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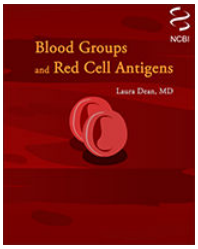

8. The Kell blood group

The Kell blood group system is complex and contains many antigens that are highly immunogenic. These antigens are the third most potent, after those of the ABO and Rh blood groups, at triggering an immune reaction.

Antibodies that target Kell antigens can cause transfusion reactions and hemolytic disease of the newborn (HDN). In the case of HDN, ABO and Rh incompatibility are more common causes. However, disease caused by maternal anti-ABO tends to be mild, and disease caused by maternal anti-Rh can largely be prevented. The infrequent cases of HDN caused by Kell immunization tend to result in severe fetal anemia because maternal anti-Kell target fetal red blood cell (RBC) precursors, suppressing the fetal production of RBCs.

At a glance

Antigens of the Kell blood group.

Number of antigens	**25** The K antigen is one of the most clinically significant Kell antigens.
Antigen specificity	**Protein** Amino acid sequence determines the specificity of Kell antigens
Antigen-carrying molecules	**Glycoprotein with enzymatic function** The Kell glycoprotein is a transmembrane, single-pass protein that carries the Kell antigens. It is an endothelin-3-converting enzyme; it cleaves "big" endothelin-3 to produce an active form that is a potent vasoconstrictor (1).
Molecular basis	**The KEL gene encodes the Kell antigens.** KEL is highly polymorphic. It has two major codominant alleles, k and K, which result from a SNP (698C→T), and the corresponding k and K antigens differ by a single amino acid change (T193M).
Frequency of Kell antigens	**~100%:** k, Kp^b, Ku, Js^b, K11, K12, K13, K14, K18, K19, Km, K22, K26, K27 **K antigen: 2%** in Blacks, **9%** in Caucasians, up to **25%** in Arabs **~2%:** Kp^a, $U1^a$ **~0.01%:** Js^a (0.01% in Caucasians, 20% in Blacks), Kp^c, K23 Others: K17 (~0.3%), K24 (rare), VLAN (rare), K16 (unknown) (2)
Frequency of Kell phenotypes	**K-k+** in 91% Caucasians and 98% Blacks **K+k-** in 0.2% Caucasians and is rare in Blacks **K+k+** in 8.8% Caucasians and 2% Blacks **Kp (a-b+)** in 97.7% Caucasians and 100% Blacks **Js (a-b+)** in 100% Caucasians and 80% Blacks (2)

Antibodies produced against Kell antigens.

Antibody type	**IgG** IgM is uncommon

continued from previous page.

Antibody reactivity	**Does not bind complement** If hemolysis does occur, it is extravascular in nature.
Transfusion reaction	**Can cause a severe hemolytic transfusion reaction** Anti-K and anti-Ku are capable of causing a severe reaction. A milder reaction is caused by anti-k, anti-Kp^a, anti-Kp^b, anti-Js^a, and anti-Js^b.
Hemolytic disease of the newborn	**Can cause severe fetal anemia** Kell isoimmunization is the third most common cause of HDN after Rh and ABO. Anti-Kell causes severe fetal anemia by suppressing fetal RBC synthesis (3, 4).

Background information

History

The Kell blood group system was discovered in 1946. It was named for Mrs. Kelleher, a patient in whom anti-Kell antibodies had resulted in hemolytic disease of her newborn child (the child's RBCs expressed K antigen which were bound by anti-K in the mother's serum). Since this time, a total of 25 Kell antigens have been discovered and they are expressed in different frequencies in different populations. But the original K antigen remains of prime importance in transfusion medicine and HDN.

Nomenclature

- Number of Kell antigens: 25
- ISBT symbol: KEL
- ISBT number: 006
- Gene symbol: KEL
- Gene name: Kell blood group

Basic biochemistry

Common Kell phenotypes

The Kell blood group system is complex. The Kell locus is highly polymorphic and gives rise to many Kell antigens. There are, however, two major codominant allelic genes that produce two important antigens: K and k (previously known as Kell and Cellano, respectively), which differ by a single amino acid. The k antigen is more common than the K antigen in most populations, the K-k+ phenotype is found in 98% of Blacks and 91% of Caucasians (2).

Uncommon Kell phenotypes

Null phenotype

The Kell system has a rare null phenotype, K_o, in which RBCs lack all Kell antigens. Individuals with this phenotype are healthy but produce anti-Ku when they encounter RBCs that do express Kell antigens. Anti-Ku is capable of causing a mild to severe transfusion reaction with at least one fatal case being reported (5). Therefore, if K_o individuals ever require a blood transfusion, they should only be transfused with K_o blood products.

McLeod syndrome

In the RBC membrane, the Kell glycoprotein is covalently linked to the XK protein, a multipass membrane protein thought to have a role in transport. In the absence of XK, a condition called McLeod syndrome, Kell antigens are only weakly expressed and the RBCs are abnormal with spiky projections (acanthocytosis). Systemic

findings include muscular dystrophy, cardiomyopathy, psychiatric disturbances, and neurological defects, such as loss of reflexes and movement disorders (1).

Expression of Kell antigens

Kell antigens were once thought to be restricted to blood cells of erythroid origin (i.e., RBCs and their precursors), but they have recently been found to be expressed in myeloid tissues (6, 7).

The Kell antigen is also expressed in a small amount on a number of organs including lymphoid organs, muscle (both cardiac and skeletal), and the nervous system (2).

Functions of the Kell glycoprotein

The Kell glycoprotein is an endothelin-3-converting enzyme. By cleaving an inactive precursor (big endothelin-3), it creates active endothelin-3, which is a potent constrictor of blood vessels.

Clinical significance of Kell antibodies

The K antigen is the most immunogenic antigen after the antigens of the ABO and Rh blood group systems.

Transfusion reactions

Anti-Kell antibodies are usually of the antibody class IgG (IgM is far less common). The antibodies that have been implicated in causing transfusion reactions, which can occasionally be severe in nature include, anti-K, anti-k, anti-Kp^a, and anti-Js^b (2). The production of anti-Ku in patients with K^o has resulted in a fatal hemolytic transfusion reaction (5).

Hemolytic disease of the newborn

Anti-Kell is an important cause of HDN. It tends to occur in mothers who have had several blood transfusions in the past, but it may also occur in mothers who have been sensitized to the Kell antigen during previous pregnancies.

In contrast to Rh and ABO sensitization, HDN attributable to Kell sensitization is caused by anti-K suppressing the fetal production of RBCs. Unlike Rh and ABO, Kell antigens are expressed on the surface of RBC precursors, and anti-K promotes the immune destruction of K+ erythroid early progenitor cells by macrophages in the fetal liver (rather than only mature fetal RBCs). Because the RBC precursors do not contain hemoglobin, less bilirubin is released during the hemolysis, and jaundice in the newborn period is less common. However, the underlying anemia may be severe (8).

Various case studies have reported the following antibodies causing HDN: anti-K (7, 9-12), anti-k (13), anti-Kp^a (14), anti-Kp^b (15), anti-Js^a (16, 17), anti-Js^b (16, 18), and anti-$U1^a$ (19).

Molecular information

Gene

The KEL gene is found on chromosome 7, at 7q33, and contains 19 exons that span more than 21 kbp of genomic DNA. The KEL gene is highly polymorphic, with different alleles at this locus encoding the 25 antigens that define the Kell blood group.

View the sequences of KEL alleles at the
dbRBC Sequence Alignment Viewer

The K/k blood group polymorphism represents a point mutation resulting in an amino acid switch from threonine 193 (in the k antigen) to methionine 193 (in the K antigen) in the Kell glycoprotein. The K antigen is more potent at triggering an immune reaction than the k antigen. Its higher level of antigenicity may be because, unlike other Kell antigens, it is *not* glycosylated at residue 191 (20).

Other common Kell blood group polymorphisms include Kp^b/Kp^a which arises from a 961C→T SNP causing the R281W amino acid change, and Js^b/Js^a which arises from a 1910T→C SNP causing the L597P amino acid change (21).

Protein

The Kell protein is a polypeptide chain of 732 amino acids in length that becomes glycosylated at five different sites. It makes a single pass through the RBC membrane.

The Kell protein is anchored to the surface of the RBC by being linked to an integral RBC membrane protein, XK, by a single disulfide bond. XK is a transmembrane protein that traverses the RBC membrane 10 times. If XK is absent, the multisystemic syndrome, McLeod's syndrome, results.

The Kell protein has both sequence and structural homology to a large family of zinc-dependant endopeptidases (enzymes that cleave proteins within the peptide chain, not near the N or C terminus). The Kell protein and other proteins in this family contain a pentameric sequence which is essential for zinc binding and catalytic activity.

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