An introduction to blood groups

CHAPTER 1

What is a blood group?

In 1900, Landsteiner showed that people could be divided into three groups (now called A, B, and O) on the basis of whether their red cells clumped when mixed with separated sera from people. A fourth group (AB) was soon found. This is the origin of the term 'blood group'.

A blood group could be defined as, 'An inherited character of the red cell surface, detected by a specific alloantibody'. Do blood groups have to be present on red cells? This is the usual meaning, though platelet- and neutrophil-specific antigens might also be called blood groups. In this book only red cell surface antigens are considered. Blood groups do not have to be red cell specific, or even blood cell specific, and most are also detected on other cell types. Blood groups do have to be detected by a specific antibody: polymorphisms suspected of being present on the red cell surface, but only detected by other means, such as DNA sequencing, are not blood groups. Furthermore, the antibodies must be alloantibodies, implying that some individuals lack the blood group.

Blood group antigens may be:

- proteins;
- glycoproteins, with the antibody recognising primarily the polypeptide backbone;
- glycoproteins, with the antibody recognising the carbohydrate moiety;
- glycolipids, with the antibody recognising the carbohydrate portion.

Blood group polymorphisms may be as fundamental as representing the presence or absence of the whole macromolecule (e.g. RhD), or as minor as a single amino acid change (e.g. Fy^a and Fy^b), or a single monosaccharide difference (e.g. A and B).

Blood group proteins and glycoproteins are integral structures of the red cell membrane. Diagrammatic representations of some blood group proteins and glycoproteins in the membrane are shown in Fig. 1.1. Some pass through the membrane once. These generally have an external N-terminal domain and a cytoplasmic C-terminal domain (Type 1), though
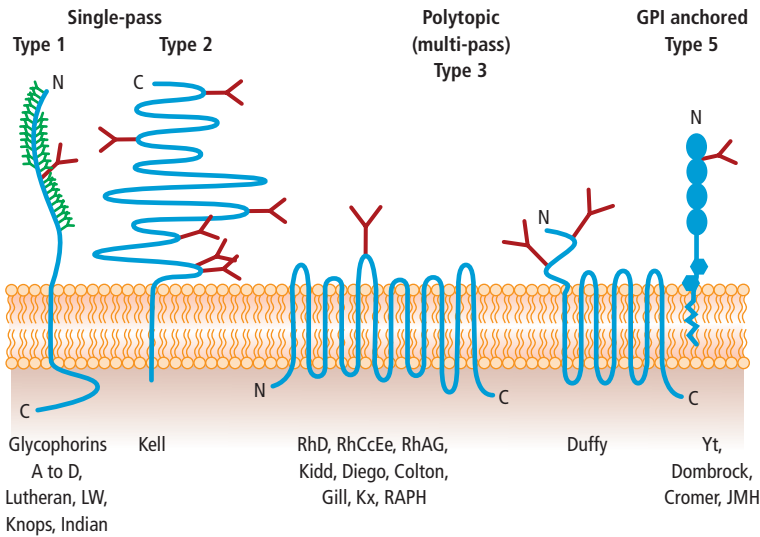
Fig. 1.1 Diagram of different types of blood group active proteins and glycoproteins, based on their integration into the red cell surface membrane. Listed below are examples of blood group antigens for each type. (Type 4 proteins are cytoplasmic and not present in red cells.)

in one case (the Kell glycoprotein) the C-terminus is external and the N-terminus is internal (Type 2). Some are polytopic (Type 3); that is, they cross the membrane several times. Usually both termini are cytoplasmic, but the Duffy glycoprotein has an odd number of membrane-spanning domains and an extracellular N-terminal domain. Finally, some have no membrane-spanning domain, but are anchored to the membrane by a lipid tail (called a glycosylphosphatidylinositol or GPI anchor), which is attached to the C-terminus of the protein through carbohydrate (Type 5). There are no Type 4 glycoproteins, which have no external domain, in the red cell membrane.

Most red cell surface proteins are glycosylated, the only exceptions being the Rh and Kx proteins. This glycosylation may be (1) *N*-glycosylation, large, branched sugars attached to asparagine residues of the amino acid backbone or (2) *O*-glycosylation, smaller glycans (usually tetrasaccharides) attached to serine or threonine residues.

Blood group antibodies

Blood groups are antigens and, by definition, a molecule cannot be an antigen unless it is recognised by an antibody (or T-cell receptor). So all blood group specificities are defined by antibodies. Most adults have antibodies

to the A or B antigens, or to both; that is, they have 'naturally occurring' anti-bodies to those ABO antigens they lack. For most other blood groups corresponding antibodies are not 'naturally occurring', but are only formed as a result of immunisation by transfused red cells or by fetal red cells leaking into the maternal circulation during pregnancy or childbirth.

Blood group antibodies are usually IgM or IgG, although some may be IgA (see Chapter 6). 'Naturally occurring' antibodies are usually predominantly IgM, whereas 'immune' antibodies are predominantly IgG. As a general rule, IgM antibodies will directly agglutinate antigen-positive red cells in a saline medium, whereas most IgG antibodies require potentiators or anti-human globulin to effect agglutination (see Chapter 2).

Clinical importance of blood groups

Blood groups are of great clinical importance in blood transfusion and in transplantation. In fact, the discovery of the ABO system was one of the most important factors in making the practice of blood transfusion possible. Many blood group antibodies have the potential to cause rapid destruction of transfused red cells bearing the corresponding antigen, giving rise to a haemolytic transfusion reaction (HTR), either immediately or several days after the transfusion. At their worst, HTRs give rise to disseminated intravascular coagulation, renal failure, and death. At their mildest, they reduce the efficacy of the transfusion (see Chapter 6).

IgG blood group antibodies can cross the placenta during pregnancy and haemolyse fetal red cells expressing the corresponding antigen. This may cause alloimmune fetal haemolytic anaemia, more commonly known as haemolytic disease of the fetus and newborn (HDFN). Many blood group antibodies have the potential to cause HDFN, but the most common culprits are D and c of the Rh system and K of the Kell system.

Biological importance of blood groups

The biological importance of many blood group antigens is either known or can be surmised from their structure. The following functions have been attributed to blood group antigens: transporters of biologically important molecules across the red cell membrane; receptors of external stimuli and cell adhesion; regulators of autologous complement to prevent red cell destruction; enzymes; anchors of the red cell membrane to the cytoskeleton; and providers of an extracellular carbohydrate matrix to protect the cell from mechanical damage and microbial attack. Very little is known, however, about the functions of the blood group polymorphisms, but it is likely that they arose from selection pressures created by

pathogens exploiting blood group molecules for attachment to the cells and subsequent invasion.

Blood group systems

The International Society of Blood Transfusion (ISBT) recognises 285 blood group antigens; 245 of these are classified into one of 29 blood group systems (Table 1.1 and see http://blood.co.uk/ibgrl/). Each blood group system represents either a single gene or a cluster of two or three closely linked genes of related sequence and with little or no recognised

Table 1.1 The blood group systems.

No.	Name	Symbol	No. of antigens	Gene name(s)	Chromo-some
001	ABO	ABO	4	*ABO*	9
002	MNS	MNS	43	*GYPA, GYPB, GYPE*	4
003	P	P1	1	*P1*	22
004	Rh	RH	49	*RHD, RHCE*	1
005	Lutheran	LU	19	*LU*	19
006	Kell	KEL	25	*KEL*	7
007	Lewis	LE	6	*FUT3*	19
008	Duffy	FY	6	*DARC*	1
009	Kidd	JK	3	*SLC14A1*	18
010	Diego	DI	21	*SLC4A1*	17
011	Yt	YT	2	*ACHE*	7
012	Xg	XG	2	*XG, MIC2*	X/Y
013	Scianna	SC	5	*ERMAP*	1
014	Dombrock	DO	5	*ART4*	12
015	Colton	CO	3	*AQP1*	7
016	Landsteiner–Wiener	LW	3	*ICAM4*	19
017	Chido/Rodgers	CH/RG	9	*C4A, C4B*	6
018	Hh	H	1	*FUT1*	19
019	Kx	XK	1	*XK*	X
020	Gerbich	GE	8	*GYPC*	2
021	Cromer	CROM	13	*CD55*	1
022	Knops	KN	8	*CR1*	1
023	Indian	IN	2	*CD44*	11
024	Ok	OK	1	*BSG*	19
025	Raph	RAPH	1	*CD151*	11
026	John Milton Hagen	JMH	1	*SEMA7A*	15
027	I	I	1	*GCNT2*	6
028	Globoside	GLOB	1	*B3GALNT1*	3
029	Gill	GIL	1	*AQP3*	9

recombination occurring between them. Consequently, each blood group system is a genetically discrete entity. The MNS system comprises three genes, Rh, Xg, and Chido/Rodgers, two genes each, and each of the remainder represents a single gene. Rh and MNS are the most complex systems, with 48 and 43 antigens, respectively; nine systems consist of just a single antigen.

Blood group terminology and classification

Since the discovery of the ABO system in 1900, a multitude of blood group antigens have been identified and many different styles of terminology have been used. These include the following to represent alleles: upper case letters (e.g. A, B; M, N); upper and lower case letters to represent allelic antigens (S, s; K, k); superscript letters (Fy^a, Fy^b), and numbers (Lu6, Lu9). A variety of different styles of terminology have been used even within one system (e.g. Kell system: K, k; Kp^a, Kp^b, Kp^c; K12, K13).

In 1980, the ISBT established a Working Party to devise a genetically based numerical terminology for blood groups. This terminology is based on the blood group systems (Table 1.1). Each system has a three-digit number plus a three to five upper case letter symbol. For example, the Kell system is 006 or KEL (Table 1.2). Each antigen within that system has a three-digit number. K is 001 and Kp^a is 003, and so become 006001 or KEL1 and 006003 or KEL3, respectively. The full numerical symbol is seldom used and the alpha-numerical symbols, with the redundant zeros removed, are more commonly employed. Phenotypes consist of the system symbol, followed by a colon, followed by a list of antigens shown to be present. Absent antigens are also listed, preceded by a minus symbol (Table 1.2). Genes have the system symbol followed by an asterisk, followed by the number of the antigen encoded by the allele.

Table 1.2 Some examples of blood group terminology.

	Original	Numerical
Antigen	K, k, Kp^a, Kp^b	KEL1, KEL2, KEL3, KEL4
	Co^a, Co^b	CO1, CO2
Phenotype	K− k+ Kp(a−b+)	KEL: −1, 2, −3, 4
	Jk(a−b+)	JK: −1,2
Gene	*K, k, Kp^a, Kp^b*	*KEL*1, KEL*2, KEL*3, KEL*4*
	Fy^a, Fy^b	*FY*1, FY*2*
Genotype/haplotype	*kKp^b/kKp^b*	*KEL*2,4/2,4*
	MS/Ms	*MNS*1,3/1,4*

For an antigen to join an existing blood group system there must be substantial evidence that it is encoded by the gene (or cluster of genes) producing the other antigens in the system. For one or more antigens to form a new system, they must be shown to be genetically discrete from all the existing systems.

Because the ISBT terminology is based on the blood group systems, it functions as a blood group classification. It is not essential to use the numerical terminology. Indeed, it is not generally used in this book. It is, however, important to understand it, so as to understand the classification of blood groups.

Some blood group antigens have not been allocated to systems, owing to insufficient genetical evidence. If they are of low frequency, they are placed in the 700 Series of antigens and if of high frequency, in the 901 Series. If two or more antigens are categorised together on the basis of genetical, serological, or biochemical information, but, due to lack of appropriate evidence, cannot be allocated to a system or form a new system, then they can form a blood group collection. The series and collections are described in Chapter 5.