

Reviews

Demystified . . .

Adhesion molecule deficiencies

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Abstract

The basic physiology of leucocyte emigration from the intravascular space into the tissues is now known to be dependent on a class of cell surface molecules that have come to be known as adhesion molecules. Many cell-cell interactions are dependent on adhesion and signal transduction via the various adhesion molecules, particularly the integrins. The study of the functions of these molecules has been enhanced by the development of blocking and activating monoclonal antibodies, knockout mice, and by the rare "experiments of nature" in the human population, in whom there is absence or dysfunction of one of the adhesion molecules. This review describes these leucocyte adhesion defects and discusses how they have provided important insights into the function of these molecules.

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Over the past 15 years, the basic physiology of leucocyte emigration from the intravascular space into the tissues has been investigated extensively. The classic steps of rolling, firm adhesion, diapedesis, and chemotaxis are now known to be dependent on a class of cell surface molecules that have come to be known as adhesion molecules. The major families of cell adhesion molecules include the selectins, the immunoglobulin superfamily, and the integrins. The selectins are important for leucocyte homing to particular tissues and can be expressed on leucocytes (L-selectin (CD62L)), vascular endothelium (P-selectin (CD62P) and E-selectin (CD62E)), and platelets (P-selectin). The immunoglobulin superfamily includes intercellular cell adhesion molecule 1 (ICAM-1), ICAM-2, and vascular cell adhesion molecule 1 (VCAM-1). Integrins are a large family of proteins that mediate cell adhesion, migration, activation, embryogenesis, growth, and differentiation¹ (table 1), and it is not just leucocytes and endothelial cells that express these molecules. Many cell-cell interactions are now known to be dependent on adhesion and signal transduction via the various adhesion molecules, particularly the

integrins. The study of the functions of these molecules has been enhanced by the development of blocking and activating monoclonal antibodies, knockout mice, and by the rare "experiments of nature" in the human population, in whom there is absence or dysfunction of one of the adhesion molecules.

Among the many types of adhesion molecule, the only known human deficiencies to date are of the branched pentasaccharide sialyl Lewis x (CD15s) antigen and two members of the integrin family, the leucocyte integrin CD18 and the platelet integrin CD41/CD61 (GPIIb/IIIa). In this review, we describe these defects and discuss how affected patients have provided important clues to the function of these molecules.

Background

Each member of the integrin family consists of a non-covalently linked heterodimer of an α chain and a β chain, transmembrane glycoproteins with short cytoplasmic tails. They are subdivided according to the different subunits, and more than 20 different combinations have been recognised.² Some bind to extracellular matrix proteins and take part in the interactions between cells and the extracellular matrix. Others bind to cell membrane proteins (for example, ICAM-1 and ICAM-2) and mediate cell-cell adhesion and cell-cell communication. In this way, they are able to integrate the activation of the extracellular matrix and the cytoskeleton (hence the term "integrin"). Ligand specificity is determined by the particular $\alpha\beta$ subunit combination of the integrin.

Table 1 Some important integrins mentioned in the text and their ligands

β subunit	β_2 (CD18)	β_3 (CD61)
α_L (CD11a)	LFA-1 CD11a/CD18 ICAMs	
α_M (CD11b)	Mac-1 CD11b/CD18 ICAM-1, fibrinogen	
α_X (CD11c)	p150.95 CD11c/CD18 iC3b	
α_V (CD51)		CD51/CD61 Vitronectin
α_{IIb} (CD41)		GPIIb/IIIa CD41/CD61 Fibrinogen

The ligands are given in italics.

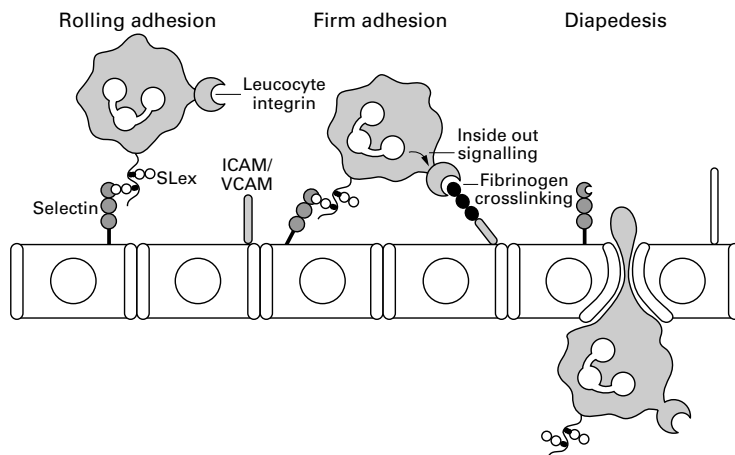


Figure 1 Mechanisms of leucocyte-endothelial interaction. Rolling adhesion mediated by sialyl Lewis x (SLex) and other glycosylated structures and selectins. Firm adhesion and diapedesis mediated by integrins and molecules of the immunoglobulin superfamily. ICAM, intercellular cell adhesion molecule; VCAM, vascular cell adhesion molecule.

Integrin ligands, including fibrinogen, use specific amino acid sequences as recognition motifs for receptor binding. The prototype motif is RGD.³ However, numerous other amino acid sequences are now recognised as integrin ligands, some of which are much longer than the originally described RGD motif.⁴ Fibrinogen is important in the leucocyte-endothelial interaction. Although leucocyte integrins are able to bind to endothelial ICAM-1 in the absence of fibrinogen, fibrinogen greatly enhances leucocyte binding to the endothelium, probably by acting as a bridge between leucocyte Mac-1 and endothelial ICAM-1 (fig 1).⁵ Platelet GPIIb/IIIa binds to three motifs in the fibrinogen chain: AGDV at the C-terminal γ 408–411 of the fibrinogen chain,^{6–8} an RGDS sequence at α 572–575, and an RGDV sequence at α 95–98.⁹ The ability of GPIIb/IIIa to bind fibrinogen is essential in platelet-platelet and platelet-endothelial interactions and might also be important in platelet-neutrophil interactions.^{10–11} Attachment between adjacent platelets after platelet activation is via a GPIIb/IIIa fibrinogen bridge. GPIIb/IIIa also mediates platelet adhesion to the intact endothelial surface via a bridging mechanism using fibrinogen and endothelial ICAM-1 or $\alpha_v\beta_3$ (fig 2).¹²

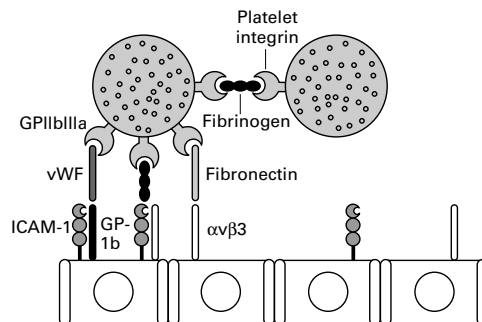


Figure 2 Platelet-endothelial and platelet-platelet interactions. Platelets may bind via one of several bridging mechanisms to intact endothelium. Platelet-platelet interactions are mediated via GPIIb/IIIa and a fibrinogen bridge. ICAM-1, intercellular cell adhesion molecule 1; vWF, von Willebrand factor.

In conclusion, there is a complex network of cellular adhesive events between platelets, leucocytes, and endothelial cells dependent upon adhesion molecules, particularly integrins and their ligands, linking the processes of haemostasis, thrombosis, and inflammation.

Defects of integrin expression

LEUCOCYTE ADHESION DEFICIENCY TYPE 1 (LAD-1)

LAD-1 is an immune deficiency characterised by the inability of leucocytes, particularly neutrophils, to emigrate from the intravascular space to sites of tissue inflammation. The syndrome was first described by Hayward *et al* in 1979.¹³ In its classic form, it is an autosomal recessive disease characterised by recurrent bacterial infections, impaired pus formation, abnormal wound healing, and persistent peripheral blood leucocytosis. A delay in separation of the umbilical cord may be the first sign of the disease. It is caused by the absence or dysfunction of CD18. The genetic defect is at chromosome 22q21 and consists of a variety of mutations in the common β_2 chain, including splicing, frame shift, missense, and initiation codon abnormalities (fig 3). The aberrant CD18 precursor protein is either undetectable or synthesised in a mutant form unable to associate with its α subunit. Thus, the expression of all three of the leucocyte β_2 integrins is either completely absent or deficient.

The phenotype of this condition is variable, with disease severity correlating to a large extent with the levels of expression of β_2 integrin. Patients with < 1% expression present early in life, have recurrent life threatening infections, and require bone marrow transplantation for long term survival.²⁶ Patients with a moderate phenotype—having 2.5–6% of the normal concentrations of protein—have periodontitis, delayed wound healing, skin infections, and skin inflammation resembling pyoderma gangrenosum^{27–28} (fig 4). Delayed umbilical cord separation is not a feature of the moderate phenotype disorder. Heterozygous relatives of the patients have 40–60% of the normal amount of β_2 integrins and are clinically normal.²⁹

Recently, it has become apparent that the severity of the moderate phenotype disease is dependent upon the relative binding of the mutant CD18 molecule to the three CD11 proteins. A detailed molecular analysis of patients with CD18 values between 1% and 10% of normal values has revealed that the specific CD18 mutations in these individuals lead to greatly different levels of CD11a/CD18, CD11b/CD18, and CD11c/CD18 expression. For example, a mutation in the CD18 gene that leads to an A270V substitution in the CD18 protein supports some expression and function of CD11b/CD18 and CD11c/CD18 but not of CD11a/CD18. As more of these mutations are examined in detail, the importance of different regions of the CD18 molecule for expression and function will be elucidated.

Although an absence of CD18 is clearly detrimental in the long term, there has been interest in short term blocking of integrin function

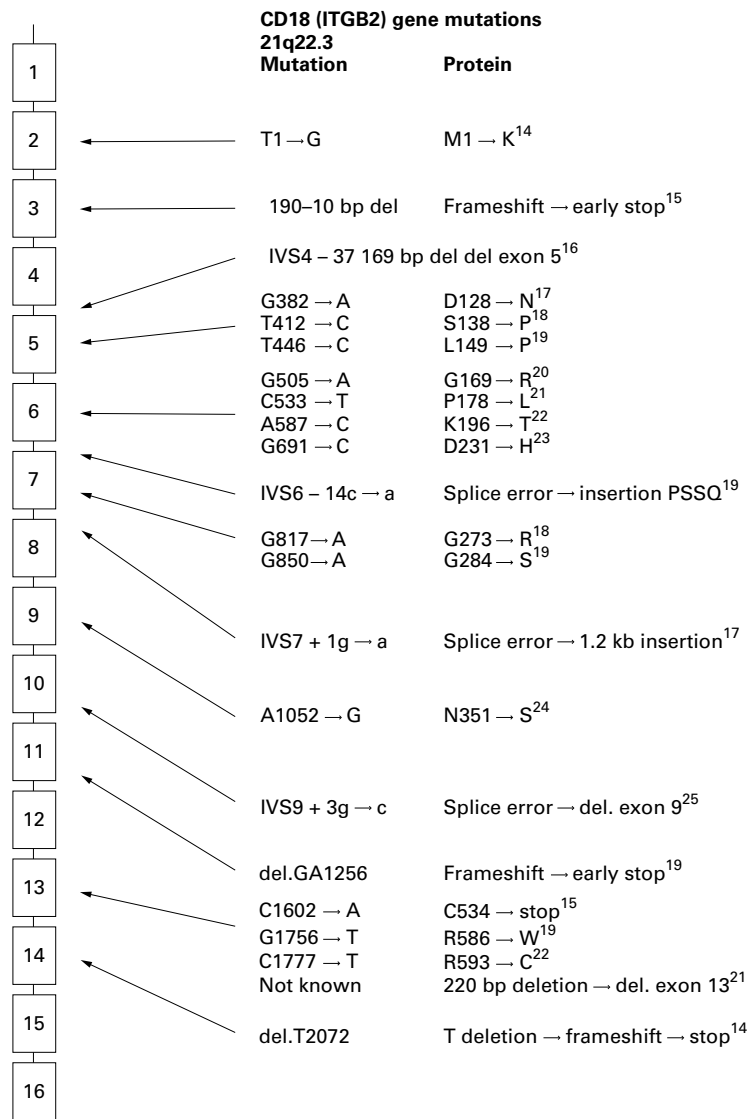


Figure 3 Exon map of the gene encoding CD18 (ITGB2) showing the gene mutations identified to date and the resultant changes in the protein product.

using monoclonal antibodies in several inflammatory conditions, including bone marrow transplant associated graft versus host disease,³⁰ meningitis,³¹ acute respiratory distress syndrome (ARDS)³² and psoriasis.³³

GLANZMANN'S THROMBASTHENIA

Glanzmann's thrombasthenia is an autosomal recessive disease characterised by a normal platelet count, a prolonged bleeding time, poor or absent clot retraction, and abnormal platelet aggregation. The disease was first described in 1918,³⁴ and is now known to result from absent or defective platelet GPIIb/IIIa.³⁵ Several mutations have been identified both in GPIIb (CD41) and in GPIIIa (CD61). In GPIIb, these mutations lead to defects in mRNA splicing,³⁶ mRNA stability,³⁷ subunit association,³⁸ intracellular trafficking,³⁹ and ligand binding.⁴⁰ Mutations in the GPIIIa gene include nucleotide substitutions, splicing defects, small deletions, gross deletions, and complex rearrangements, and they all affect integrin mediated signal transduction⁴¹ (fig 5).

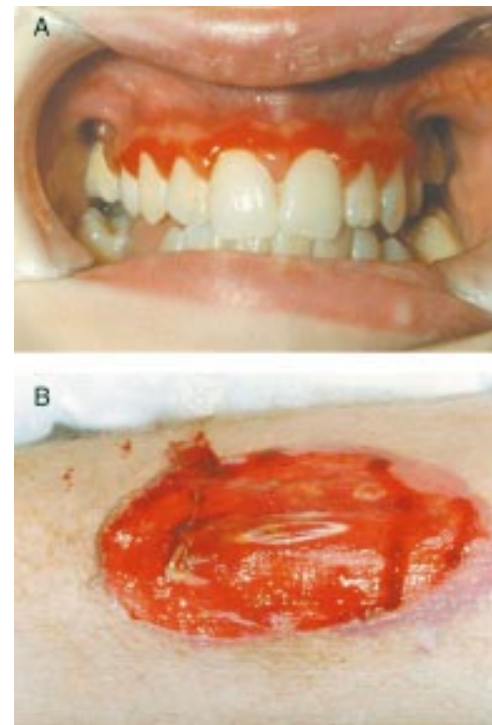


Figure 4 (A) Gingivitis and (B) non-healing in a patient with leucocyte adhesion deficiency type 1 (LAD-1).

The absence of GPIIb/IIIa means that although activated platelets can bind to the subendothelium, they cannot recruit additional platelets or bind to intact endothelium.

Glanzmann's thrombasthenia has been classified into two types: type 1, in which GPIIb/IIIa is completely absent; and type 2, in which 5–20% of the β_3 integrin is expressed. Clot retraction is completely absent in type 1 and decreased in type 2. Clot retraction depends on conformational changes in the platelet cytoskeleton demonstrating that "outside in" signalling via GPIIb/IIIa is functionally important. However, the classification has no clinical relevance because, in contrast to the leucocyte adhesion defects, the haemorrhagic tendency in Glanzmann's thrombasthenia is not related to the quantity of GPIIb/IIIa on the platelet surface.

Several GPIIb/IIIa blockers are now in clinical use and under development. These are antibody and peptide based antagonists given intravenously, or non-peptides with parenteral or oral routes of administration. Abciximab is the Fab fragment of a monoclonal antibody against GPIIb/IIIa that has been humanised to reduce immunogenicity.⁶¹ Eptifibatid is based upon the snake disintegrin, barbourin, which contains the amino acid sequence KGN within a disulphide ring.⁶² Specific for GPIIb/IIIa, this blocker is believed to be an analogue of the AGDV sequence at the extreme C-terminus of the γ -chain of fibrinogen, which mediates the binding of fibrinogen to the receptor.⁶³ RGD was the starting point for the design of tirofiban.⁶⁴ All three of these GPIIb/IIIa blockers, and the others in clinical testing, react with the resting and active forms of GPIIb/IIIa. Many of the oral GPIIb/IIIa blockers also are mimetics of the γ -chain or RGD peptides. There have been several clinical trials of these

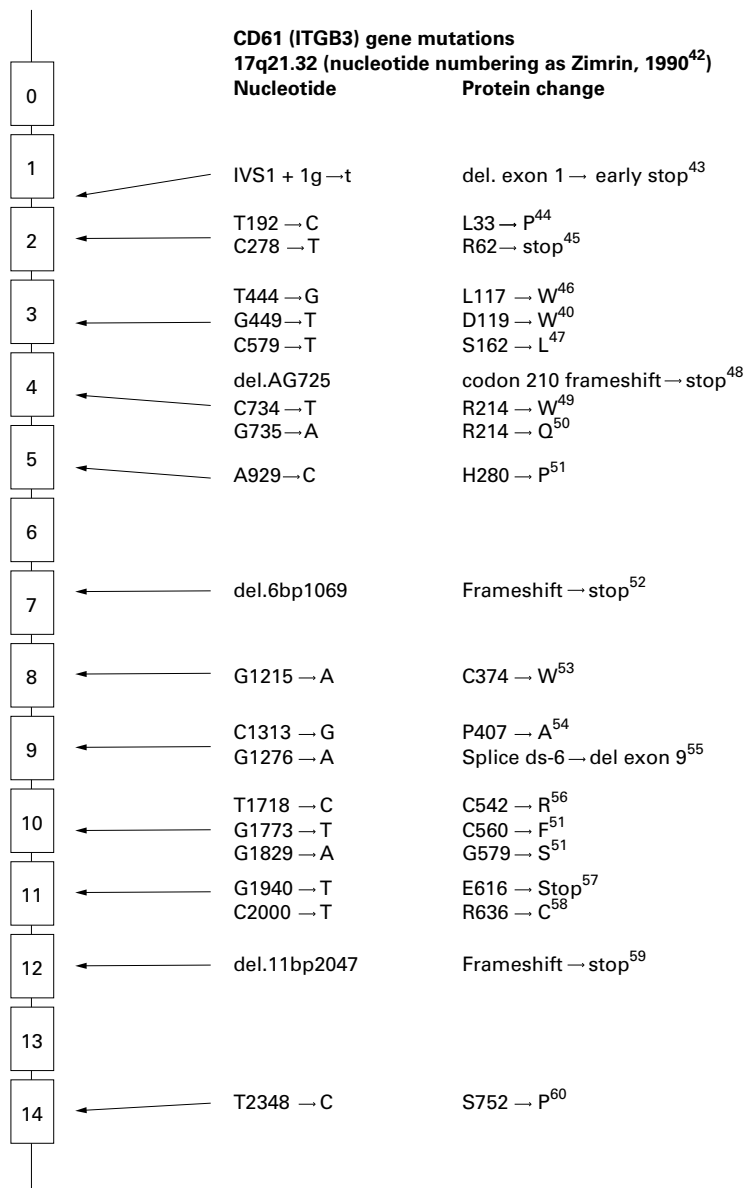


Figure 5 Exon map of the gene encoding CD61 (ITGB3) showing the gene mutations identified to date and the resultant changes in the protein product. The complex rearrangements del 1 kb, inv 15 kb are not shown.^{60a}

drugs reporting favourable results in acute coronary syndromes and stroke, and their use is likely to become widespread.⁶⁵

Defects of integrin function: LAD and Glanzmann's variants

Integrins change their conformation and shape during ligand binding and activation (fig 6).⁶⁶⁻⁶⁸ This property allows integrins to play a role in both "outside in" and "inside out" signalling. Through the outside in signalling pathway, binding of ligand to integrins alters gene expression and affects cellular proliferation and differentiation.⁶⁹ The inside out signal pathway is important for leucocyte recruitment and platelet aggregation because conformational changes in the integrin heterodimer expose the high affinity integrin binding site, substantially increasing the binding of specific ligand. Integrin intracellular signalling is poorly understood, but it is known to be dependent on

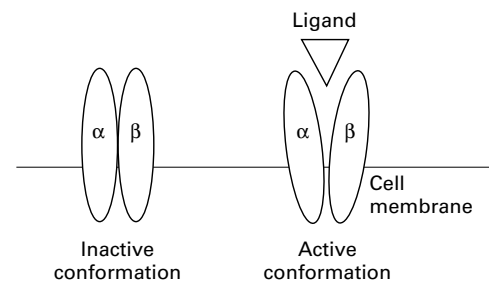


Figure 6 The integrin heterodimer exists in two conformational forms. On the left is the inactivated form. Activation may occur by binding of ligand (right). This may cause "outside in" signalling, in which intracellular events occur as a result of ligand binding. Alternatively, "inside out" signalling may occur, changing the conformation of the integrin from inactive to active, exposing the ligand binding site, and making the integrin much more likely to bind to its ligand.

the presence of divalent cations.⁷⁰ Several antibodies exist that are known as "activation reporters"; that is, they bind at or very near to the ligand binding site of the integrin. Mab 24 identifies the active site of CD11b/CD18⁷¹ and Pac-1 identifies the active site of GPIIb/IIIa.⁷² Alternatively, because fibrinogen is an integrin ligand, its binding to either molecule can be used as a proxy measure of the activation state (figs 7 and 8).

We have recently described a defect of integrin function in a 15 year old boy who had "moderately severe" LAD-1, but whose CD18 expression was 40-60% of normal,¹⁸ which should be sufficient for normal integrin function. However, this patient's neutrophils did not bind to the integrin ligands and did not display a β_2 integrin activation epitope after stimulation. Sequencing of the two CD18 alleles revealed that the patient was a compound heterozygote with two different mutations in the β_2 subunit conserved domain. Cells transfected with the first mutation were totally unable to express CD18, just as in LAD-1. Normal expression of CD18 was observed in cells that were transfected with the second mutation, but these β_2 integrins could not be activated and did not support integrin function. Thus, this unique patient expressed adequate amounts of CD18, but the failure of CD18 function led to a disease that is clinically indistinguishable from the severe form of LAD-1.

Defects in integrin function have also been found in variant forms of Glanzmann's thrombasthenia. A single case has been described similar to ours in which a boy with 50% of the normal values of β_3 integrin detectable by flow cytometry had a clinical syndrome indistinguishable from Glanzmann's thrombasthenia.⁴¹ This boy was also found to be a compound heterozygote with different mutations in each of his two β_3 integrin alleles. One of these mutations resulted in a truncated protein containing only the first eight of the 47 amino acids normally present in the cytoplasmic domain, whereas the other resulted in a frame shift and early termination. In this case, the truncated cytoplasmic portion of the β_3 integrin was thought to interrupt inside out signal transduction and thus disrupt function, preventing integrin activation and fibrinogen binding.

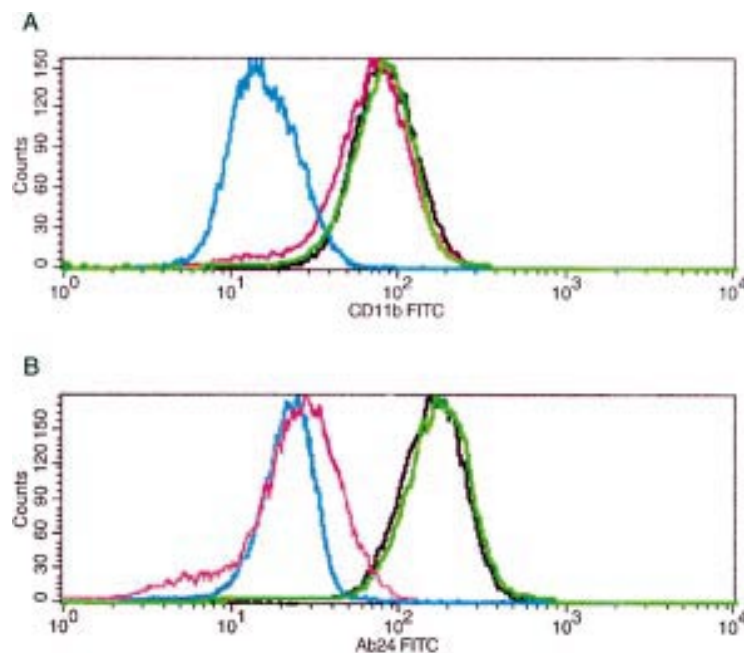


Figure 7 Flow cytometry plots showing (A) neutrophil CD11b expression and (B) Mab 24 binding after maximal stimulation with *f-met-leu-phe*. Blue, leucocyte adhesion deficiency type 1 (LAD-1); red/pink, leucocyte integrin activation abnormality; green, Glanzmann's thrombasthenia; black/brown, immunocompetent control.

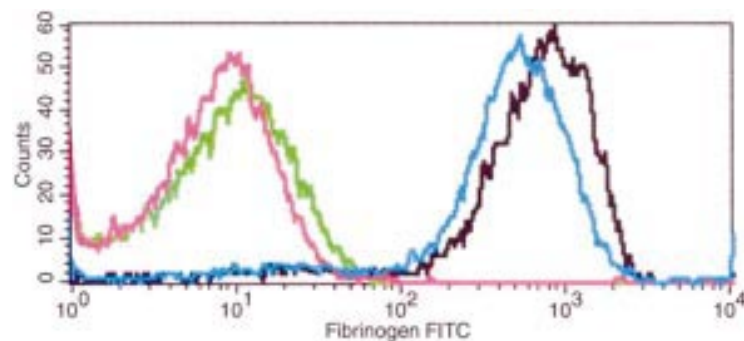


Figure 8 Flow cytometry plots showing platelet fibrinogen binding after maximal stimulation with thrombin. Blue, LAD-1; red/pink, Glanzmann's type 1; green, Glanzmann's type 2; black/brown, immunocompetent control.

Tako Kuijpers and colleagues⁷³ recently described a patient with defective function of both the β_2 (LAD-1) and β_3 (Glanzmann's thrombasthenia) integrins. Although both molecules were present on cell surfaces, they did not express activation epitopes on stimulation, and both leucocyte adhesion and platelet aggregation were impaired. Clinically, the child had features of both moderate type LAD-1 and Glanzmann's thrombasthenia. This patient and several similar cases are likely to have defective inside out signalling of both β_2 and β_3 integrins, leading to a failure of high avidity ligand binding.

LEUCOCYTE ADHESION DEFICIENCY TYPE 2 (LAD-2) Sialyl Lewis x is a carbohydrate component existing on neutrophils, monocytes, and eosinophils that is involved in the very first step of the leucocyte-endothelial interaction, rolling adhesion. This step is mediated via an interaction between leucocyte sialyl Lewis x and endothelial adhesion molecules of the CD62 selectin family (fig 1). LAD-2 is a very rare autosomal recessive disease, so far reported in

only two families, which is characterised by recurrent infections and neutrophil motility dysfunction, but normal β_2 integrin expression. It is related to defective expression in leucocytes of sialyl Lewis x, a fucosylated ligand for endothelial selectins.⁷⁴ Neutrophil rolling on vascular endothelium and hence recruitment to sites of infection is extremely limited. These patients have severe mental retardation, the rare Bombay blood group, and are Lewis negative, suggesting a generalised defect of fucose metabolism. The defect in LAD-2 has been localised to the *de novo* pathway of GDP fucose biosynthesis,⁷⁵ but the molecular basis is still unknown.

Conclusion

The adhesion molecules are of profound importance in health and disease. There are several human "experiments of nature" that illustrate their central role in thrombosis, haemostasis, and inflammation. They have a role in cell adhesion, migration, activation, embryogenesis, growth, and differentiation. Therapeutic advances based upon this new knowledge have already been made, with a new class of drugs for use in acute coronary syndromes and stroke, the GPIIb/IIIa antagonists. A basic understanding of the adhesion molecules is important because, as our understanding increases, it is likely that blocking strategies will be developed against other adhesion molecules in variety of clinical conditions.

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