16 LW Blood Group System

16.1 Introduction and history

A phenotypic relationship between LW and the Rh antigen D delayed recognition of LW as an independent blood group system for at least 20 years until 1963. Only in 1982 was LW resolved into a three-antigen system (Table 16.1).

The first anti-LW, described by Landsteiner and Wiener [1] in 1940, was called anti-Rhesus and resulted from immunising rabbits, and later guinea pigs, with blood from the monkey *Macacus rhesus*. This antibody appeared to be of the same specificity as a human alloantibody described, but not named, by Levine and Stetson [2] in 1939. Both human and animal antibodies were called anti-Rh.

As early as 1942, Fisk and Foord [3] demonstrated that guinea pig anti-Rh differed from human anti-Rh (later called anti-D) when they observed that red cells from all neonates, whether Rh-positive (D+) or Rh-negative (D–) as defined by the human anti-Rh, were positive with guinea pig anti-Rh. Anti-Rh could be produced by immunising guinea pigs with either Rh-positive or Rh-negative adult human red cells, or with heat extracts from those cells [4]. Levine *et al.* [5,6] repeated and confirmed this work and also showed that animal anti-Rh agglutinated D+ cells with the D antigen 'blocked' by non-agglutinating anti-D; effective blocking was demonstrated by the failure of these cells to be agglutinated by human anti-D. Furthermore, adsorption/elution tests demonstrated that the animal anti-'D-like', as it was now called, bound to D– cells, although it only agglutinated D+ cells.

Two D+ women made alloantibodies that appeared to be anti-D, but which behaved atypically since they were easily adsorbed by D– cells and, therefore, resembled animal 'D-like' antibodies [7]. The red cells of these women did not react with guinea pig anti-Rh, even by adsorption/elution [8]. Since the name Rh was firmly established in the literature and in common usage for the clinically important CDE groups, Levine *et al.* [8] suggested that the antigen defined by the animal and rare human 'D-like' antibodies be called LW in honour of Landsteiner and Wiener.

Although LW and D are different antigens, they are phenotypically related. D+ cells of adults express LW more strongly than D– cells, so anti-LW is easily mistaken for anti-D unless adsorption tests are done or rare D+ LW– cells are used. Rh_{null} cells, which lack all Rh antigens, also lack LW [8].

Swanson *et al.* [9] observed that red cells of LW– people with anti-LW in their serum were not always mutually compatible. A new low incidence antigen, Ne^a, present in 5–6% of the Finnish population [10], was found to have a phenotypic relationship with D similar to that of LW [11]. Sistonen and Tippett [12] observed that anti-Ne^a and most anti-LW were detecting the products of alleles. This led to the renaming of the LW system antigens: Ne^a became LW^b (LW7), the antithetical antigen LW^a (LW5), and those LW antibodies that reacted with LW(a–b+) red cells became anti-LW^{ab} (LW6) (Table 16.1). The LW^a, LW^b, LW^{ab} notation will be used in this chapter wherever possible, although this is sometimes difficult as many publications predate the discovery of anti-LW^b and it is not always possible to decide whether 'anti-LW' were really

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Table 16.1 Antigens of the LW system.

Antigen				Molecular basis*		
No.	Name	Frequency	Antithetical antigen	Nucleotides	Exon	Amino acids
LW5	LW^a	High	LW6	299A (G)	1	Gln100 (Arg)
LW7	LW^b	Low	LW5	299G>A	1	Arg100Gln
LW6	LW^{ab}	High		Various	1	Various

LW1 to LW4 are obsolete as they were previously used as phenotype designations.
*Molecular basis of antigen-negative phenotype in parentheses.

anti-LW^a or anti-LW^{ab}. In the ISBT numerical notation, the numbers LW1 to LW4 were avoided to prevent confusion with an obsolete phenotype designation.

LW antigens reside on an intercellular adhesion molecule ICAM-4 (CD242) (Sections 16.2 and 16.8). The LW^a/LW^b polymorphism is associated with a Gln70Arg substitution (Section 16.3.2).

The *ICAM4* (*LW*) locus is located on chromosome 19p13.3.

16.2 The LW glycoprotein (ICAM-4) and the gene that encodes it

Immunochemical analyses with alloanti-LW^{ab} and monoclonal anti-LW^{ab} demonstrated that LW antigens are located on a red cell membrane component of MW 40 kDa [13–16]. A broad band representing MW 37–47 kDa obtained by immunoblotting under non-reducing conditions was 'sharpened' to 36–43 kDa when sialidase-treated ghosts were used, suggesting that the size range results from heterogeneity of sialylation [13]. LW glycoprotein is *O*- and *N*-glycosylated: its MW was reduced by 2 and 17 kDa following treatment with *O*-glycanase and *N*-glycanase, respectively [16]. The presence of ethylenediaminetetra-acetic acid (EDTA) inhibits expression of LW^a, LW^b, and LW^{ab} on red cells [14]. Antigen expression could be restored to normal by Mg^{2+} ions, but not by Mn^{2+} or Ca^{2+}.

The product of PCR amplification from primers based on partial amino acid sequences from purified LW glycoprotein was used to screen a human bone marrow cDNA library [17]. The nucleotide sequence of an isolated cDNA clone predicted a polypeptide of MW 26.5 kDa. A rabbit antibody raised to a synthetic peptide with a sequence corresponding to the 15 N-terminal amino acids reacted with the purified LW glycoprotein on immunoblots and agglutinated, in an antiglobulin test, all red cells tested apart from those with the LW(a–b–) phenotype. D+ cells were more strongly agglutinated than D– cells. LW(a–b+) D+ cells reacted only weakly. The original *LW* sequence [17] contained errors involving three bases affecting the sequence of 16 amino acids in the signal peptide [18].

LW cDNA encodes a 271 amino acid protein with a 30-residue signal peptide, a 208 amino acid N-terminal extracellular domain, a 21 amino acid hydrophobic membrane-spanning domain, and a 12 amino acid C-terminal cytoplasmic domain [17]. There are potential *N*-glycosylation sites at Asn68, Asn78, Asn190, and Asn223 (counting from the translation-initiating methionine). Typical *N*-glycosylation at all four sites would produce a glycoprotein of 38–46 kDa. The proposed presence of three disulphide bonds at three pairs of cysteine residues (Cys69/Cys113, Cys153/Cys210, Cys73/Cys117) is supported by the sensitivity of LW antigens to thiol reducing agents.

The LW glycoprotein is a member of the immunoglobulin superfamily (IgSF), with two I-set IgSF domains (see Section 6.2.2). It is structurally related to the intercellular adhesion molecule ICAM-2, and to the first two IgSF domains of ICAM-1 and ICAM-3. Three-dimensional models of LW glycoprotein have been built, based on the crystal structure of ICAM-2 [19,20] (Figure 16.1). The potential function of LW glycoprotein, ICAM-4, is discussed in Section 16.8.

The LW glycoprotein, which appeared to be co-precipitated with an MW 31 kDa Rh protein [16], is part of the band 3 macrocomplex, which also contains the Rh proteins (see Section 10.7 and Figure 10.2). Red cells of

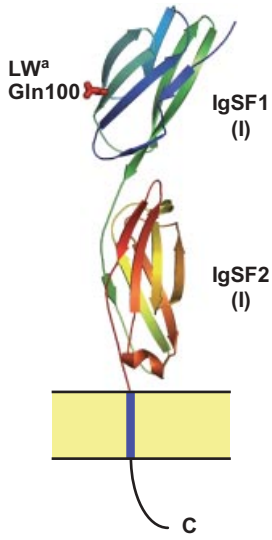

Figure 16.1 Ribbon model of the two extracellular I-set IgSF domains of the LW glycoprotein (ICAM-4), showing the position of Gln100 associated with LW^a expression (Based on Spring *et al.* [20]; model provided by N. Burton.)

a child with only trace quantities of band 3 had only about 6% of normal levels of LW glycoprotein [21].

The 2.65 kb *ICAM4* gene is organised into three exons [22]. Exon 1 encodes the 5′ untranslated sequence (96 bp), the signal peptide, and the first IgSF domain (amino acids 29 to 102). Exon 1 is separated by a 129 bp intron from exon 2, which encodes the second IgSF domain (amino acids 102–203) and is separated by a 147 bp intron from exon 3, which encodes the transmembrane domain, the cytoplasmic tail, and 3′ untranslated sequence (amino acids 203–241). The promoter region has no TATA- or CAAT-box, but includes potential binding sites for transcription factors, including those involved in erythroid and megakaryocytic expression [22]. LW has not, however, been detected on megakaryocytes.

When *ICAM4* was shown to be closely linked to *C3* and *LU*, it joined the chromosome 19 linkage group that also contained the fucosyltransferase genes *FUT1* (H), *FUT2* (secreted H), and *FUT3* (Lewis) [23,24] (see Section 6.2.4). Location of *ICAM4* on 19p13.3 was confirmed by *in situ* hybridisation [22].

A mouse homologue of human *ICAM4* encodes a protein with 68% identity to human ICAM-4 [25]. A secreted isoform of LW glycoprotein in mice results from the loss of the product of exon 3 and, therefore, loss of the transmembrane domain.

16.3 LW^a and LW^b (LW5 and LW7)

16.3.1 Frequency

In most populations, LW^a and LW^b are antigens of very high and low frequency, respectively. Polymorphism of LW was first observed in the Finnish population [10,12]. The highest frequency of LW^b has been found in Baltic Latvians and Lithuanians, and LW^b appears to be a Baltic marker, its presence in other populations being an indicator of the degree of Baltic genetic influence [26].

The calculated gene, genotype, and phenotype frequencies for the Finnish population are:

*LW*A*	0.971	*LW*A/A*	LW(a+b–)	0.9429
		*LW*A/B*	LW(a+b+)	0.0563
*LW*B*	0.029	*LW*B/B*	LW(a–b+)	0.0008

16.3.2 Inheritance LW^a and LW^b and the molecular basis of the LW polymorphism

Prior to the identification of anti-LW^b, all LW(a–) propositi with normal Rh groups were ascertained through their antibody. The inherited LW(a–) phenotype could only be distinguished from the acquired phenotype by family studies. Family studies have confirmed that *LW*A* and *LW*B* are co-dominant alleles and confirmed that *LW* is independent of the Rh genes [10,27].

The LW^a/LW^b polymorphism is associated with Gln100Arg in the first IgSF domain of the LW glycoprotein [18] (Table 16.1, Figure 16.1). This was confirmed by detection of LW^a and LW^b on COS-7 simian cells transiently transfected with cDNA from the corresponding alleles. *LW*B* lacks a *Pvu*I restriction site present in *LW*A*. Monoclonal anti-LW^{ab} bound more strongly to COS-7 cells transfected with *LW*A* cDNA, than with those transfected with *LW*B* cDNA [18].

16.4 LW(a–b–) and LW^{ab} (LW6)

Inherited LW(a–b–) phenotype is exceedingly rare. Of 10 552 Canadians tested with anti-LW^{ab}, none was negative [28]. The original propositus, a white Canadian antenatal patient (Mrs Big.) with anti-LW^{ab}, had an LW(a–b–) brother [28,12]. Red cells of her three children reacted with her anti-LW^{ab}, but the cells of two of them reacted only weakly. The LW-null phenotype of Mrs Big. results from homozygosity for a 10 bp deletion in exon 1 (codons 86–89) of an *LW*A* allele, which introduces a premature

stop codon and encodes a truncated protein lacking transmembrane and cytoplasmic domains [22].

Two other LW(a–b–) propositi had anti-LW^{ab}: one had a deletion of 46T introducing a premature stop codon; the other 2T>A, Met1Lys [83].

16.5 LW expression and effects of enzymes and reducing agents

16.5.1 Phenotypic relationship to D

Stronger reactions with D+ than D– cells have been noted for many anti-LW^a and -LW^{ab}, and for some sera this difference is so great that the antibody could be misidentified as anti-D. Estimation of antigen site density with monoclonal anti-LW^{ab} gave the following results: D+ adult, 4400; D– adult, 2835; D+ cord, 5150; D– cord, 3620 [13].

The strength of expression of LW on D+ red cells is not obviously influenced by the CcEe antigens or by D zygosity [30], but does reflect D antigen strength: DcE/DcE cells had more D and LW than DcE/dce, which had more than DCe/dce cells [31]. Red cells with weak D (D^u) gave similar strength reactions to D– cells in titrations of anti-LW^a [30]. LW^b has a similar relationship with D [11].

16.5.2 Development of LW

LW is expressed strongly on the red cells of neonates. Animal anti-LW react more strongly with red cells from cord blood samples, both D+ and D–, than with those of adults; human anti-LW do not always make this distinction so clearly. The strength of LW antigens, as judged by guinea pig anti-LW, decreases from birth until the adult level is reached at about five years of age [30]. During *ex vivo* erythropoiesis LW appears either at the CFU-E stage [32] or later at the proerythroblast stage [33].

16.5.3 Effects of enzymes and reducing agents

LW^a, LW^b, and LW^{ab} are unaffected by treatment of intact cells with the proteases papain, ficin, trypsin, or chymotrypsin, but are destroyed by pronase. Treatment of intact red cells with sialidase has no affect on their reaction with anti-LW^a or anti-LW^{ab}. The disulphide bond reducing agents DTT and AET either destroy or greatly reduce LW^a and LW^{ab} activity on red cells [34–36].

16.6 Acquired LW-negative phenotypes and transient anti-LW

The expression of LW on red cells can be affected by non-genetic factors. The acquired LW-negative phenotype is associated with loss of LW^a and possibly LW^{ab} and LW^b, and is generally found through the presence of anti-LW^a or -LW^{ab} in the patient's serum. Both antigen loss and antibody production may be temporary.

The first and fullest description of this phenomenon is the report by Giles and Lundsgaard [37] of transient anti-LW in the serum of a D– woman during her first pregnancy. Just before delivery her serum contained anti-C+D and -LW, and her cells were considered LW–, although they gave a weakly positive DAT. A year after delivery her red cells were LW+ and her anti-LW had disappeared. Chown *et al.* [38] suggested that transient production of anti-LW may not be very rare when they reported three more examples, two in pregnant D– women and one in a transfused D+ patient. They proposed that the red cells had genuinely lost their LW antigens and that the phenotype did not result from blocking of antigen sites by anti-LW.

Eleven of 18 D– men immunized with D+ red cells transiently produced an antibody resembling anti-LW, suggesting that anti-LW may be an antecedent in the immune response leading to production of anti-D [38]. Three months after transplantation of a D+ boy with bone marrow from his D– sister, anti-LW and anti-D were present, presumably resulting from a primary response of transplanted lymphocytes [39]. After two years the anti-LW had disappeared and very weak anti-D remained.

The expression of LW on red cells may be depressed during some diseases and re-expressed at normal strength in remission. Several similar examples are known in patients with lymphoma, leukaemia, sarcoma, and other forms of malignancy [40–43]. Two cycles of relapse associated with LW(a–) phenotype and production of anti-LW^a, followed by regaining of LW^a antigen and disappearance of antibody during chemotherapy-induced remission, occurred in a Japanese patient with malignant lymphoma [43]. Occasionally transient LW-negative phenotype occurs in the absence of malignancy, apparent immunological disorder, or pregnancy [44,45].

There appears to be a reciprocal relationship between the amount of LW antigen expressed on red cells and the broadness of the specificity of anti-LW in the serum [38]. Red cells of some LW(a–b–) patients are LW^{ab}+ and their

transient antibodies behave as anti-LW^{a}; others are LW^{ab}-negative and make anti-LW^{ab}. Many transient 'anti-LW' cannot be fitted neatly into anti-LW^{a} or anti-LW^{ab} specificity, presumably reflecting an intermediate stage.

Red cells of a patient with anti-LW^{a} in his serum were LW(a–) LW^{ab}+, but later became LW^{ab}-negative during terminal illness [27]. They were LW(b–) by direct testing, but adsorbed anti-LW^{b}, suggesting that LW^{b} may be lost with the other LW antigens. A brother and two daughters of the patient, who was married to his cousin, were LW(a–b+) LW^{ab}+.

16.7 LW antibodies

16.7.1 Alloantibodies

16.7.1.1 Anti-LW^{a}

Alloanti-LW^{a} are found in the sera of immunised LW(a–b+) individuals. Unless the red cells of the antibody maker are tested with anti-LW^{b}, other LW(a–) individuals are present in the family, or the antibody maker is shown to be *LW*B/B* by genomic testing, it is almost impossible to distinguish true alloanti-LW^{a} from that associated with an acquired LW(a–) phenotype. Most examples of alloanti-LW^{a} have probably been stimulated by transfusion; one is attributed solely to pregnancy [40], another to immunisation of a male volunteer for production of anti-D [46].

16.7.1.2 Anti-LW^{ab}

There are only four examples of alloanti-LW^{ab}, the antibodies of the only four propositi known to have an inherited LW(a–b–) phenotype [28,29,83]. The first propositus (Mrs Big.) had been pregnant three times, but never transfused. Initially, the anti-LW^{ab} was very potent, reacting much more strongly with D+ (1:32 000) than with D– cells (about 1:1000). When the antibody decreased in titre it no longer distinguished D+ from D– cells [28].

16.7.1.3 Anti-LW^{b}

Several anti-LW^{b} have been found, all in Finnish multitransfused patients [47]. Although the original anti-LW^{b} serum did not contain any other irregular antibodies, other reagents have contained additional antibodies such as anti-K, -Kp^{a}, and -Ul^{a}.

16.7.1.4 Transient antibodies

Transient antibodies should probably be considered autoantibodies since they are produced by genetically LW+ individuals. Although red cells of people with transient LW antibodies often give a positive DAT, in some cases the red cells have an acquired LW– phenotype and the anti-LW behaves as an alloantibody (Section 16.6). These antibodies are difficult to distinguish from true alloantibodies and, from a transfusion point of view, are generally managed in the same way. True alloantibodies, transient antibodies, and those of undetermined status will be considered together for clinical significance.

16.7.1.5 Clinical significance

No LW antibody has been responsible for an HTR or for HDFN. Many patients with anti-LW^{a} or -LW^{ab} have been successfully transfused with crossmatch-incompatible D– red cells [41,43–45,48,49] and the very potent anti-LW^{ab} of Mrs Big. caused no more than minimal evidence of HDFN in her D– third baby [28].

LW antibodies are mostly IgG, with IgG1 the main component [44,46,48], though one anti-LW^{a} was inactive by an antiglobulin test and was probably IgM [50]. In most patients with anti-LW^{a} or -LW^{ab}, where *in vitro* phagocytosis assays or *in vivo* red cell survival studies have been carried out, the results predicted that transfusion with D– cells would be efficacious [43,44,46,48,49]. Exceptions were two examples of IgG3 anti-LW^{ab} [42,51]: both antibodies produced high scores in mononuclear phagocyte assays and in one patient only 53% of radiolabelled D– LW+ red cells remained one hour after injection. *In vivo* red cell survival tests in a patient with potent anti-LW^{b} resulted in a rapid elimination of radiolabelled LW(b+) (D type not specified) cells, with a half-life of 2–5 hours [10].

16.7.2 Autoantibodies

16.7.2.1 Cold autoanti-LW

Ten examples of autoanti-LW were found by screening 45 000 blood samples, but the antibodies could only be detected by a low-ionic strength polybrene method in an AutoAnalyser at temperatures below 37°C; they were not detectable by manual techniques [20]. Most of the antibody makers were healthy blood donors or were pregnant and the antibodies were not associated with any increased red cell destruction.

16.7.2.2 Autoimmune haemolytic anaemia (AIHA) and HDFN

Levine [52] suggested that anti-LW is the most frequent antibody in cases of AIHA with a positive DAT. In two surveys of red cell eluates from 14 patients with AIHA, 12 eluates contained anti-LW, one of which contained

only anti-LW [53,54]. Severe AIHA has been associated with anti-LW as the sole autoantibody [55].

Autoanti-LW^{a} implicated in mild HDFN was treated successfully with phototherapy [56].

16.7.3 Animal antibodies

Anti-LW was first made in rabbits [1] and later, more successfully, in guinea pigs. Anti-LW has been stimulated in these animals by injections of red cells from rhesus monkeys (*Macaca mulatta*), from baboons, and from D+ or D– humans [1–6,30,57–59]. Heat extracts of human D+ and D– cells also stimulate anti-LW [4–6].

LW(a–b+) and LW(a–b–) (Mrs Big.) red cells are able to stimulate anti-LW in guinea pigs [54,57]; only Rh_{null} cells have failed to elicit any such response in animals [52,57,60]. The response to red cells of Mrs Big. is surprising considering the nature of the mutation responsible for her LW-null phenotype, as no LW glycoprotein would be expected to be present in her red cell membranes (Section 16.4).

16.7.4 Monoclonal anti-LW^{ab}

Of four monoclonal antibodies identified as anti-LW^{ab}, three (IgG1) were derived from mice immunised with human red cells [61,62], and one (IgM) from a mouse immunised with rhesus monkey red cells [63]. Binding of the murine anti-LW^{ab} to red cells could be totally blocked by human anti-LW^{ab} and partially blocked by human anti-LW^{a}; anti-D did not inhibit the reaction [61]. Domain-deletion experiments suggested that the epitopes for the three IgG antibodies are on the first IgSF domain [19]. Five other monoclonal antibodies to the LW glycoprotein, five binding to domain 1 and one to domain 2, were produced by immunising mice with a recombinant chimeric protein consisting of the two IgSF domains of LW and the Fc fragment of IgG1 [64].

16.8 Functional aspects and disease association

ICAMs are intercellular adhesion molecules, a group of five related structures belonging to the immunoglobulin superfamily (IgSF, see Section 6.2.2) [65,66]. The N-terminal domain of ICAM-4, the LW glycoprotein, is an I-set IgSF domain that shares about 30% sequence identity with that of the other ICAMs [17]. ICAM-2 (CD102), like ICAM-4, has two IgSF domains. ICAM-1 (CD54) and ICAM-3 (CD50) each have five IgSF domains, ICAM-5 has nine domains [66].

ICAMs are ligands for integrins, adhesion molecules consisting of heterodimers for α and β transmembrane subunits. Eighteen different α subunits combine with eight different β subunits to form over 24 different heterodimers [67]. ICAMs bind the αLβ2 integrin (LFA-1), which is present on lymphocytes, granulocytes, monocytes, and macrophages [66]. ICAM-4, however, differs from other ICAMs as it interacts with a variety of integrins in addition to αLβ2: αMβ2 (Mac-1), αXβ2, αVβ1, αVβ3, αVβ5, α4β1 (VLA-1), and αIIbβ3 the platelet fibrinogen receptor [19,20,66,68–73], though the α4β1 binding is disputed [71]. A glutamic acid residue critical for binding of other ICAMs to integrin is replaced by arginine in ICAM-4, demonstrating that another mechanism must be involved. Domain deletion and single amino acid site-directed mutagenesis experiments revealed that the first IgSF domain is most important to binding, but that the second domain also contributes, with the possible exception of binding to αLβ2 [19,70,71,74] (reviewed in [75]).

ICAMs 1, 2, and 3 are adhesion molecules of lymphocytes, granulocytes, and monocytes, and may be more widely expressed, but ICAM-4 appears to be restricted to erythroid cells and possibly placenta [66]. During *ex vivo* erythropoiesis LW is detected around the CFU-E to proerythroblast stage [32,33]. During the latter stages of erythropoiesis erythroblasts cluster around bone marrow macrophages to form erythroblastic islands, where the erythroblasts extrude their nuclei, which are ingested by the macrophage [76]. Adhesive interactions between ICAM-4 and α4β1 integrin on adjacent erythroblasts and between ICAM-4 on erythroblasts and αV integrins on macrophages may assist in maintaining the stability of the erythroblastic islands [20,66,77]. This supposition is supported by experiments on mice: ICAM-4 knockout mice have 64% less islands than wild-type mice and peptides that block ICAM-4 to αV binding decreased *in vitro* reconstitution of islands from single cell suspensions of wild-type mouse marrow [77]. A secreted isoform of ICAM-4 in mice is upregulated late in terminal erythroid differentiation and could assist young reticulocytes in detaching from the erythroblastic islands [25,77]. Downregulation of α4β1 integrin once the cells have enucleated may also aid in their release from the erythroblastic islands.

Binding of ICAM-4 on red cells to αXβ2 integrin on macrophages in the spleen may play a role in the removal of senescent red cells [70,75]. Through binding to the platelet integrin αIIbβ3, ICAM-4 could be involved in interactions between platelets and red cells during

coagulation [73]. As part of the band 3/Rh red cell surface macrocomplex, ICAM-4 might also assist in facilitating transient adhesive interactions between the red cell and the vascular endothelium to maximise gas transfer [21]. The functional importance of ICAM-4, however, must be considered in light of the absence of any obvious pathology associated with its absence in the rare inherited LW-null and Rh_{null} phenotypes, and in ICAM-4 knockout mice.

Like the Lutheran glycoprotein, expression of ICAM-4 may be elevated on sickle red cells, and antibodies to ICAM-4 partially inhibit adhesion of sickle red cells to activated endothelium [66,72,78]. Interactions between ICAM-4 on red cells and αVβ3 integrin on the endothelial cells of vessel walls may be involved in the microvascular occlusions that produce the painful crises of sickle cell disease. Peptides or mimetics representing ICAM-4 reduce adhesion and vessel blockage, and may have therapeutic potential [78]. Stimulation of β_2-adrenergic receptor by the physiological stress mediator epinephrine induces increased levels of cyclic adenosine monophosphate (cAMP) in SS red cells. This elevation of cAMP may induce serine phosphorylation of the cytoplasmic domain of ICAM-4, through abnormal activation of extracellular signal-regulated kinase-1/2 (ERK1/2), and could induce conformational changes to the external domain of ICAM-4, modulating its attraction to αVβ3 on endothelial cells [72,79,80].

16.9 LW antigens in animals

Summarising work with animal anti-LW from several laboratories shows that LW antigen has been detected on red cells of all primate species tested, including chimpanzee, gorilla, orangutan, baboon, and a variety of other species of monkey [1,6,58,81,82]. LW has not been found on the red cells of any of the non-primate species tested: rabbit, mouse, rat, sheep, goat, horse, and cattle.

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