22 Ok Blood Group System

22.1 Introduction

The three antigens of the Ok system, Ok^a (OK1), OK2, and OK3, are of very high frequency and located on the immunoglobulin superfamily (IgSF) molecule basigin, a receptor for *Plasmodium falciparum* invasion. The rare antigen-negative phenotypes result from single amino acid substitutions on basigin (Table 22.1).

22.2 Basigin, the Ok glycoprotein

Immunoblotting of membranes from Ok(a+) red cells with murine monoclonal anti-Ok^a or human alloanti-Ok^a showed that Ok^a is situated on a glycoprotein ranging in apparent MW 35–68 kDa [1]. The N-terminal 30 amino acids of purified Ok glycoprotein [2] were found to be identical to those of basigin, also known as CD147 or EMMPRIN [3,4]. Mouse NS-0 cells transfected with basigin cDNA expressed Ok^a, except when the cDNA was from an Ok(a–) individual [2].

Human basigin cDNA was isolated both by screening a human cDNA library with a fragment of mouse basigin cDNA [5] and by expression cloning of cDNA derived from human T cell and B cell libraries [6]. Basigin is a single chain transmembrane molecule with a signal peptide of 18 amino acids, an N-terminal extracellular domain of 187 amino acids, a 24 amino acid membrane-spanning domain, which contains a single charged glutamic acid residue and a leucine zipper, and a 40-residue cytoplasmic domain. It is a member of the immunoglobulin superfamily of adhesion molecules and receptors (see Chapters 6 and 16) and the extracellular domain is organised into one C2 set and one V set IgSF domains (Figure 22.1) [6,7]. Three *N*-glycans, one on the C2 set domain and two on the V set domain, comprise about 50% of the mass of the glycoprotein.

BSG, the gene encoding basigin, consists of 10.8 kb organised into eight exons (Figure 22.1) [8]. Approximately 95 kb of the 5′ flanking sequence contained three Sp1 and two AP2 sites, but no TATA or CAAT box. *BSG* was mapped to 19p13.3 by fluorescence *in situ* hybridisation [9].

22.3 OK antigens and antibodies

22.3.1 Ok^a (OK1)

The producer of the original anti-Ok^a (S.Ko.G) came from a small Japanese island. Her parents were consanguineous and two of her three siblings were also Ok(a–) [10]. No other Ok(a–) individual was found as a result of testing red cells from 400 people from S.Ko.G's home island, 870 donors from other parts of Japan, 3976 American blood donors of 'Oriental appearance', 9053 white Americans, 1570 African Americans, and 1378 Mexican Americans.

Basigin cDNA from three Ok(a–) individuals contained a mutation encoding Glu92Lys in the N-terminal C2-set IgSF domain [2] (Table 22.1). One other Japanese and one Korean Ok(a–) individuals were also homozygous for the Glu92Lys mutation. Another Ok(a–)Japanese was heterozygous for the Glu92Lys mutation; no mutation was detected in the other allele [11]. No Ok(a–) allele (274A) was detected in 907 Chinese and Tibetans [12].

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Table 22.1 Antigens of the Ok system.

Antigen			Molecular basis*		
No.	Name	Frequency	Nucleotides	Exon	Amino acids
OK1	Ok^a	High	274G (A)	4	Glu92 (Lys)
OK2	OKGV	High	176G (T)	2	Gly59 (Val)
OK3	OKVM	High	178G (T)	2	Val60 (Met)

*Molecular basis of antigen-negative phenotype in parentheses.

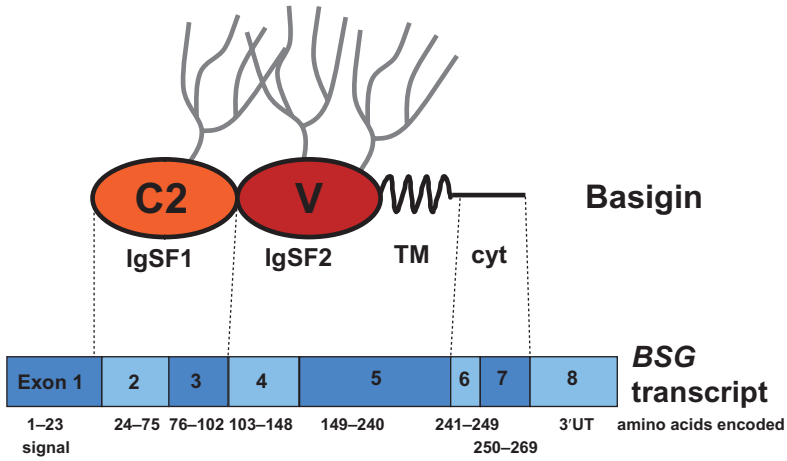

Figure 22.1 Diagrammatic representation of basigin showing the C2 and V set IgSF domains with one and two *N*-glycans, respectively, the transmembrane domain (TM), and the cytoplasmic tail (cyt). Also shown is the relationship of the protein structure to the eight exons of *BSG*, including a 23 amino acid signal peptide.

Ok^a is not affected by treatment of intact cells with trypsin, chymotrypsin, papain, pronase, or sialidase, or with the disulphide bond reducing agent AET.

22.3.2 Anti-Ok^a

S.Ko.G had not been pregnant, but had been transfused at least once. Her Ok(a–) sister had five children, at least two of whom were Ok(a+), but had not made anti-Ok^a. Three hours after injection of radiolabelled Ok(a+) red cells, only 10% remained in the circulation of S.Ko.G. A mononuclear phagocyte assay with anti-Ok^a gave similar values to those obtained with antibodies known to have caused significant shortening of red cell survival [10]. Ideally antigen-negative red cells would be selected for transfusion to a patient with anti-Ok^a, but, owing to their extreme rarity, least incompatible red cells should be used with extreme caution.

IgG, IgM, and IgA monoclonal anti-Ok^a have been produced from spleen cells of mice immunised with human teratocarcinoma or embryonic kidney cell lines [1,13].

22.3.3 OK2 (OKGV) and OK3 (OKVM)

Two alloantibodies resembled anti-Ok^a as they did not react with Ok(a–) red cells, but were made by patients whose red cells reacted with alloanti-Ok^a and at least some monoclonal anti-Ok^a. The patients were homozygous for different mutations encoding single amino acid substitutions in basigin (Table 22.1). Anti-OK2 was produced by a previously transfused woman of Iranian origin with a history of recurrent miscarriages [11] and anti-OK3 by a prenatal patient with no known history of transfusion or previous pregnancy [14].

22.4 Tissue distribution and function of basigin

Basigin is present on all leucocytes and human leukaemic cell lines and has been detected on all human cells examined, although some tissues show differentiation-related expression [1,2,6]. Early haemopoietic progenitors express Ok^a strongly, but the level of expression decreases during erythroid development [15].

Basigin is a pleiotropic molecule with multiple functions (reviewed in [4,16]). It has also been named extracellular matrix metalloproteinase inducer (EMMPRIN) because on tumour cells it induces production of collagenase and other extracellular matrix metalloproteinases (MMP) and basigin may be involved in tumour invasion and metastasis. In healthy tissue, basigin may function in embryonic development or wound healing by causing dermal fibroblasts to increase their MMP production, thus facilitating tissue remodelling [7]. Basigin is a leucocyte activation-associated glycoprotein and is highly expressed on activated T and B lymphocytes, monocytes, and macrophages [6]. Basigin interacts with integrins in the cell membrane and probably regulates binding of cells to laminin in basement membranes [4]. In breast carcinoma cells, interactions between hyaluronan, CD44 (Chapter 21), and basigin contribute to the localisation and function of the monocarboxylate transporters MCT1 and MCT4 in the plasma membrane [17]. Basigin-null mice are blind owing to deficiency of MCTs in the retina. Fetal basigin-null mice have severely impaired implantation and males are sterile [4].

On red cells, basigin also appears to interact specifically with MCT1 and MCT4, which transport monocarboxylates, such as lactate and pyruvate, across the plasma membrane [18]. Basigin functions as a chaperone for translocation of the MCTs to the plasma membrane, where its continued presence and correct conformation are critical for transporter function [19]. In mice, masking of basigin by $F(ab')_2$ fragments of monoclonal anti-basigin disrupts the migration of red cells out of the spleen, inducing splenomegaly, anaemia and, consequently, erythropoietin-mediated erythropoiesis [20]. Basigin may, therefore, play an important role in the recirculation of mature red cells from the spleen into the general circulation.

22.5 Basigin and malaria

Glycophorins A, B, and C, and CR1 are red cell surface proteins with blood group activity that have been recognised as receptors for some strains of the most virulent human malaria parasite, *Plasmodium falciparum* (Chapters 3, 18, and 20). None, however, is required for red cell entry of all strains of the parasite. PfRh5 is a member of the *P. falciparum* reticulocyte-binding protein homologue family that appears to play an essential role in red cell selection and invasion by merozoites of all strains of *P. falciparum* [21]. In 2011, Crosnier *et al.* [22] screened a library of 40 red cell surface proteins with PfRh5 and found that the parasite ligand bound basigin. Red cell invasion by *P. falciparum* was inhibited by soluble basigin, blocked by two basigin (anti-Ok^a) antibodies, and substantially reduced in red cells from two unrelated Ok(a–) individuals and in cultured red cells in which basigin expression was knocked-down by inhibitory RNA. Ok(a–) red cells, which have an altered form of basigin, had reduced affinity for PfRh5. The requirement for basigin in red cell entry applied to 15 strains of *P. falciparum* implying a universal entry pathway and anticipation of the development of an effective malaria vaccine.

References

1 Williams BP, Daniels GL, Pym B, *et al.* Biochemical and genetic analysis of the Ok^a blood group antigen. *Immunogenetics* 1988;27:322–329.

2 Spring FA, Homes 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;27:891–897.

3 Staffler G, Stockinger H. CD147. *J Biol Regul Homeost Agents* 2000;14:327–330.

4 Iacono KT, Brown AL, Greene MI, Saouaf SJ. CD147 immunoglobulin superfamily receptor function and role in pathology. *Exp Mol Pathol* 2007;83:283–295.

5 Miyauchi T, Masuzawa Y, Muramatsu T. The basigin group of the immunoglobulin superfamily: complete conservation of a segment in and around transmembrane domains of human and mouse basigin and chicken HT7 antigen. *J Biochem* 1991;110:770–774.

6 Kasinrerk W, Fiebiger E, Stefanová I, *et al.* Human leukocyte activation antigen M6, a member of the Ig superfamily, is the species homologue of rat OX-47, mouse basigin, and chicken HT7 molecule. *J Immunol* 1992;149:847–854.

7 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: 434–439.

8 Guo H, Majmudar G, Jensen TC, *et al.* Characterization of the gene for human EMMPRIN, a tumor cell surface inducer of matrix metalloproteinases. *Gene* 1998;220:99–108.

9 Kaname T, Miyauchi T, Kuwano A, *et al*. Mapping basigin (BSG), a member of the immunoglobulin superfamily, to 19p13.3. *Cytogenet Cell Genet* 1993;64:195–197.
10 Morel PA, Hamilton HB. Ok[a]: an erythrocytic antigen of high frequency. *Vox Sang* 1979;36:182–185.
11 Karamatic Crew V, Daniels G, Poole J. A new variant in the Ok blood group system. *Transfus Med* 2003;13(Suppl. 1):32 [Abstract].
12 Liu M, Jiang D, Liu S, Zhao T. Frequencies of the major alleles of the Diego, Dombrock, Yt, and Ok blood group systems in the Chinese Han, Hui, and Tibetan nationalities. *Immunohematology* 2003;19:22–25.
13 Tian MH, Halverson GR. Characterization of three novel monoclonal anti-Ok[a]. *Immunohematology* 2010;25:174–178.
14 Karamatic Crew V, Thomas R, Gillen B, Poole J, Daniels G. A novel variant in the Ok blood group system. *Transfus Med* 2006;16(Suppl. 1):41 [Abstract].
15 Bony V, Gane P, Bailly P, Cartron J-P. Time-course expression of polypeptides carrying blood group antigens during human erythroid differentiation. *Br J Haematol* 1999;107:263–274.
16 Agrawal SM, Yong VW. The many faces of EMMPRIN: roles in neuroinflammation. *Biochim Biophys Acta* 2011;1812:213–219.
17 Slomiany MG, Grass DG, Robertson AD, *et al*. Hyaluronan, CD44, and Emmprin regulate lactate efflux and membrane localization of monocarboxylate transporters in human breast carcinoma cells. *Cancer Res* 2009;69:1293–1301.
18 Halestrap AP, Price NT. The proton-linked monocarboxylate transporter (MCT) family: structure, function, and regulation. *Biochem J* 1999;343:281–299.
19 Wilson MC, Meredith D, Fox JEM, *et al*. Basigin (CD147) is the target for organomercurial inhibition of monocarboxylate transporter isoforms 1 and 4. *J Biol Chem* 2005;280:27213–27221.
20 Coste I, Gauchat J-F, Wilson A, *et al*. Unavailability of CD147 leads to selective erythrocyte trapping in the spleen. *Blood* 2001;97:3984–3988.
21 Baum J, Chen L, Healer J, *et al*. Reticulocyte-binding protein homologue 5: an essential adhesin involved in invasion of human erythrocytes by *Plasmodium falciparum*. *Int J Parasitol* 2009;39:371–380.
22 Crosnier C, Bustamante LY, Bartholdson SJ, *et al*. Basigin is a receptor essential for erythrocyte invasion by *Plasmodium falciparum*. *Nature* 2011;480:534–538.