Review

The Vel blood group system: a review

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The blood group antigen Vel has been one of immunohematology's greatest enigmas: the variation in antigen strength from one individual to another, the property of anti-Vel to readily hemolyze Vel+ red blood cells (RBCs), and the difficulty to screen for sufficient numbers of Vel– blood donors had made Vel a tough nut to crack. In 2013, a small, previously unknown protein called small integral membrane protein 1 (SMIM1) was identified on the RBC by three independent research groups using different approaches, and all three groups demonstrated that Vel– RBCs lacked SMIM1. This discovery correlated with homozygosity for deletion c.64_60del in *SMIM1* and meant that for the first time there was a universal method to screen for Vel– blood donors. This finding was not the whole answer, however, and an explanation behind the variability in antigen strength was later shown to be due to polymorphism in *SMIM1* intron 2, a region that is responsible for gene transcription. Clinically, anti-Vel is important and has caused severe transfusion reactions, although hemolytic disease of the fetus and newborn caused by anti-Vel is uncommon. However, while screening for Vel– blood donors has become easier, the function of SMIM1 is still unknown, and despite its well-conserved sequence across the animal kingdom, the enigma continues. ***Immunohematology* 2017;33:56–59.**

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The first report of anti-Vel was published in the French journal *Revue d'Hematologie* by Sussman and Miller in 1952 and concerned a patient in New York who received 2 units of crossmatch-compatible blood.[1] As reviewed by Sussman some 10 years later, the original proband was a patient with colon cancer who suffered a severe and immediate transfusion reaction following the second transfusion in a 3-day period. Although she had a history of uneventful pregnancies and transfusions prior to this occasion, her serum several days post-transfusion was strongly incompatible with the second unit transfused, although it remained compatible with the first unit.[2] Subsequent screening of 10,000 donors with the patient's serum in New York revealed only 4 compatible units in addition to the serendipitous compatible unit. This antibody displayed a clear dosage effect reacting with a titer of 64–128 with red blood cells (RBCs) from one group of individuals and more weakly (titer of 8–16) with RBCs from a second group that included the (presumed heterozygous) children of the patient.[2]

A second example of anti-Vel followed 3 years later, described by Levine et al., in a 67-year-old woman diagnosed with diverticulitis of the colon.[3] She had received 1 unit of crossmatch-compatible blood 6 years previously following surgery for removal of an ovarian cyst, and she had a history of two pregnancies. At the time of the report, the patient's serum contained a hemolytic antibody that was shown to be compatible only with the RBCs of the original proband and incompatible with over 1000 donors tested. Hemolytic reactivity has been a hallmark of anti-Vel, and Sussman had reported earlier that anti-Vel from 12 of 19 patients hemolyzed RBCs in vitro.[2]

In a study of Vel– families in northern Sweden, a disproportionate number of Vel– individuals were found to demonstrate a P_2 phenotype,[4] although this apparent association has been subsequently disproved.[5] An association between Vel and Gerbich antigens was first demonstrated in a patient with anti-Ge.[6] The patient's RBCs were nonreactive with some Vel antibodies. Subsequent testing of 14 Vel antibodies with eight examples of Ge:–2,–3,4 RBCs revealed three antibodies that failed to react with at least four of the RBC samples, and two other antibodies that were nonreactive with some. Subsequent elegant flow cytometry studies by Haer-Wigman et al.[7] showed that there was no differential expression of glycophorin C (GPC) on Vel– RBCs when compared with that on Vel+ RBCs, but that variation could be attributed to the rs1175550 single-nucleotide polymorphism known to influence Vel antigen expression (see the Molecular Basis section).

Lastly, serological evidence suggested that the high-prevalence antigen ABTI was related to Vel; in the original report of ABTI, it was noted that of eight Vel– samples, six reacted only weakly with anti-ABTI, and one did not react at all.[8] In a second report, two new examples of anti-ABTI reacted only weakly with several examples of Vel– RBCs, confirming a serological connection, at least.[9] Based on these reports, an International Society of Blood Transfusion (ISBT) collection, 200212, was created to accommodate Vel and ABTI. ABTI was returned to the 901 series (901015), following the identification of *SMIM1* as the gene responsible for the Vel– phenotype. Indeed, *SMIM1* sequence analysis of ABTI– individuals did not reveal a mutation that could account for the phenotype, and thus the ABTI blood group antigen remains uncharacterized.[10]

Although Vel has been detected on fetal RBCs from 12 weeks of gestation, it is expressed less strongly on cord cells than on adult cells.[11,12] Vel is not detected on lymphocytes, granulocytes, or monocytes.[13]

The nomenclature for Vel is presented in Table 1.

Table 1. Nomenclature of Vel blood group system

Blood group system	Vel
Blood group system number	34
Antigen number	VEL1
Alternate name	Vel
Prevalence	High
Gene	*SMIM1*
Chromosomal location	1p36

Genetics/Inheritance

The Vel blood group antigen is inherited as a dominant trait. It is dependent on the expression of small integral membrane protein 1 (SMIM1), encoded by *SMIM1,* which is located on chromosome 1 at 1p36. The prevalence of the Vel– phenotype in Europe varies from ~1 in 5000 in southern regions to ~1 in 1200 in Sweden.[7,14,15] Its prevalence is much lower in people of African and Asian descent, where the prevalence of the mutated allele has been observed as 0.56 percent and 0.6 percent of these respective populations.[7]

Molecular Basis

Although Vel has been well defined serologically and there is a large set of observational data concerning the antibodies produced in response to Vel, nothing is known about the structure that carries Vel. The molecular basis of the Vel– phenotype was identified as a deletion of 17 bp in the coding region of the *SMIM1* gene, *SMIM1* c.64_80del.[14,16,17] This deletion has been shown to be the primary molecular basis for the Vel– phenotype in all populations. Expression of Vel can be very weak, however, and varies considerably from the RBCs of one individual to another. Missense mutations at nucleotide position 152 (c.152T>A or c.152T>G; p.Met51Lys and p.Met51Arg, respectively) have been identified in individuals who type as Vel+^{w},[16,17] and expression studies in an HEK293T cell line using constructs with these two mutations demonstrated that Vel was markedly diminished in cells transfected with the *SMIM1* c.152A construct and not expressed at all by HEK293T cells transfected with *SMIM1* c.152G.[7] Table 2 lists the molecular changes in the coding region of *SMIM1* associated with the Vel antigen.

The identification of the molecular basis underlying the Vel– phenotype has enabled the development of polymerase chain reaction–based screening. This strategy has been successfully used to identify new Vel– donors in several laboratories.[7,14,15,18]

There are other noncoding polymorphisms in the regulatory region in *SMIM1* intron 2 that have also been shown to correlate with Vel antigen expression. The rs1175550 was first identified in 2012 in the investigation of genes that affect RBC morphology and function and was shown to be correlated with a lower mean corpuscle hemoglobin count (MCHC).[19] This single nucleotide polymorphism has been extensively investigated, and the more common allele, rs1175550A, is associated with weak expression of Vel. The less frequent allele, rs1175550G, is associated with stronger expression that is zygosity-dependent.[7,20] The mechanism for this is not entirely understood, although the change of A>G disrupts a recognition site for the erythroid-specific transcription factor, GATA-1. It was first postulated that this GATA-1 site acted as a negative regulator for *SMIM1,* but further evaluation of this region has shown that there are other transcription factors that play a role—for example, TAL1, which was shown to bind preferentially to the rs1175550G allele and to upregulate Vel antigen expression.[21,22] Another polymorphism, a trinucleotide insertion, rs143702418, also correlates with *SMIM1* and with Vel antigen expression; the less frequent insertion is associated with downregulation and thus reduced expression.[22]

Biochemistry

SMIM1 encodes SMIM1. This protein is a single-pass membrane protein of 78 amino acids whose physiological role

Table 2. Alleles of the Vel blood group system recognized by the ISBT†

Phenotype	Allele name	Nucleotide change in *SMIM1*	Exon	Predicted amino acid change
Vel+	*VEL*01*			
Vel–	*VEL*–01*	c.64_80delAGCCTAGGGGCTGTGTC	3	p.Ser22Glnfs
Vel+^{w}	*VEL*01W.01*	c.152T>A	4	p.Met51Lys
Vel+^{w}/Vel–	*VEL*01W.02*	c.152T>G	4	p.Met51Arg

ISBT = International Society of Blood Transfusion; w = weak.

†Only the polymorphisms in the coding region that have been found to affect antigen expression are shown. For further variation in the gene, see www.erythrogene.com and www.ensembl.org.

and membrane topology remain unclear. Arnaud et al.[23] used recombinant hybrids of SMIM1 and Flag protein, as well as Kell-SMIM1 hybrids, in different orientations to show that SMIM1 was a type II membrane protein with an extracellular C-terminus. Western blotting experiments following different protease treatments of intact RBCs indicated α-chymotrypsin sensitivity, however, which suggested that the protein exposed the N-terminus extracellularly.

There is more work to be done! SMIM1 does not appear to be glycosylated but is readily phosphorylated in vitro.[23] Phosphoproteomics analysis of human RBCs following invasion by *Plasmodium falciparum* showed that SMIM1 was phosphorylated in association with the schizont stage of the parasite life cycle,[24] and although any role of SMIM1 in parasite invasion has not been described, these results are tantalizing. It is unknown whether SMIM1 associates with other (glyco) proteins in the RBC membrane, but it is a very small protein, and it would not be atypical for it to form a functional complex.

Antibodies in the System

Anti-Vel is the only antibody in the Vel blood group system. Antibodies to Vel are produced after immunization and are not naturally occurring. Unlike most antibodies to blood group antigens, anti-Vel sera are usually a mixture of IgM and IgG, fix complement readily in vitro, and demonstrate a wide thermal range of reactivity.[25] Blood group antigen-specific IgM antibodies that do not readily class-switch to IgG antibodies are suggestive of an immune response to carbohydrate antigens such as A, B, H, P, and so forth. Unlike anti-Vel, however, these antibodies are almost invariably naturally occurring. Many Vel antibodies are readily adsorbed by rabbit RBCs or red cell stroma, although this is apparently not a specific adsorption but more that these reagents preferentially adsorb IgM antibodies.[26,27] The ability to hemolyze Vel+ RBCs, at least in the days when serum was used for testing, has been a hallmark of anti-Vel and, in his review, Sussman reported that anti-Vel from 12 of 19 patients hemolyzed RBCs in vitro.[2]

The serological reactivity of anti-Vel with RBCs treated with papain, ficin, trypsin, and α-chymotrypsin is greatly enhanced, and serum containing anti-Vel will often readily hemolyze papain-treated RBCs, for example. Vel antigen is also unaffected by neuraminidase treatment.[28] The effect of 200 mmol/L dithiothreitol (DTT) treatment of Vel+ RBCs varies, with some anti-Vel recognizing a DTT-sensitive antigen, while the majority are unaffected.[14,29] Rainer et al.[29] demonstrated that of 11 antibodies tested, one sample was completely nonreactive with DTT-treated RBCs, four samples showed a decrease in reactivity of greater than or equal to 1+, and six samples were unaffected by the DTT treatment. Additionally, one report described the enhancement of anti-Vel reactivity following treatment of test RBCs with sodium hypochlorite.[30]

Screening for Vel– blood donors has been hampered by the lack of suitable anti-Vel reagent, and blood centers have been restricted to limited volumes of the antibody from patients. Recently, a human monoclonal anti-Vel was produced by the French blood service, thus providing the potential for a long-awaited serologic screening and typing reagent.[31] As of today, more than 950,000 blood donations in France have been screened for Vel with this monoclonal reagent, and 320 new Vel– blood donors were identified (unpublished data, personal communication with Michel Hennion, Etablissement Français du Sang Nord de France, Lille, France).

Clinical Significance

Anti-Vel is clinically important and has caused transfusion reactions ranging from mild to severe.[28] In one case in which reactivity of an anti-Vel was attributed to a clinically insignificant cold-reactive antibody, 2 units of Vel+ blood were transfused, and the patient suffered a severe transfusion reaction and died 8 hours later.[32] In France, it has been estimated that a mean of one severe hemolytic transfusion reaction caused by anti-Vel occurred per year between 1995 and 2009 (mean annual incidence of 1.7 per 10^8 inhabitants).[5] Hemolytic disease of the fetus and newborn caused by anti-Vel has been described but is rare,[33,34] possibly due in part to the weaker expression of Vel on cord RBCs. Examples of autoanti-Vel have also been reported. The first described was an IgM autoanti-Vel in an untransfused male patient with aplastic anemia.[35] No shortened survival of ^{51}Cr-labeled Vel+ RBCs was demonstrated. In contrast, a young girl with steroid-resistant warm autoimmune hemolytic anemia and an associated autoanti-Vel suffered a severe transfusion reaction when given 2 units of Vel+ blood.[36] Vel– blood was tolerated well.

In conclusion, the Vel blood group system is a simple system consisting of just one antigen to date. Its complexity lies in the variation in antigen expression, which in turn makes anti-Vel sometimes difficult to identify, as well as the lack of availability of Vel– blood donors in most parts of the world. Vel is an antibody to be treated with respect because even weak antigen expression can have clinical consequences, as witnessed with the very first patient.

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