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Defects in the Leukocyte Adhesion Cascade

Amos Etzioni

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Abstract Leukocyte trafficking from bloodstream to tissue is important for the continuous surveillance for foreign antigens as well as for rapid leukocyte accumulation at sites of inflammatory response or tissue injury. Leukocyte interaction with vascular endothelial cells is a pivotal event in the inflammatory response and is mediated by several families of adhesion molecules. The crucial role of the β_2-integrin subfamily in leukocyte emigration was established after leukocyte adhesion deficiency (LAD) I was discovered. Patients with this disorder suffer from life-threatening bacterial infections, and in its severe form, death usually occurs in early childhood unless bone marrow transplantation is performed. The LAD II disorder clarifies the role of the selectin receptors and their fucosylated ligands. Clinically, patients with LAD II suffer not only from a less severe form of infectious episodes resembling the moderate phenotype of LAD I but also from severe psychomotor and growth retardation. LAD III emphasizes the importance of the integrin-activation phase in the adhesion cascade. All hematopoietic integrin activation processes are defective, which lead to severe infection as observed in LAD I and to marked increase tendency for bleeding problems (defective activation of β_1, β_2, and β_3 integrins). The various genetic defects leading to all adhesion molecules syndrome will be discussed.

Keywords Adhesion · Leukocyte · Integrin · Selectins · Chemokines · LAD syndrome · Sialyl Lewis X · Rap1

A. Etzioni (✉)
Meyer Children Hospital, Rappaport School of Medicine, Technion,
Haifa, Israel
e-mail: etzioni@rambam.health.gov.il

Introduction

The migration of leukocytes from the bloodstream to the tissue occurs in several distinct steps [1, 2]. Leukocytes in the circulation must resist shear forces in order to arrest along the vascular endothelium. Under normal conditions, leukocytes move rapidly in the laminar flow stream of blood and do not adhere to the endothelium. However, with activation of the endothelium due to local trauma or inflammation, leukocytes immediately begin to roll along the venular wall. The endothelial selectins (expressed after endothelial activation) will bind to the leukocytes through their carbohydrate ligands and, thus, cause the leukocytes to roll on the endothelium. This first transient and reversible step is a prerequisite for the next stage, the activation of leukocytes. Binding to the selectins tethers the leukocytes, exposing them to stimuli in the local microenvironment mainly chemokines, which will activate the integrins. This process will increase their affinity (through conformational changes) and avidity (through clustering) [3]. Integrin activation is followed by firm adhesion, i.e., sticking which is an extremely rapid phase, after which transmigration occurs [4]. Each of these steps involves different adhesion molecules and can be differentially regulated. Several years after reporting the structure of the leukocyte integrin molecule, a genetic defect in the subunit of the molecule (ITGB2) was discovered. This syndrome, now called LAD I (OMIM 116920), has been described in more than 300 children and is characterized by delayed separation of the umbilical cord, recurrent soft tissue infections, chronic periodontitis, marked leukocytosis, and a high mortality rate at early age.

Ten years later, in 1992, a second defect, LAD II (OMIM 266265), was discovered and was found to be due to defect

in the synthesis of selectin ligands. The clinical course with respect to infectious complications is a milder one than LAD I. However, LAD II patients present other abnormal features, such as growth and mental retardation. The primary genetic defect is mutation in the specific fucose transporter to the Golgi apparatus (FUCT1).

Recently, a third rare LAD syndrome has been described. Patients with LAD III suffer from severe recurrent infections, similar to LAD I, and a severe bleeding tendency. Although integrin structure is intact, a defect in integrins activation is the primary abnormality in LAD III. Defects both in Kindlin 3 and CAL-DAG-GEF1 [5] were found to cause LAD III (Table 1).

LAD I

LAD I is an autosomal recessive disorder caused by mutations in the common chain (CD18) of the β_2 integrin family. Up to now, several hundreds of patients have been reported worldwide. The prominent clinical feature of these patients is recurrent bacterial infections, primarily localized to skin and mucosal surfaces. Sites of infection often progressively enlarge, and they may lead to systemic spread of the bacteria. Infections are usually apparent from birth onward, and a common presenting infection is omphalitis with delayed separation of the umbilical cord. The most frequently encountered bacteria are *Staphylococcus aureus* and Gram-negative enteric organisms, but fungal infections are also common. The absence of pus formation at the sites of infection is one of the hallmarks of LAD I. Severe gingivitis and periodontitis are major features among all patients who survive infancy. Impaired healing of traumatic or surgical wounds is also characteristic of this syndrome [6].

The recurrent infections observed in affected patients result from a profound impairment of leukocyte mobilization into extravascular site of inflammation. Skin windows yield few, if any, leukocytes, and biopsies of infected tissues demonstrate inflammation totally devoid of neutrophils. These findings are particularly striking considering that marked peripheral blood leukocytosis (five to 20 time normal values) is consistently observed during infections. In contrast to their difficulties in defense against bacterial and fungal microorganisms, LAD I patients do not exhibit a marked increase in susceptibility to viral infections [7].

The severity of clinical infectious complications among patients with LAD I appear to be directly related to the degree of CD18 deficiency. Two phenotypes, designated severe deficiency and moderate deficiency, have been defined [8]. Patients with less than 1% of the normal surface expression exhibited a severe form of disease with earlier, more frequent, and more serious episodes of infection, often leading to death in infancy, whereas patients with some surface expression of CD18 (2.5–10%) manifested a moderate to mild phenotype with fewer serious infectious episodes and survival into adulthood.

The defective migration of neutrophils from patients with LAD I was observed in studies in vivo as well as in vitro. Neutrophils failed to mobilize to skin sites in the in vivo Rebuck skin-window test. In vitro studies demonstrated a marked defect in random migration as well as chemotaxis to various chemoattractant substances. Adhesion and transmigration through endothelial cells were found to be severely impaired. With the use of an

Table 1 Leukocyte adhesion deficiency syndromes

	LAD I	LAD II	LAD III
Clinical manifestation			
Recurrent severe infections	+++	+	+++
Periodontitis	++	++	?
Skin infection	++	+	++
Delayed separation of the Umbilical cord	+++	–	+++
Developmental abnormalities	–	+++	
Bleeding tendency	–	–	+++
Laboratory Findings			
Neutrophilia	+++	+++	+++
CD18 expression	↓↓↓ or Absent	N	N
SLeX expression	N	Absent	N
Neutrophil rolling	N	↓↓↓	N
Neutrophil adherence	↓↓↓	↓	↓↓↓
Platelet aggregation	N	N	↓↓↓
Primary genetic defect	+(ITGB2)	+(FUCT1)	+(Kindlin 3)

intravital microscopy assay, it was found that fluorescein-labeled neutrophils from a LAD I boy rolled normally on inflamed rabbit venules, suggesting that they were capable of initiating adhesive interactions with inflamed endothelial cells [9]. However, these cells failed to perform activation-dependent, β2 integrin-mediated adhesion steps and did not stick or emigrate when challenged with a chemotactic stimulus.

Patients with LAD I exhibit neutrophilia in the absence of overt infection with marked granulocytosis with neutrophils in peripheral blood reaching levels of up to 100,000/μl during acute infections.

Early studies showed that patients with this disorder were uniformly deficient in the expression of all three leukocyte integrins (Mac-1, LFA-1, p150, 95), suggesting that the primary defect was in the common β2-subunit, which is encoded by a gene located at the tip of the long arm of chromosome 21q22.3.

Subsequently, several LAD I variants were reported in which there was a defect in β2-integrin adhesive functions despite normal surface expression of CD18. A child with classical LAD I features with normal surface expression of CD18 was reported [10], in whom a mutation in CD18 was found to lead to a nonfunctional molecule.

The molecular basis for CD18 deficiency varies [11]. In some cases, it is due to the lack or diminished expression of CD18 mRNA. In other cases, there is expression of mRNA or protein precursors of aberrant size with both larger and smaller CD18 subunits. Analysis at the gene level has revealed a degree of heterogeneity, which reflects this diversity. A number of point mutations have been reported, some of which lead to the biosynthesis of defective proteins with single amino acid substitutions, while others lead to splicing defects, resulting in the production of truncated and unstable proteins.

Notably, a high percentage of CD18 mutations identified in LAD I is contained in the extracellular domain of the CD18 (on exon 9) which is a highly conserved regions. Domains within this segment are presumably required for association and biosynthesis of precursors and may represent critical contact sites between the α- and β-subunit precursors. Thus, LAD I can be caused by a number of distinct mutational events, all resulting in the failure to produce a functional leukocyte β2 subunit. Recently, a case of somatic mosaicism due to in vivo reversion of the mutant CD18 was reported [12]. Reversion mutations in LAD I may be a relative common event in this rare disease [13].

In any infant male or female with recurrent soft tissue infection and a very high leukocyte count, the diagnosis of LAD I should be considered. The diagnosis is even more suggestive if a history of delayed separation of the umbilical cord is present. To confirm the diagnosis, absence of the α and β subunits of the β2-integrin complex must be demonstrated. This can be accomplished with the use of the appropriate CD11 and CD18 monoclonal antibodies by flow cytometry. Sequence genetic analysis to define the exact molecular defect in the β2 subunit is a further option.

As leukocytes express CD18 on their surface at 20 weeks of gestation, cordocentesis performed at this age can establish a prenatal diagnosis. In families in whom the exact molecular defect has been previously identified, an earlier prenatal diagnosis is possible by chorionic biopsy and mutation analysis.

Furthermore, recently pre implantation diagnosis was also performed [14].

Patients with the moderate LAD I phenotype usually respond to conservative therapy and the prompt use of antibiotics during acute infectious episodes. Prophylactic antibiotics may reduce the risk of infections.

Although granulocyte transfusions may be lifesaving, their use is limited because of difficulties in supply of daily donors and immune reactions to the allogeneic leukocytes.

At present, the only corrective treatment that should be offered to all cases with the severe phenotype is bone marrow transplantation [15]. The absence of host LFA-1 may be advantageous in these transplants because graft rejection appears to be in part dependent upon the CD18 complex.

The introduction of a normal β2-subunit gene (ITGB2) into hematopoietic stem cells has the potential to cure children with LAD I [16]. Recently, successful gene therapy has been reported in canine model of LAD I [17], applying that this procedure may be beneficial also in humans in the future.

LAD II

LAD II syndrome (OMIM266265) results from a general defect in fucose metabolism, causing the absence of SLeX and other fucosylated ligands for the selectins. LAD II was first described in two unrelated Arabs consanguineous parents [18]. This is an extremely rare condition with only six patients reported [19].

Affected children were born after uneventful pregnancies with normal height and weight. No delay in the separation of the umbilical cord was observed. They have severe mental retardation, short stature, distinctive facial appearance, and rare Bombay (hh) blood phenotype. From early life, they have suffered from recurrent episodes of bacterial infections, mainly pneumonia, periodontitis, otitis media, and localized cellulitis. During times of infections, the neutrophil count increases up to 150,000/μl. Several mild to moderate skin infections without obvious pus have also been observed [20]. The infections have not been life-threatening events and are usually treated in the outpatient

clinic. Interestingly, after the age of 3 years, the frequency of infections has decreased, and the children no longer need prophylactic antibiotics. At older age, their main infectious problem is severe periodontitis as is also observed in patients with LAD I [21].

Overall, the infections in LAD II appear to be comparable to the moderate rather than the severe phenotype of LAD I. It is possible that the ability of LAD II neutrophils to adhere and transmigrate via β2-integrin under conditions of reduced shear forces [9] may permit some neutrophils to emigrate at sites of severe inflammation where flow may be impaired, thereby allowing some level of neutrophil defense against bacterial infections.

Rolling, the first step in neutrophil recruitment to site of inflammation, is mediated primarily by the binding of the selectins to their fucosylated glycoconjugate ligands. Using intravital microscopy, it was observed that the rolling fraction of normal donor neutrophils in this assay was around 30%, and LAD I neutrophils behaved similarly. In contrast, LAD II neutrophils rolled poorly (only 5%) and failed to emigrate [9].

Since the first two LAD II patients identified were the offspring of first-degree relatives and since the parents were clinically unaffected, autosomal recessive inheritance was assumed.

In addition to the Bombay phenotype (absence of the H antigen), the cells of LAD II patients were also found to be Lewis a- and b-negative and the patients were non-secretors. The three blood phenotypes (Bombay, Lewis a and b) have in common a lack of fucosylation of glycoconjugates. These facts suggested that the primary defect in LAD II must instead be a general defect in fucose production.

After the observation that the defect in the Arab patients may be localized in the de novo GDP-1-fucose biosynthesis pathway [22], the two enzymes involved with this pathway, GMD and FX protein, were measured and were found to be normal with no mutation in cDNA isolated from LAD II patients. Another child, from a Turkish origin, was also described with LAD II in whom decreased GDP-1-fucose transport into the Golgi vesicles was detected [23].

Using the complementation cloning technique, the human gene encoding the fucose transporter was found to be located on chromosome 11. The Turkish child was found to be homozygous for a mutation at amino acid 147 in which arginine is changed to cysteine, while the two Arab patients examined were found to have a mutation in amino acid 308 in which threonine is changed to arginine [24]. Both mutations are located in highly conserved transmembrane domains through evolution. LAD II is, thus, one of the groups of congenital disorders of glycosylation (CDG) and is classified as CDG-IIc. In some cases, the mutated (nonfunctional) transporter is correctly located in the Golgi apparatus, while in two patients, the truncated transporter was unable to localize to the Golgi complex [25]. Although only four mutations were described so far, some genotype–phenotype correlation can be observed. Recent studies using a mouse model in which the GDP fucose transporter was knocked out showed compatible results to LADII patients. These mice showed severe growth retardation [26] and severe impairment in P–E and L-selection rolling on cremaster muscle venules.

From the biochemical aspect, once the primary defect was found, several studies were done to clarify the defect. As growth and mental retardation are prominent features of LAD II, and Notch proteins, which are important in normal development, contain fucose, Sturla et al. [27] looked at the fucosylation process of Notch in LAD II. Fractionation and analysis of the different classes of glycants indicated that the decrease in fucose incorporation is not generalized and is mainly confined to terminal fucosylation of N-linked oligosaccharides. In contrast, the total levels of protein O-fucosylation, including that observed in Notch protein, were unaffected. Indeed, it was recently observed that the O-fucosylation process take place in the endoplasmatic compartment and not in the Golgi apparatus [28]. Thus, it is still unclear what leads to the severe developmental delay observed in LAD II.

LAD II is a very rare syndrome described so far only in six children. As the clinical phenotype is very striking, the diagnosis can be made based on the presence of recurrent, albeit mild infections, marked leukocytosis, and the Bombay blood group, in association with mental and growth retardation.

An analysis of peripheral blood leukocytes by flow cytometry using a CD15a monoclonal antibody should be performed to determine SLeX expression. To confirm the diagnosis, sequence analysis of the gene encoding the GDP-fucose transporter should be performed.

Each of the patients described so far with LAD II suffered from several episodes of infections, which responded well to antibiotics. No serious consequences were observed, and prophylactic antibiotic is not needed. The patients' main chronic problem has been periodontitis, a condition that is especially difficult to treat in children with severe mental retardation [21]. The oldest LAD II patient is now 19 years and has a severe psychomotor retardation with only mild infectious problems.

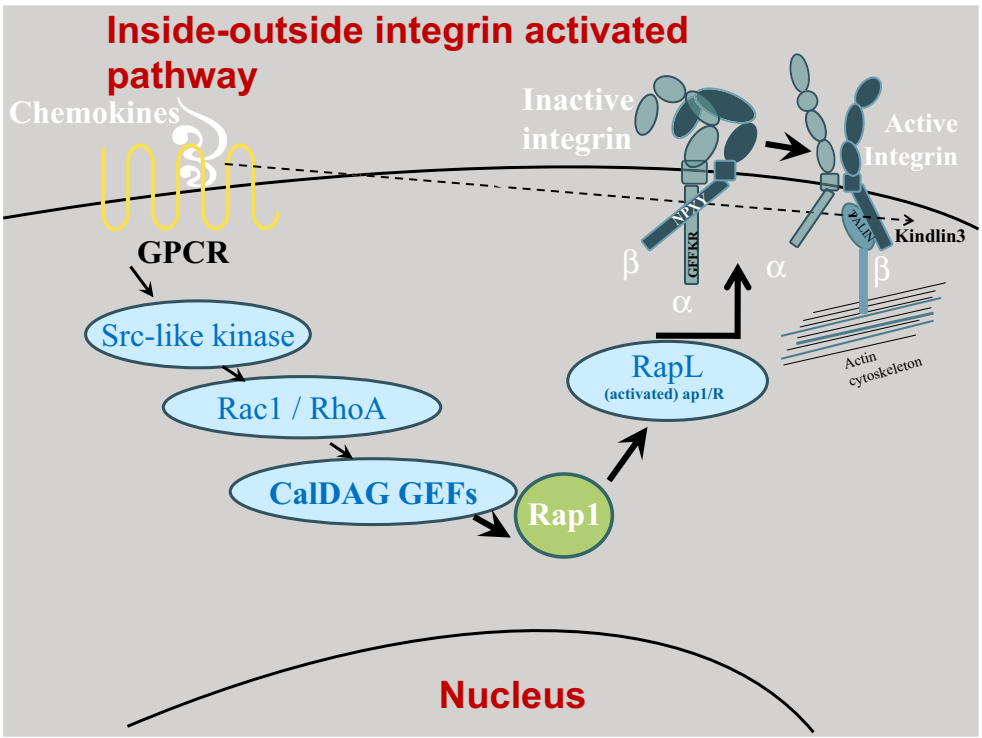
Because of the proposed defect in fucose production, supplemental administration of fucose to the patients has been suggested. Indeed fucose supplementation caused a dramatic improvement in the condition of the Turkish child [29]. A marked decrease in leukocyte count with improved neutrophil adhesion was noted. Unfortunately,

while using exactly the same protocol, no improvement in laboratory data or clinical features were seen in two Arab children [30]. This difference may be due to the fact that the genetic defect in the Turkish child leads to a decreased affinity of the transporter for fucose; thus, an increase in the cytosolic concentration of fucose would be expected to overcome, at least in part, the defect in fucose transport.

LAD III

Recently, a rare autosomal recessive LAD syndrome that is distinct from LAD I has been reported [31]. Although leukocyte integrin expression and intrinsic adhesive activities to endothelial integrin ligands were normal, in situ activation of all major leukocyte integrins, including LFA-1, Mac-1, and VLA-4, by endothelial displayed chemokines or chemoattractants, was severely impaired in patient derived lymphocytes and neutrophils. Although LAD leukocytes rolling on endothelial surfaces was normal, they failed to arrest on endothelial integrin ligands in response to endothelial displayed chemokines. G-protein coupled receptor (GPCR) signaling on these cells appeared to be normal and the ability of leukocyte to migrate towards a chemotactic gradient was not impaired. The key defect in this syndrome was attributed to a genetic loss of integrin activation by rapid chemoattractant-stimulated GPCR signals [32]. This novel LAD shows significant similarities to three previous cases commonly referred to as LAD I variants [33–35]. All four cases had similar clinical symptoms, characterized by severe recurrent infections, bleeding tendency, and marked leukocytosis. In all cases tested, integrin expression and structure were intact with a defect in integrin activation by physiological inside-out stimuli. As these events cannot take place in LAD I leukocyte, it was proposed to designate this group of integrin activation disorders as LAD III [32]. The term LAD I variant, which has been ascribed to these unique syndromes, is inaccurate because these syndromes do not evolve from structural defects in leukocyte or platelet integrins.

In all of the LAD III cases, defects in GPCR-mediated integrin activation are also accompanied by variable defect in non-GPCR mediated inside-out activation of leukocyte integrins. A growing body of evidence implicates the Ras-related GTPase, Rap-1, as a key regulator of integrin activation by these and other inside-out stimuli. Rap-1 was also implicated in the activation of platelet and megakaryocyte GpIIbIIIa, which is defective in LAD III. It is, thus, highly attractive that one or more of the new LAD III cases involve either direct or indirect defect in Rap-1 activation of leukocyte and platelet integrins. Although lymphocytes from two cases expressed normal level of Rap-1, in one case studied, an aberrant activation pattern was observed [36].



However, the ubiquitous expression of Rap-1 in most tissues and its highly diverse functions in nonhematopoietic cells [37] make it unlikely that Rap-1 is structurally mutated in any of the new LAD III cases. It is, thus, possible that a hematopoetic specific effector of Rap-1 activity such as CAL DAG GEF1, is defective in these and related LAD III cases. Indeed, a mouse model in which such an activator (CAL-DAG- GEF1) was knocked out resembled the bleeding tendency seen in LAD III [38, 39]. In several patients indeed, mutation in CAL-DAG-GEF1 was found [40, 41]. The role of CAL-DAG-GEF1 in the pathogenesis of LADIII is still unclear, as mutations in Kindlin 3, an essential regulator of integrin activation [42], was found in all patients studied so far with LADIII (many of the patients from Turkish origin had a concomitant mutation also in CALDAGGEF 1) [40, 41]. Kindlin 3 is required for beta 2 integrin-mediated leukocyte adhesion to endothelial cells [43], and indeed fransfection of LAD III lymphocytes with Kindlin 3 complementary DNA but not CALDAGGEF1 cDNA reversed the LAD III defect, restoring integrin-mediated adhesion and migration [44, 45].

These patients need prophylactic antibiotics as well as repeated blood transfusion. The only curative treatment is bone marrow transplantation which should be performed as early as possible.

Conclusions

Leukocyte trafficking from bloodstream to tissue is important for the continuous surveillance for foreign antigens, as well as for rapid leukocyte accumulation at sites of inflammatory response or tissue injury. Leukocyte emigration to sites of inflammation is a dynamic process, involving multiple steps in an adhesion cascade. These steps must be precisely orchestrated to ensure a rapid response with only minimal damage to healthy tissue [42, 45]. Leukocyte interaction with vascular endothelial cells is a pivotal event in the inflammatory response and is mediated by several families of adhesion molecules.

The crucial role of the β2-integrin subfamily in leukocyte emigration was established after LAD I was discovered. Patients with this disorder suffer from life-threatening bacterial infections [6]. In its severe form, death usually occurs in early childhood unless bone-marrow transplantation is performed.

The LAD II disorder clarifies the role of the selectin receptors and their fucosylated ligands such as SLeX. In vitro as well as in vivo studies establish that this family of adhesion molecules is essential for neutrophil rolling, the first step in neutrophil emigration through the blood vessel [18]. Clinically, patients with LAD II suffer from a less severe form of infectious episodes, resembling the moderate phenotype of LAD I. This may be due in part to the ability of LAD II neutrophils to emigrate when blood flow rate is reduced and to the observed normal T- and B-lymphocyte function in LAD II as opposed to LAD I.

LAD III emphasizes the importance of the integrin-activation phase in the adhesion cascade. All hematopoeitic integrin molecules activation processes are defective leading to severe infection as observed in LAD I and to marked increase tendency for bleeding problems (defective activation of β_1, β_2, and β_3 integrins) [32].

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