
</tr>
</tbody>
</table>

*OK*01.01 encodes Ok⁺, OKGV, and OKVM. Nucleotide changes are based on transcript basigin (BSG)-203 (ENST00000353555.9; https://www.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000172270;r=19:571277-583493;t=ENST00000353555). ISBT = International Society of Blood Transfusion; gnomAd = Genome Aggregation Database.
In 2011, an elegant and systematic screening identified BSG as an important receptor for the malarial parasite, Plasmodium falciparum, binding to the Rh5 ligand.\textsuperscript{10} The PfRh5 protein is important for commitment and invasion into the RBC, so identification of the RBC ligand was an important finding. Interestingly, Ok(a−) RBCs showed a weaker binding affinity for PfRh5 and were not as easily invaded by \textit{P. falciparum}. Aniweh et al.\textsuperscript{11} have shown that the PfRh5–BSG interaction leads to Ca\textsuperscript{2+} signaling, downstream phosphorylation, and transient remodeling of the RBC membrane.

In addition to its important role in malarial infection, BSG was recently implicated as an alternative binding partner for the SARS-CoV-2 virus responsible for COVID-19.\textsuperscript{12–14}

In summary, although there are few variants of BSG that appear to be immunogenic and give rise to blood group antigens, our understanding of the role of BSG in health and disease is expanding.

\textbf{References}

3. Spring FA, Holmes CH, Simpson KL, et al. The Ok\textsuperscript{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.

Jill R. Storry, PhD, Technical Director, Immunohematology, Clinical Immunology and Transfusion Medicine, Department of Laboratory Medicine, Office for Medical Services, Akutgatan 8, SE-22185, Lund, Sweden, jill.storry@med.lu.se.

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