24 JMH Blood Group System

24.1 Introduction

The original John Milton Hagen (JMH1) antigen represents determinants on the signalling protein semaphorin 7A (Sema7A, CD108). JMH:–1 is usually an acquired phenotype most often found in people over 50 years old. Inherited variants of JMH lacking antigens JMH2 to JMH6 represent amino acid substitutions in Sema7A resulting from homozygosity for missense mutations in *SEMA7A*.

24.2 The JMH glycoprotein is semaphorin 7A (CD108)

Semaphorins are glycoproteins found throughout the animal kingdom; at least 20 have been found in man. Semaphorins exist as secreted, membrane-spanning, and GPI-linked forms and consist of a sema domain, a highly conserved form of a seven-blade β-propeller fold, linked through a cysteine-rich region to an immunoglobulin domain [1–3].

SEMA7A cDNA was cloned by screening human cDNA libraries with sequences derived from human expressed sequence tags (EST) identified by comparison with a herpes viral semaphorin [4] and independently from a partial amino acid sequence of a glycoprotein isolated by immunoprecipitation with a CD108 antibody [5]. Nascent Sema7A is a 666 amino acid polypeptide, which includes a 44 amino acid signal peptide and an 18 amino acid GPI anchor motif. The mature protein consists of a 438 amino acid sema domain, containing four *N*-glycosylation and six myristoylation sites, plus an 86 amino acid immunoglobulin domain of the C2 set, containing one *N*-glycosylation site (Figure 24.1) [3–6].

SEMA7A consists of 14 exons and was localised to 15q22.3-q23 by radiation hybrid mapping and fluorescence *in situ* hybridisation [4,6].

Immunoblotting and immunoprecipitation with human anti-JMH and with a monoclonal JMH-related antibody (H8) showed that JMH is located on a structure of apparent MW 76 kDa in JMH+ red cells, but not in JMH– cells [7]. This GPI-linked protein, which is cleaved from the red cell by phosphatidylinositol-specific phospholipase C and is not present on the complement-sensitive population of red cells (PNHIII) of patients with paroxysmal nocturnal haemoglobinuria [7,8] (see Chapter 19), was subsequently shown to be Sema7A [9]. Sema7A contains 19 cysteine residues, so some disulphide bonding is likely; JMH expression is destroyed by disulphide bond reducing agents. JMH variants have been shown to be associated with mutations in *SEMA7A* (Section 24.3). JMH– red cells have normal expression of the GPI-linked proteins CD55 and CD59, so their Sema7A deficiency does not result from defective biosynthesis of the GPI anchor [6].

24.3 JMH (JMH1)

Sabo *et al.* [10] coined the term anti-JMH for a collection of antibodies identified in many reference laboratories and found predominantly, but not exclusively, in elderly patients. In many cases JMH– is probably an acquired phenotype. In some patients with anti-JMH, JMH may

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not have been totally lost as the red cells give a weakly positive DAT, and in some cases anti-JMH can be eluted [6,11]. JMH– phenotype may be transient, but in some cases the JMH– phenotype remained stable for decades [6]. JMH is usually expressed only very weakly on the red cells of neonates, achieving full strength during the first few years of life. JMH is destroyed by proteases (papain, trypsin, chymotrypsin) and by the disulphide bond reducing agent AET, but is not affected by sialidase.

In a family in which the JMH– phenotype was shown to be inherited, JMH– appeared in three generations, suggesting autosomal dominant inheritance [12]. None of the JMH– members of the family had anti-JMH, and their red cells did not give a positive DAT.

No nucleotide changes encoding amino acid substitutions were detected in the coding or promoter regions of *SEMA7A* of any JMH– individuals. Reticulocytes from JMH– individuals expressed full-length *SEMA7A* transcripts, suggesting that their Sema7A deficiency results from a post-transcriptional mechanism, and their lymphocytes could be stimulated to express normal levels of Sema7A [6].

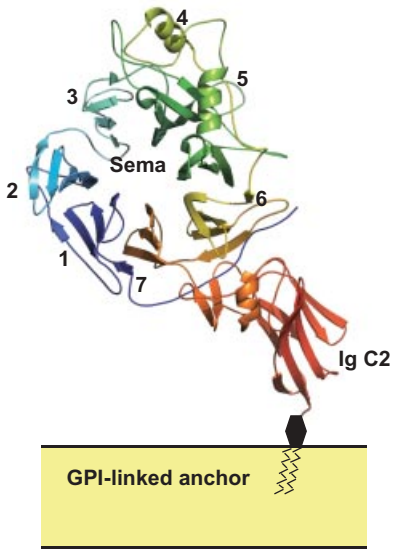

Figure 24.1 Three-dimensional model of Sema7A showing the seven propellers of the Sema domain, the loops of the Ig-like domain, and the location of the GPI-linked anchor in the red cell membrane. (3-D model provided by Nicholas Burton.)

24.4 JMH variants

Rare phenotypes have been recognised in JMH+ individuals with alloantibodies to high frequency antigens that are non-reactive with JMH– cells. These phenotypes appear to be inherited in an autosomal recessive manner. The JMH-like antibodies differ from anti-JMH because they do not react with the antibody makers' own JMH+ cells or with the JMH+ cells of some of their siblings [6,13–16]. Five of these variant phenotypes result from homozygosity for mutations in *SEMA7A* encoding single amino acid substitutions [6,16], and the associated antigens of high frequency are numbered JMH2 to JMH6 (Tables 24.1 and 24.2). Normal levels of Sema7A are expressed on red cells lacking variant JMH antigens [6].

Table 24.1 Antigens of the JMH system.

Antigen			Molecular basis*		
No.	Name	Frequency	Nucleotides	Exon	Amino acids
JMH1	JMH	High	Not known		Protein deficiency
JMH2	JMHK	High	619C (T)	6	Arg207 (Trp)
JMH3	JMHL	High	620G (A)	6	Arg207 (Gln)
JMH4	JMHG	High	1379G (A)	11	Arg460 (His)
JMH5	JMHM	High	1381C (T)	11	Arg461 (Cys)
JMH6	JMHQ	High	1040G (T)	9	Arg347 (Leu)

*Molecular basis of antigen-negative phenotype in parentheses.

Table 24.2 Reactions of anti-JMH and JMH-related alloantibodies with JMH– and JMH variant red cells [6,16].

Phenotype	Antibodies to:						Origin
	JMH1	JMH2	JMH3	JMH4	JMH5	JMH6	
JMH:–1	–	–	–	–	–	–	
JMH:–2	+	–	–	+	+	nr	Japan
JMH:–3	+	–	–	+	+	nr	Canada and Germany
JMH:–4	+	+	+	–	+	nr	USA
JMH:–5	+	+	+	–	–	nr	Poland
JMH:–6	+	nr	nr	nr	nr	–	Native Canadian

nr, not reported.

24.5 Anti-JMH

24.5.1 Human antibodies

JMH– patients with anti-JMH often have no history of transfusion or pregnancy. Of seven anti-JMH, five were IgG4 and two were IgG1 [17], although an IgG3 anti-JMH has been described [18].

There are numerous cases where patients with anti-JMH have been transfused with JMH+ blood with no adverse effects [10,11,19,20]. One such patient received 20 units of JMH+ blood in 10 months, with the expected haemoglobin rise [20]. Radiolabelled JMH+ red cells often survive normally in patients with anti-JMH [10,11,20], but there are reports of slightly accelerated clearance of JMH+ cells [14,17,21] and of JMH antibodies giving positive results in monocyte functional assays [14,17,18,21]. One JMH antibody is reported to have caused an acute intravascular HTR, but evidence that the JMH antibody was responsible for the reaction is limited [22]. Least incompatible red cells should be selected for transfusion to patients with anti-JMH.

There are no reports of JMH antibodies causing HDFN, unsurprising considering JMH antigens are expressed very weakly on cord red cells.

24.5.2 Monoclonal antibodies

Monoclonal antibodies of the CD108 cluster of differentiation may also be considered anti-JMH [9]. A monoclonal antibody (H8), produced from a mouse immunised with a human lymphoid cell line derived from a patient with acute lymphocytic leukaemia, appeared to have the same specificity as anti-JMH5 [23,24].

24.6 Functional aspects

Sema7A is widely expressed. In addition to red cells it has been detected on neurons of the brain and spinal cord, activated lymphocytes, monocytes and macrophages, and fibroblasts, and in thymus, spleen, bone, gonads, gut, heart, kidney, and placenta [1].

Most semaphorins bind directly to plexins, a family of proteins that also have a sema domain. Sema7A functions as both a neural and immune semaphorin through PlexinC1, with the β propeller structures of dimers of Sema7A and PlexinC1 interacting in an edge-on orientation [3].

Sema7A has both immune and neurological functions, although its function on red cells is not known. Sema7A interacts with integrins. The sema domain of Sema7A contains a conserved integrin-binding motif Arg-Gly-Asp (267–269), although analysis of the Sema7A crystal structure suggests that the motif is buried and unlikely to be recognised by integrins [3]. Sema7A on activated lymphocytes may assist in initiating inflammatory cascades through the α1β1 integrin by stimulating macrophages to produce proinflammatory cytokines [25]. Sema7A also promotes central and peripheral axon outgrowth through β1 integrin-dependent regulation of mitogen-activated protein kinase (MAPK) pathways [26].

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