CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin

Vanja Karamatic Crew, Nicholas Burton, Alexander Kagan, Carole A. Green, Cyril Levene, Frances Flinter, R. Leo Brady, Geoff Daniels, and David J. Anstee

Tetraspanins are thought to facilitate the formation of multiprotein complexes at cell surfaces, but evidence illuminating the biological importance of this role is sparse. Tetraspanin CD151 forms very stable laminin-binding complexes with integrins α3β1 and α6β1 in kidney and α3β1 and α6β4 in skin. It is encoded by a gene at the same position on chromosome 11p15.5 as the MER2 blood group gene. We show that CD151 expresses the MER2 blood group antigen and is located on erythrocytes. We examined CD151 in 3 MER2-negative patients (2 are sibs) of Indian Jewish origin with end-stage kidney disease. In addition to hereditary nephritis the sibs have sensorineural deafness, pretibial epidermolysis bullosa, and β-thalassemia minor. The 3 patients are homozygous for a single nucleotide insertion (G383) in exon 5 of CD151, causing a frameshift and premature stop signal at codon 140. The resultant truncated protein would lack its integrin-binding domain. We conclude that CD151 is essential for the proper assembly of the glomerular and tubular basement membrane in kidney, has functional significance in the skin, is probably a component of the inner ear, and could play a role in erythropoiesis. (Blood. 2004;104:2217-2223)

© 2004 by The American Society of Hematology

From the Bristol Institute for Transfusion Sciences, National Blood Service, Bristol; the Department of Biochemistry, University of Bristol, Bristol, United Kingdom; the Department of Nephrology and Hypertension, Kaplan Medical Center (affiliated to Hebrew University-Hadassah Medical School), Rehovot, Israel; the National Blood Group Reference Laboratory, Magen David Adom Blood Services Center, Ramat Gan, Israel; and the Evelina Children’s Hospital, Guy’s and St Thomas’ NHS Trust, London, United Kingdom.


Supported by grants from DiaMed AC (Switzerland) (V.K.C.) and from the United Kingdom NHS R&D Directorate (D.J.A., G.D., and C.A.G.) and by a studentship from the United Kingdom Medical Research Council (N.B.).


An Inside Blood analysis of this article appears in the front of this issue.

Reprints: David J. Anstee, Bristol Institute for Transfusion Sciences, Southmead Road, Bristol BS10 5ND, United Kingdom; e-mail: david.anstee@nbs.nhs.uk.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 U.S.C. section 1734.

© 2004 by The American Society of Hematology
MER2 (RAPH1), the only antigen of the RAPH blood group system, was initially recognized by 2 murine monoclonal antibodies, produced following immunization of mice with a human small cell carcinoma line.\textsuperscript{20} They defined a polymorphism on red cells in which 92\% of English blood donors were MER2\textsuperscript{+} and 8\% were apparently MER2\textsuperscript{−}.\textsuperscript{20} MER2 was assigned to chromosome 11p15 by somatic cell hybridization studies.\textsuperscript{20} Subsequently, 3 examples of human alloanti-MER2 were identified, all made by Jews originating from India and living in Israel.\textsuperscript{21} Two were sibs and the third was unrelated. All had end-stage kidney disease. In addition to nephrotic syndrome resulting from hereditary nephritis, which deteriorated to end-stage renal failure, the sibs had prethial bullous skin lesions, neurosensory deafness, bilateral lacrimal duct stenosis, nail dystrophy, and β-thalassemia minor.\textsuperscript{22} The male sib also had only one kidney and dystrophic teeth, whereas the female sib had agenesis of the distal vaginal and bilateral cervical ribs. Two additional siblings had β-thalassemia minor without other clinical problems. Fewer clinical details are available for the unrelated Israeli patient, but he had end-stage renal failure and was on dialysis for 3 years before death. One other example of alloanti-MER2 was identified in a Turkish woman, a healthy blood donor.\textsuperscript{23}

The combination of familial progressive renal failure and sensorineural deafness is well recognized and often called Alport syndrome. Most cases of classic Alport syndrome are inherited in an X-linked fashion, but up to 15\% demonstrate autosomal inheritance, which is usually recessive.\textsuperscript{24} The 3 Israeli MER2− cases have a broader phenotype than would be consistent with a diagnosis of pure Alport syndrome, but we included DNA from 2 patients with a clinical diagnosis of autosomal recessive Alport syndrome in our study for comparison.

We have demonstrated that the MER2 antigen is carried on tetraspanin CD151, the first evidence for a member of the tetraspanin superfamily on erythrocytes, and that absence of CD151 is associated with renal failure. We conclude that CD151 is essential for the proper assembly of the glomerular and tubular basement membranes in kidney, has functional significance in the skin and inner ear, and may also play a role in erythropoiesis.

Patients and methods

Patients

Blood samples were obtained from the Israeli sibs (Pt1 and Pt2), the unrelated Israeli patient (Pt3), the Turkish blood donor (D1), and 2 patients with Alport syndrome with informed consent.

The 2 patients with autosomal recessively inherited Alport syndrome were as follows. Pt4 is 1 of 7 children born to healthy, consanguineous (1st cousin) parents. The others, including 3 brothers, are all healthy. The patient presented with hematuria and proteinuria and then developed chronic renal failure and high-tone sensorineural deafness in his 30s. He had classic changes of Alport syndrome on electron microscopic examination of his renal biopsy. His 3 sons all have microscopic hematuria. Mutation screening in \textit{COLA5} (the gene involved in X-linked Alport syndrome) was negative. Pt5 is the fifth of 5 children born to consanguineous (1st cousin) Moroccan parents. His mother has hematuria, proteinuria, and a biopsy “consistent with the diagnosis of Alport syndrome.” Four of the 5 children, including Pt5, have hematuria, 1 is deaf, and 2 also have congenital cataracts. Mutation screening in \textit{COLA45} was negative.

Serologic analyses

Serologic studies involved standard indirect agglutination tests with anti-human immunoglobulin G (IgG; BPL, Elstree, United Kingdom) or anti-mouse IgG (Dako Cytomation, Glostrop, Denmark), read in a capillary. For blocking tests, 5 μL packed erythrocytes were incubated first with 10 μL human serum for 60 minutes at 37°C, then washed 4 times, incubated with mouse monoclonal antibody for 60 minutes at room temperature, then subjected to an antiglobulin test. Methods for treatment with proteases and thiol-reducing agents were as described.\textsuperscript{25}

Molecular genetic analyses

Genomic DNA was isolated from whole blood taken from Pt2 and from 3 MER2-positive control samples with a genomic DNA purification kit (Promega, Madison, WI). Genomic DNA was isolated from the plasma of Pt1, Pt3, and D1 (cell samples were not available) with the QIAamp DNA purification kit (QIagen, Crawley, United Kingdom). Genomic DNA from 2 cases of Alport syndrome (Pt4 and Pt5) was also analyzed.

All exons, intron-exon borders, and some short introns of \textit{CD151} were amplified by polymerase chain reaction (PCR). Most of the primers used for amplification were described by Whittco and McLean.\textsuperscript{25} The primer set for amplification of exon 1 was designed with assistance of primer analysis software (Oligo; Molecular Biology Insights, Plymouth, PA). Primer sets for amplification of exons 1, 4, 5, and 6; and 68°C for exons 7 and 8. Following the initial denaturing at 94°C for 10 minutes, 35 cycles of PCR were performed at 94°C for 30 seconds followed by the annealing temperature for 30 seconds and then 72°C for 1 minute. All reactions were terminated after a 10-minute extension at 72°C.

The sequences of 8 CD151 exons were determined by direct sequencing of PCR products following the electrophoresis of amplification products in 0.8% agarose gel and detection by ethidium bromide staining. PCR products were excised and purified from agarose with a QIAex II gel extraction kit (Qiagen, Crawley, United Kingdom) and directly sequenced on both DNA strands (ABI-PRISM 3100 Applied Biosystems automated DNA sequencer; Applied Biosystems). The reference sequence used for comparison was a \textit{Homo sapiens} chromosome 11 genomic contingent (GenBank accession NT_035113). The DNA and translational changes are numbered from the codon for the translation initiating methionine.

DNA fragments containing \textit{CD151} exons 5 and 6 with point mutations that altered recognition sites for restriction enzymes were amplified by the same PCR conditions as described earlier. The restriction fragment length polymorphism (RFLP) test was used to digest PCR products directly in a total volume of 20 μL. The restriction enzymes used were obtained from the New England Biolabs (United Kingdom) Ltd (Hitchin, United Kingdom) and were used in a concentration of 10 U per sample. Restriction fragments were analyzed on 1.5% agarose gels.

Furthermore, mRNA was isolated from 4 to 5 × 10\textsuperscript{6} cells from Epstein-Barr virus (EBV)-transformed lymphoblastoma cell lines derived from Pt2 and a control individual (Oligotex; Qiagen). First-strand cDNA for PCR amplification was prepared with Omniscript reverse transcriptase (Qiagen) and oligo (dT)\textsubscript{12,18} as the primer. Whole \textit{CD151} cDNA was amplified with the following primers: forward 5′-ATGGGGAGGTTCAACGAGAGAAA-3′ and reverse 5′-CTAGTAGTGCTCCAGCTTGAG-3′ (MWG Biotech AG, Ebersberg, Germany) and Expand High Fidelity PCR system (Roche Diagnostic GmbH, Mannheim, Germany). Amplification was achieved over 30 cycles at 94°C for 1 minute, 65°C for 1 minute, and 72°C for 2 minutes, followed by a final extension time of 10 minutes. The 762-bp product was isolated by gel purification and directly sequenced as described.

Erythroid cell culture

Buffy coats were prepared from whole blood units of 1 MER2− individual lacking anti-MER2 and 2 MER2+ individuals. Theuffy coats were diluted

From www.bloodjournal.org by guest on April 11, 2017. For personal use only.
sequence of CD151 EC2 was initially aligned with CD81 (25.3% sequence identity) using the ClustalW routine within Megalign 5.06 (DNASTAR, Madison WI). Manual adjustment produced 3 nonaligned loop insert regions in CD151 of 11, 6, and 2 residues. With the use of SYBYL6.9 (Tripos, St Louis, MO) the CD151 sequence was mutated to that of CD151, and conformations of nonaligned loop regions were predicted by using the Loop Search routine. The overall model was iteratively minimized by the Kollman all-atom force-field implemented in SYBYL6.9, combined with manual adjustment of Ramachandran outlier regions identified by PROCHECK. 28

Histologic analyses

The open biopsy of single right kidney (Pt1) and skin biopsy from involved skin lesions (Pt2) were performed in 1976 and 1986, respectively.

For light microscopy, tissues were fixed in 4% buffered formaldehyde, dehydrated, embedded in paraffin, sectioned, and stained with hematoxylin-eosin, Masson-trichrome, methamine silver, and periodic-acid Schiff reagents. For immunofluorescence, tissues were frozen fresh and sectioned at approximately 4 µm on cryostat.

For ultrastructural analysis, fresh samples of kidney and skin tissues were fixed in 3% glutaraldehyde and then postfixed in 1% osmium tetroxide, followed by dehydration and embedding in epoxy resin by using standard procedures. Sections (50 nm thick) were used for transmission electron microscopy (Philips EM300, cut film 3½ × 4 inch and Philips EM201, 80 kV, camera 35-mm Philips, Eindhoven, The Netherlands).

Results

MER2 is a marker for CD151

Location of CD151, like MER2, on chromosome 11p15 and apparent similarities between MER2 and CD151 regarding susceptibility to thiol and proteases led us to examine the possibility that MER2 is a marker for CD151. One example of monoclonal anti-C151 (11G5a; Serotec) reacted with human erythrocytes by an antiglobulin hemagglutination test. Erythrocytes from 40 blood donors gave comparable results by an antiglobulin hemagglutination test with the monoclonal anti-C151 and 2 monoclonal anti-MER2 (1D12 and 2F7). Incubation of MER2 + erythrocytes with human alloanti-MER2 blocked binding of murine anti-CD151 and murine anti-MER2 but not binding of an unrelated murine monoclonal antibody (BRIC 108, anti-Lu); whereas incubation of MER2 + erythrocytes with human alloanti-Fy, an unrelated antibody, did not block binding of murine anti-CD151, -MER2, or -Lu (data not shown).

Treatment of erythrocytes with papain enhanced indirect hemagglutination with monoclonal anti-MER2 and anti-CD151, whereas treatment with trypsin, α-chymotrypsin, pronase, or with the disulphide bond reducing agent 2-aminoethylisothiouronium bromide destroyed reactivity with those antibodies (data not shown).

It has been suggested that most people with MER2 + erythrocytes express MER2 on other cells and tissues and, therefore, do not produce anti-MER2. 29 An analogous situation occurs with individuals who have the Fy(a b−) phenotype resulting from an inactivating mutation in the GATA1 binding site upstream of the FY gene. 30 On this basis only 4 individuals are known who have made alloanti-MER2 and are therefore true MER2-negatives.

When erythrocytes (predominantly proerythroblasts) derived from adult MER2 + CD34 + cells were cultured in the presence of IL-3, stem cell factor (SCF), and erythropoietin (EPO) and examined for expression of MER2 and CD151 by dual staining with PE-conjugated murine monoclonal anti-MER2 or anti-CD151 and FITC-conjugated human alloanti-GPA (anti-M) the same pattern of staining was observed with anti-MER2 and anti-CD151 (Figure 1A). These results clearly demonstrate that CD151 and
CD34+ cells were not available from any of the MER2- individuals with anti-MER2. However, comparative analysis of lymphoblastoid cell lines derived from a MER2+ individual and from 1 of the Israeli sibs with anti-MER2 (Pt2) demonstrated strong reactivity with 2 monoclonal anti-CD151 and 2 monoclonal anti-MER2 with the lymphocytes from the MER2+ donor and complete absence of reactivity with the lymphoblastoid cell line from Pt2 (Figure 1D). Collectively these results establish that MER2 is a marker for CD151 and show that CD151 is expressed on erythrocytes, at a higher level in erythroid precursors than on mature erythrocytes.

Analysis of CD151 in individuals who have made alloanti-MER2

Direct sequencing of all CD151 exons from Pt1, Pt2, and Pt3, the Israeli patients with anti-MER2 and renal failure, revealed a single nucleotide insertion G383 in exon 5 of the gene (Figure 2A). The mutation was homozygous and caused a frameshift after Lys127, introducing a premature stop signal at codon 140. The mutation in Pt2 was confirmed by cDNA sequencing. The nucleotide insertion would result in a translated protein lacking most of the large extracellular loop (EC2) between transmembrane domains 3 and 4 and transmembrane domain 4. It is doubtful whether this truncated protein would reach the plasma membrane32 or that the severely truncated EC2 region would fold to a functional protein domain. D1, the Turkish blood donor with anti-MER2, was homozygous for a G533A mutation in exon 6 (Figure 2A), encoding Arg178His. No other mutations were detected in the 8 exons and flanking intronic sequences of CD151 in the 4 individuals. Analysis of CD151 in 2 patients with recessive inheritance of Alport syndrome in which the causative mutation is unknown did not reveal any abnormalities (data not shown).

A model of the CD151 protein

We modeled the structure of CD151 EC2 by using the coordinates of the crystal structure of CD81 (Figure 2B).37 The absence of most of EC2 would prohibit association with integrin subunits α3 and α6, which bind with CD151 through the same site (Q194RD) on EC2 (Figure 2B).31 The G533A mutation in D1 results in a change at codon 178 in EC2 spatially distinct from the Q194RD motif, consistent with the lack of clinical phenotype (Figure 2B). The model suggests the change from arginine to histidine at this site is likely to be tolerated within the protein fold, implying this exchange produces a functional tetraspan with an altered surface not recognized by human alloanti-MER2. We have, however, no immunochemical evidence that CD151 was present in this individual.

Histologic examination of kidney biopsy material

Kidney biopsy from Pt1, one of the Israeli patients with renal failure, was obtained. Under light microscopy, except for focal thickening of the basement membrane in occasional glomeruli, no apparent abnormalities were seen (not shown). Similarly, immunofluorescence failed to reveal evidence of fibrinogen, immunoglobulin, or complement deposition (not shown). Electron microscopy, however, showed splitting of the tubular basement membrane and thickening, reticulation and fragmentation of the lamina densa of the glomerular basement membrane with inclusion of electron-dense particles (Figure 3). Clusters of foam cells in the interstitium were also noted.

Pretibial epidermolysis bullosa in the Israeli patients

Pt1 and Pt2, the 2 Israeli sibs with hereditary nephritis, also had pretibial epidermolysis bullosa. Figure 4A shows bullous skin lesions with adjacent atrophy and scarring in patient Pt2.
Figure 2. Sequence and RFLP analyses of CD151 and structure of CD151 large extracellular region. (A) Sequence and RFLP analyses of CD151. (i) DNA sequence of the MER2 patient with a hereditary nephritis (Pt2) exhibiting a G383 insertion in CD151 exon 5. The G383 insert introduced a novel recognition site 381GG-ACN to BsmIF. PCR-RFLP gel analysis: wild-type allele was cut into restriction fragments of 86 and 401 bp and the mutation in 3 MER2-negative patients with end-stage renal disease (Pt1, Pt2, Pt3) caused further reduction of the 401-bp fragment to 2 additional 135- and 266-bp fragments. Lanes are identified as a standard 10-kb DNA ladder (m), blank control (w), uncut allele (u), and control samples (c). (ii) DNA sequence of the MER2–healthy blood donor D1 with the G533A mutation in CD151 exon 6. The PCR product from D1 was cut at a novel restriction site 528TG3-CCA for MboI to fragments of 160 and 326 bp, whereas the wild-type allele was left intact, PCR-RFLP gel analysis lanes labeled as in (i). (iii) Schematic representation of CD151 gene and the relative placement of the 2 mutations. (B) Structure of CD151 large extracellular region. (i, left) Homology model of a monomer of the CD151 large extracellular loop (EC2) is shown as a Cα-ribbon cartoon. The amino terminus (residue 112) is labeled N, and the carboxy terminus (residue 220) is labeled C. Because of the incorporation of a stop codon at position 140 in the MER2 patients, all residues represented by the green ribbon are not expressed. The side chain is shown for Arg 178 (purple), which is mutated to His in D1. Residues constituting the QRD proposed integrin binding site are shown in red, and the single N-linked glycosylation site (Asn 160) in blue. (ii, right) Tetraspanins readily form homodimers.21 Proposed homodimeric assembly of CD151, based on the observed oligomerization in the crystal structure of CD81. Coloring and labels as described for panel i.

Under light microscopy skin specimens from Pt2 demonstrated complete separation of the epidermis from the dermis with moderate focal edermal edema. The upper dermis showed mild mononuclear perivascular infiltration (not shown). Immunofluorescence studies revealed essentially negligible deposition of C3 and immunoglobulin A (not shown). Electron microscopy showed slitlike separation of epidermis from dermis (Figure 4B).

Findings by light microscopy and immunofluorescence on skin specimens from Pt1 were similar with those of Pt2. Repeated attempts to identify the basal membrane by means of electron microscopy performed at the time of active bullous disease were unsuccessful.

Discussion

The study of human blood groups has led to advances in our understanding of many of the integral proteins of the human erythrocyte membrane. Most of the 29 blood group systems have null phenotypes in which homozygosity for inactivating mutations in the blood group gene leads to an absence of the blood group protein from the erythrocytes and any other cells in which it is usually expressed.29 These null phenotypes, natural human knockouts, are generally rare but are often disclosed by the presence of alloantibodies, produced in response to transfusion or pregnancy.

MER2, the only antigen of the RAPH blood group system, is apparently absent from erythrocytes of 8% of Caucasians.20 However, these probably represent the low end of a spectrum of erythrocyte expression, with a site density below the threshold for detection by indirect agglutination techniques. We have shown that expression of MER2 on erythroid cells decreases throughout ex vivo erythropoiesis and is detectable on erythroid progenitors of apparently MER2–individuals (confirming studies by Lucien et al14) (Figure 1B). We have also shown that MER2 is abundant on platelets of individuals with both MER2+ and MER2−erythrocyte phenotypes, although there may be some degree of correlation between strength of antigen expression on erythrocytes and platelets (Figure 1C). The reason for the individual variation in the expression of MER2 on erythrocytes and platelets is presently unknown.

We obtained blood samples from the 4 known individuals who lack the MER2 antigen and have made anti-MER2. Three of these are Indian Jews living in Israel and all have end-stage kidney disease.21,22 All 3 had a frameshift mutation in exon 5 of CD151, a nucleotide insertion that would result in a translated protein lacking most of the large extracellular loop (EC2) between transmembrane domains 3 and 4. It is doubtful whether this truncated protein would reach the plasma membrane or that the severely truncated EC2 region would fold to a functional protein domain. In addition to nephrotic syndrome, which deteriorated to end-stage renal failure, other symptoms associated with this mutation are pretribial bullous skin lesions, neurosensory deafness, bilateral lacrimal duct stenosis, nail dystrophy, and β-thalassemia minor.22 The fourth individual with anti-MER2, a blood donor with no apparent clinical phenotype,23 was homozygous for a missense mutation encoding an amino acid substitution at a site in EC2 of CD151 that, according to our model, is likely to be tolerated within the protein fold.

The glomerular basement membrane (GBM) of the kidney contains the ECM proteins laminin 11 and type-IV collagen. In humans, mutations in type IV collagen genes are frequently associated with hereditary glomerulonephritis (Alport syndrome).24 Mutation of the β2 chain of laminin 11 in mice results in a severe congenital nephrotic syndrome.25 A kidney biopsy from one of the Israeli patients with renal failure (Pt1) revealed thickening and splitting of the tubular basement membrane and thickening, reticulation, and fragmentation of the lamina densa of GBM with inclusion of electron-dense particles (Figure 3). Clusters
of foam cells in the interstitium were also apparent. In human kidney CD151 is strongly expressed in glomeruli and colocalizes with α3β1 at the GBM side of cells. Mice with an inactive α3 integrin gene also have abnormal kidneys with thickening and fragmentation of the glomerular basement membrane. In renal tubular cells CD151 and α6β4 are concentrated at the tubular basement membrane. CD151 associates with α3 and α6 during biosynthesis. Abnormal basement membranes in our patients may result from the absence of this association and consequent failure to transport α3β1 and α6β1 to the plasma membrane.

The 2 Israeli sibs (Pt1 and Pt2) exhibited sensorineural deafness. This is also found in Alport syndrome. Type IV collagen was absent from the inner ear in a canine model of X-linked Alport syndrome, and sensorineural hearing loss has also been linked to a defect in the laminin α2 chain in mice. Laminin 11 is found in the basilar membrane in humans. To our knowledge CD151 has not been described in the inner ear, but our results suggest it may be important for ECM assembly in this organ.

The 2 Israeli sibs (Pt1 and Pt2) also had pretibial epidermolysis bullosa (Figure 4A). Skin biopsy (Pt2) revealed complete separation of the epidermis from the dermis with moderate focal epidermal edema. The upper dermis showed mild mononuclear perivascular infiltration. In humans, CD151 is co-distributed with integrins α3β1 and α6β4 at the basolateral surface of basal keratinocytes where it is concentrated in hemidesmosomes. CD151 is the only tetraspanin identified in hemidesmosomes and its recruitment is regulated by α6β4. Integrin α6β4 binds the basement membrane protein laminin 5 and tightens the dermal-epidermal junction by also binding the amino-terminal NC-1 domain of type VII collagen. Mutations in the type VII collagen gene (COL7A1) are associated with epidermolysis bullosa, as are mutations in the genes encoding laminin 5 and integrins β4 and α6. CD151-deficiency may cause epidermolysis bullosa in our patients by reducing the expression of α6β4 in hemidesmosomes and thereby compromising the stability of the dermal-epidermal junction.

Analysis of DNA from 2 patients with recessive inheritance of Alport syndrome of unknown origin did not reveal any mutations in CD151. Because the MER2 patients we studied also have pretibial epidermolysis bullosa, a condition not associated with Alport syndrome, these observations suggest that mutations in CD151 are unlikely to represent a previously unrecognized genetic mechanism giving rise to autosomal recessive Alport syndrome.

CD151 is a common link between laminin binding complexes in kidney and skin, and its absence provides the most likely explanation for the concomitant occurrence of nephritis, sensorineural deafness, epidermolysis bullosa, and the other abnormalities, apart from thalassemia minor, seen in the Israeli patients. Complexes between CD151 and α3β1 and CD151 and α6β4 are exceptionally strong when compared with other tetraspanin-integrin interactions. The CD151-deficient patients we studied show that these interactions are critical for the correct assembly of kidney basement membranes and play an important role in the integrity of basement membranes in skin, inner ear, and other tissues.

Severe anemia observed in the CD151-deficient patients studied here can be attributed, in part at least, to the occurrence of β-thalassemia minor. The endogenous blood levels of erythropoietin were 129 and 135 mU/mL in Pt1 and Pt2, respectively.
(normal range, 10-30 mU/mL). However, these patients require much higher doses of recombinant erythropoietin to maintain their hemoglobin levels between 8 and 10 g/dL than other patients with β-thalassemia trait undergoing chronic hemodialysis, suggesting their marrow response to erythropoietin is impaired. Integrins and growth factor receptors act through common signaling pathways to regulate cell cycle progression in mammalian cells. The impaired marrow response to erythropoietin found in CD151-deficient patients may result from defects in the membrane assembly of integrin(s) in erythroid progenitors that affect signaling pathways also used by the erythropoietin receptor.

References

CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin

Vanja Karamatic Crew, Nicholas Burton, Alexander Kagan, Carole A. Green, Cyril Levene, Frances Flinter, R. Leo Brady, Geoff Daniels and David J. Anstee