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LEUKOCYTE ADHESION DEFICIENCY: MOLECULAR BASIS AND FUNCTIONAL CONSEQUENCES

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Leukocyte adhesion deficiency disease is characterized by a mutation in the gene encoding the β-subunit shared by three adhesive heterodimers, LFA-1, Mac-1 (CR3) and p150,95 expressed by leukocytes. An absent or abnormal β-subunit leads to defective expression of the three heterodimers. Severe and moderate phenotypes of the disease are defined by absent and low surface expression of the adhesion molecules. The disease causes an inability of phagocytic cells to adhere to endothelial cells and thereafter to migrate to sites of infections. Severe widespread life-threatening bacterial and fungal infections are the consequences of this abnormality. Cure of the disease can be effected by allogeneic bone marrow transplantation. T-lymphocyte adhesion to various cells is also impaired; its consequences are, however, limited because of the existence of other T-cell-adhesive pathways. Nevertheless, haploidentical bone marrow graft rejection does not occur in the severe phenotype, an indication for possible immunotherapy with LFA-1 specific monoclonal antibodies.

KEY WORDS: Leukocyte adhesion deficiency, LFA-1, Mac-1, p150,95, haploidentical bone marrow transplantation.

INTRODUCTION

In the 1970s there were several reports of patients suffering from widespread recurrent bacterial infections that led to early death. The leukocytes from these patients were found to lack the oxidative burst in response to opsonized particles and to have impaired chemotaxis[1–7]. These abnormalities were shown by Crowley *et al.* to be associated with the lack of a major surface protein of 110 000 Mr[8]. Other reports subsequently described similar patients whose granulocytes did not express a surface protein of 150 000 or 180 000 Mr[9,10]. Meanwhile, monoclonal antibodies were produced specific (1) for a lymphocyte function associated antigen (LFA-1) containing subunits of 177 000 and 95 000 Mr and (2) for a phagocyte cell membrane molecule with subunits of 165 000 and 95 000 (Mac-1, Mo1 or

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CR3)[11-18]. LFA-1 and Mac-1 were identified as adhesion-mediating molecules by the ability of the specific monoclonal antibodies to block various cell-to-cell interactions. It was recognized that the major surface component missing on patients' leukocytes was Mac 1 and, soon thereafter, that LFA-1 and p150,95, a third molecule, were missing as well. Phenotyping with monoclonal antibodies showed that different groups of patients had the same disease. This disease is defined by defective expression of three α–β heterodimeric molecules, Mac-1, LFA-1 and p150,95, which share a common β-subunit[19-22]. Similar patients, reported to have granulocyte actin dysfunction[23], on later evaluation have the same adhesion protein deficiency.

Since the molecular identification of the basis of the syndrome, 30 patients with recurrent bacterial infections have been found to lack the Mac-1, LFA-1 and p150,95 glycoproteins, and a similar number have been reported in the literature; several deceased patients may be assigned retrospectively to this group[1-10,19-37]. The syndrome has been called LFA-1, Mac-1, p150,95 glycoprotein deficiency, leu CAM deficiency and M 01 deficiency. We will use the name "leukocyte adhesion deficiency" (LAD) as proposed by Anderson and Springer[36]. The precise analysis of the structural defect underlying LAD and its functional consequences have illuminated the biology of leukocyte adhesion.

THE LFA-1, Mac-1, p150,95 ADHESIVE GLYCOPROTEIN FAMILY

The molecules are α–β heterodimers, the expression of which is restricted to leukocytes. The 95 000 Mr β-subunit is common to the three molecules, as shown by cDNA and amino acid sequencing[38-40]. The β-subunit has been defined by specific monoclonal antibodies (such as TS1/18, MHM 23, 60.3), and is also designated CD18. The β-subunit sequence has homology with the β-subunit of fibronectin receptor, chicken integrin and VLA molecules[39]. The three α-subunits are distinct according to molecular weight, sequence analysis and physico-chemical properties[38]. They are designated LFA-1 or CD11a, Mac-1 (or CR3) or CD11b, and p150 or CD11c. LFA-1, Mac-1 and p150 α-subunits have an amino acid sequence identity (33–50%), suggesting a common ancestral gene[42].

The three complexes have a distinct cell distribution, since LFA-1 is expressed on all leukocytes while Mac-1 is expressed on phagocytic cells and large granular lymphocytes; p150,95 is also expressed on some activated lymphocytes including cytolytic T cells and hairy leukemia cells[43,44].

Alpha- and β-subunits are synthesized as precursors glycosylated with N-linked high mannose carbohydrate groups. The α–β-subunit association precedes complex-type glycosylation that occurs in the Golgi apparatus. Glycoproteins are then transported to the cell surface (LFA-1, Mac-1 and p150,95) or to granules (Mac-1 and p150,95)[18,45]. α–β complexes contain one α- and one β-subunit[42]. Mac-1 and p150,95 expression on the cell surface of granulocytes and of monocytes can be upregulated by a variety of mediators such as C5a or f-Met-Leu-Phe[24,46,47]. The mechanism of increased expression is due to fusion with the plasma membrane of granules containing high concentrations of these glycoproteins, e.g. secondary granule secretion in granulocytes.

All three molecules mediate adhesion of either phagocytic cells or lymphocytes. In all cases, adhesion is temperature-(37°C) and Mg^{2+}-dependent, suggesting a

common physio-chemical mechanism[38,48]. iC3b has been shown to be one of the ligands of Mac-1 CR3 activity and p150,95[14,15,49]. Mac-1 is a physiologically important complement receptor and is denoted the CR3. Adherence of granulocytes to substrates appears to be mediated by a second binding site of Mac-1[48,49]. Intercellular adhesion molecule-1 (ICAM-1) is one of the ligands of LFA-1 in many interactions of lymphocytes with distinct cells[50,50a,71].

STRUCTURAL DEFECT UNDERLYING LAD

Membrane expression of LFA-1, Mac-1 (CR3) and p150,95 is deficient in the LAD syndrome. This has been shown by the use of specific anti-α and β monoclonal antibodies as well as by iC3b coated erythrocyte rosetting. The three α–β complexes are similarly deficient on the distinct leukocytes cell types. No other membrane molecules deficiency has been detected.

One important finding relates to the magnitude of the deficiency. In some patients there are no detectable α–β complexes on leukocytes (severe deficiency)[19,22,24,46,52]. Upregulation of Mac-1 and p150,95 by inflammatory mediators does not occur. Activated T and B lymphocytes are also deficient. In contrast, on leukocytes from other patients one can detect some expression of Mac-1, p150,95 and LFA-1[19,22,24], i.e. moderate deficiency. Quantification by immunofluorescence flow cytometry, ^{125}I Mab binding and scanning of membrane immunoprecipitates run on SDS-PAGE shows a 1–10% expression in partial LAD.

On some occasions, activated lymphocytes may express higher levels of LFA-1[30]. Interestingly enough, the degree of adhesion protein expression correlates with the severity of clinical manifestations. Lack of expression results in the severe phenotype, low expression in the moderate phenotype.

The mutation in LAD has been shown to be in the gene for the common β-subunit by studies utilizing somatic cell hybrids, biosynthesis, and β-subunit cDNA clones. Studies have focused on the LFA-1 molecule in patient and normal mitogen-activated T lymphocytes and EBV-transformed B lymphocytes. The LFA-1 α-subunit precursor is always synthesized in normal quantity and is normal in size and charge[19,24,36,52]. The β-subunit precursor may be missing or present in only trace amounts, present in normal quantity but abnormal in size, or normal in size[28,54,55] (Table 1). When present, the β-subunit does not associate with the α-subunit and no carbohydrate processing occurs, suggesting that α–β association is a prerequisite for transport to the Golgi. In hybrids between patient and mouse lymphocytes, the human LFA-1 α-subunit associates with the mouse β-subunit and is expressed on the cell surface. While the β-subunit from normal human lymphocytes can be expressed in association with the mouse α-subunit, this is not the case for patient lymphocytes[53]. This study with a patient who synthesizes a β-subunit precursor suggests the presence of a mutation in the β-subunit that prevents association with the α-subunit. Studies with the β-subunit cDNA probe[39,39a,55] show that the presence or absence of mRNA and protein precursor is corrlated (Table 2). Eighteen patients have been investigated[54,55] (M.T. Dimanche *et al.*, in preparation). These studies define at least five distinct classes of mutation and further subdivide the moderate and severe clinical phenotypes. One mutation that results in an abnormally small β-subunit precursor has been characterized in detail. The mutant mRNA is missing 90 nucleotides that precisely correspond to an

Table 1 The LFA-1, CR3 and p150,95 glycoprotein family.

	LFA-1	*CR*3	*p*150,95
Structure	α L 177 000 Mr β 94 000 Mr	α M 165 000 Mr β 94 000 Mr	α 150 000 Mr β 94 000 Mr
Cell distribution	Lymphocytes	Granulocytes	Granulocytes
	Large granular lymphocytes	Monocytes	Monocytes
		Large granular lymphocytes	Large granular lymphocytes
			Cytotoxic T lymphocytes
Known ligand	I-CAM-1	iC3b	iC3b

Table 2 Classification of LAD mutations, adapted from T.K. Kishimoto *et al.*[55]

Number of patients[b]	*βmRNA levels*	*β-Subunit precursor*	*α-β Membrane expression*
3	None detectable	None detectable	None detectable[a]
4	Low	Trace or none	Low or none[a]
4	Normal	Aberrantly small	Low
1	Normal	Aberrantly large[c]	None[a]
6	Normal	Normal size	Low or none[a]

[a]None = < 0.3% normal expression.
[b]References 54, 55 and M.T. Dimanche *et al.*, unpublished results.
[c]Due to an aberrant additional glycosylation site.

exon, suggesting an abnormality in mRNA splicing due to a mutation in a splice site (Kishimoto and Springer, unpublished). A small amount of the mRNA appears to be spliced normally, which may explain why this mutation results in a moderate phenotype.

INHERITANCE

LAD is inherited as an autosomal recessive disease. Evidence for this is provided by the frequency of consanguinity (Figure 1)[24,27,28,31], by the finding of an equal number of male and female patients, i.e. 29 and 25 respectively and by the fact that leukocytes from heterozygous carriers express approximately half of normal amounts of the common β-subunit[17,21,24,36]. The disease has been observed in several parts of the world (North America, Europe, North Africa, Iran and Japan) without known clusters.

Marlin *et al.*[53] have shown that the β-subunit encoding gene is located on chromosome 21 by human X mouse lymphocyte hybrid studies. Since in most, if not all, cases the genetic lesion affects the β-subunit gene, it is mapped to chromosome 21. The β-subunit gene is located on the most distal portion of the

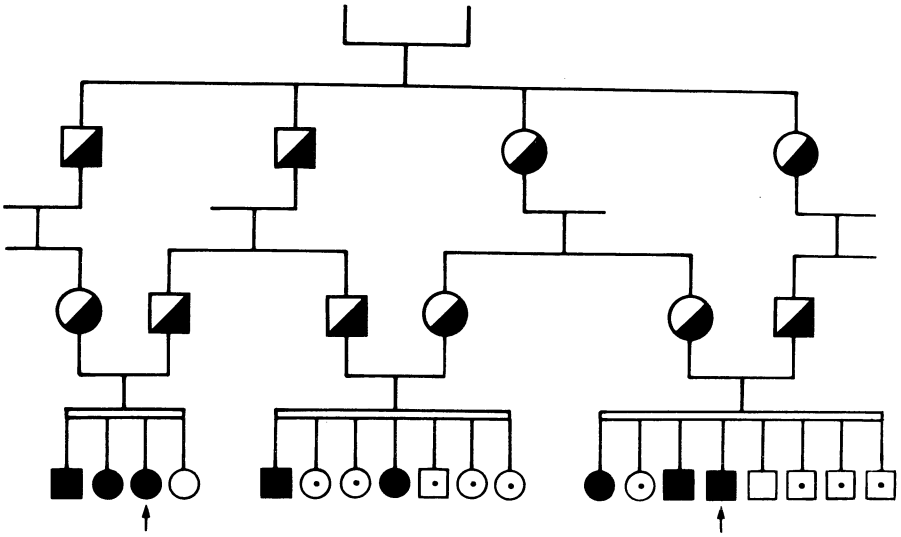

Figure 1 Pedigree of LAD in a Tunisian family. Arrows indicate referred patients.
= : consanguineous union
· : not tested for adhesion proteins expression

long arm of chromosome 21 (21q22.3), as shown by deletions of chromosome 21 and restriction fragment length polymorphism (G. Stewart *et al.*, unpublished) and *in situ* hybridization (A. Corbi *et al.*, *J. Exp. Med.*, in press).

The amino acid sequences of the α- and β-subunits of the leukocyte adhesion receptors are 25–49% identical to the α- and β-subunits of the receptors for extracellular matrix components (fibronectin, vitronectin and collagen) and the platelet glycoprotein IIbIIIa[39a,39b]. These homologies define a supergene family (integrins) of adhesion receptors that evolved by gene duplication from single ancestral α- and β-subunit genes. In inherited deficiency of GPIIbIIIa (Glanzmann's thrombasthenia), expression of LFA-1, Mac-1 and p150,95 is unaffected[51]. Conversely, GPIIbIIIa is expressed normally on platelets of LAD patients.

CLINICAL MANIFESTATIONS[1–10,19–37]

The 54 known patients can be divided into two groups[24].

Severe Phenotype ($n = 30$)

These patients have the most pronounced clinical consequences of the disease due to a complete absence of adhesion molecules or leukocytes (less than 0.2% expression). The natural history of the severe phenotype leads very often to death within the first years of life. However, a few older patients are alive (Figure 2). The prominent clinical features of these patients are bacterial infections primarily localized at the surface of the organism (skin, oral and urogenital orifices, intestinal and respiratory tract).

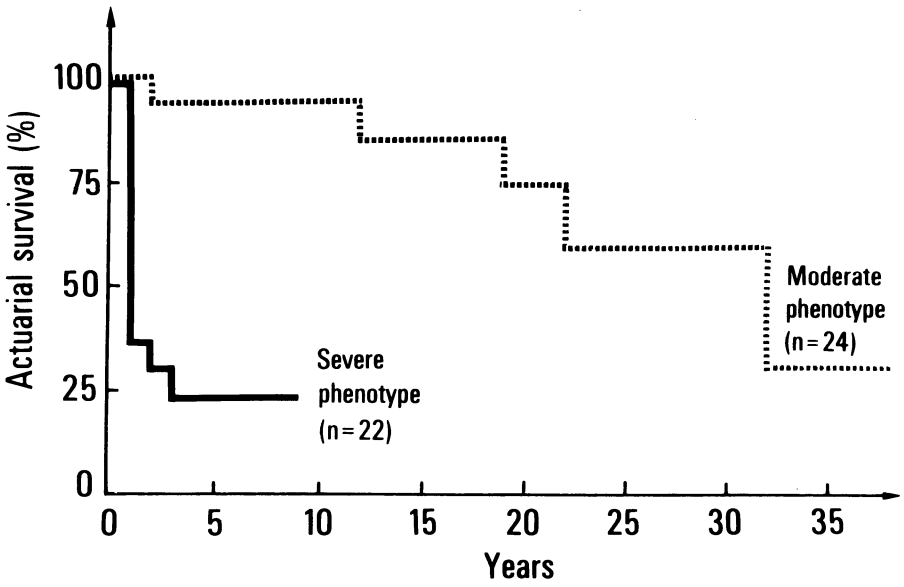

Figure 2 Actuarial survival of patients with LAD. Patients who have undergone bone marrow transplantation are not included. Patients with the severe phenotype were quoted in Refs. 2, (5 patients), 5 (4 patients), 10 (1 patient), 29 (1 patient), 34 (2 patients), 35 (2 patients), 36 (4 patients), 37 (1 patient) and one from Paris is unpublished. Patients with the moderate phenotype were quoted in Refs. 1 (1 patient), 4 (1 patient), 8 (1 patient), 9 (1 patient), 10 (1 patient), 29 (4 patients), 30 (2 patients), 31 (1 patient), 32 (2 patients), 33 (1 patient), 36 (7 patients) and one from Paris is unpublished.

These infections are indolent, necrotic and tend to recur. Infections sites progressively enlarge and may provoke systemic diffusion. Ulcerative, necrotic skin lesions heal very slowly, leading to dysplastic scars. The most frequently encountered bacteria are *Staphylococcus aureus* and the Gram-negative enteric bacteria. In this group, infections start usually from birth onwards and the most frequent primary infection is omphalitis. One of the hallmarks of the severe phenotype is a delayed umbilical cord loss. Such omphalitis may progress to peritoneo-intestinal necrotic infection and/or to sepsis.

The characteristics of these bacterial infections are very similar to those observed in agranulocytic patients: this also includes a susceptibility to fungi, causing localized or disseminated infections (candida and aspergillus organisms have been commonly grown). Similar clinical features are also found in a rare disease characterized by the absence of secondary granules in PMN. All three diseases are characterized by the absence of pus at infectious sites, while transfused normal granulocytes can migrate normally to infectious sites. Blood granulocyte counts are extremely high (up to 100 000/μl during infections). These characteristics are in contrast with those of bacterial and fungal infections observed in chronic granulomatous diseases predominating in organs rich in resident macrophages (lymph nodes, liver, lung, Peyer patches)[57]. It seems that patients suffering from a complete absence of leukocyte adhesive proteins are not unusually susceptible to viral infections. Several of these patients have had normal course of

varicella, cytomegalovirus or herpes simplex virus infections. Aseptic meningitis has been observed, although no causal virus has been found[24]. However, one patient has died from a pico RNA virus disseminated respiratory tract infection[24].

Non-infectious manifestations that are specific of the disease, i.e. delayed umbilical cord loss and dysplastic scars of skin wounds (of any origin), could be attributed to defective release by macrophages of enzymes and cytokines involved in the process of healing[3,24,27,57].

Moderate Phenotype ($n = 24$)

These patients are less prone to severe life-threatening overwhelming bacterial infections, as shown by their life expectancy (Figure 2). However, some of these patients have died between 12 and 32 years of age. Although infections are less frequent and usually less severe, they tend to disclose characteristics similar to those of the severe phenotype in terms of location, evolution and causal agents. Recurrent otitis, oesophagitis, sinusitis and pneumonitis have especially been noted. Local soft-tissue infections may lead to pyoderma gangrenosum. In one patient, a distal gas gangrene was cured by a life-saving amputation[10].

As in agranulocytic patients, severe chronic gingivitis and periodontitis developed in the teenage years, leading to progressive loss of deciduous and permanent dentition[24,58].

Recently a similar disease has been described in the dog, leading to the same types of infections[59].

FUNCTIONAL ABNORMALITIES OF PHAGOCYTIC CELLS

One of the hallmarks of LAD is the absence of granulocytes (pus) at infectious sites, whereas high blood granulocyte counts are found. This suggests a defective migration from blood vessels to extravascular sites. *In vivo*, leukocyte mobilization has been measured by the Rebuck skin-window test, showing no mobilization of granulocytes and monocytes in deficient patients. In moderately deficient patients mobilization is diminished and delayed. After granulocyte transfusion, normal granulocytes are able to migrate with normal kinetics to the window[10]. The binding of patients' phagocytic cells to endothelial cells has been found abnormal in different *in vitro* studies. *In vitro* adhesion-dependent chemotaxis of granulocytes and monocytes is impaired[2,3,8,10,21,23,24,25,26,29,34,36]. Chemotaxis appears abnormal because it requires adhesion. Cells adhere poorly to protein-coated glass or plastics and are unable to spread. f-Met-Leu-Phe or PMA does not increase adherence of severely deficient granulocytes and causes a modest increase in adherence of partially deficient granulocytes[24,36]. Adhesion-dependent functions, including chemotaxis and aggregation, are deficient whatever the stimulatory agent. The magnitude of defective responses is related to the level of expression of adhesion proteins.

iC3b-opsonized particles fail to induce phagocytosis and thus the respiratory burst. Phagocyte-mediated, antibody-dependent cellular cytotoxicity is also abnormal. In contrast, adherence-independent functions are preserved. They include f-Met-Leu-Phe binding, cellular polarization, oxidative metabolism and degranulation when stimulated by soluble stimuli, and, in most cases, intracellular killing of microorganisms[21,24,34].

The defective adhesion of phagocytic cells to serum-coated substrates is secondary to the low or absent surface expression of Mac-1 and p150,95. This has been shown by *in vitro* experiments in which monoclonal antibodies specific for the α-subunit or Mac-1 or p150 block cell adhesion. The potency of inhibition is anti-βAb$\rangle$anti-Mac-1 αAb$\rangle$anti-p150Ab$\rangle$anti-LFA-1 αAb[36,46].

Finally, Mac-1 expression on neonatal granulocytes appears to be decreased, an observation that may explain the known impaired adhesion and chemotaxis functions of neonatal compared to adult granulocytes. Thus, a partial deficiency in Mac-1 expression (there is no data about p150,95 and LFA-1 expression) may partly underlie the known susceptibility of newborn infants to infection[60,60a].

LYMPHOCYTE ABNORMALITIES

A variety of *in vitro* abnormalities in lymphocyte function have been found using patients' lymphocytes. They affect nearly all types of lymphocyte functions. The *in vivo* relevance of these findings remains partially unclear.

All known membrane molecules expressed by T and B lymphocytes apart from LFA-1 are normally expressed by patients' lymphocytes.

Non-Specific and Antigen-Specific T-Lymphocyte Activation

LFA-1 deficient T lymphocytes have been shown to respond poorly to low concentrations of lectins and of anti-CD3 monoclonal antibodies, while a normal proliferative response is observed at optimal concentrations of reagents[22,34,61]. Similarly, antigen-induced T-cell proliferation in response to low concentrations of antigens is usually diminished. Although anti-LFA-1 monoclonal antibodies partially inhibit activation of LFA-1$^+$ T cells at the levels of both antigen-presenting cells and T lymphocytes[62], the combination of either HLA identical LFA-1(−) or (+) monocytes and LFA-1(−) or (+) T lymphocytes does not result in significantly impaired antigen-specific T-cell activation (A. Fischer *et al.*, unpublished data).

Cytotoxicity

LFA-1(−) lymphocytes have impaired cytotoxic activity. This is the case for T cells, NK cells and cells mediating antibody-dependent cellular cytotoxicity[27,63–65]. Defective cytotoxic T-cell activity is associated with low γ interferon production[25,34]. However, repeated allogeneic stimulations of LFA-1(−) T cells induces cytotoxic functions[65]. LFA-1(−) cells are relatively good targets for cytotoxic T cells, suggesting that LFA-1 does not play a major role on target cells except when cytotoxic T cells do not express LFA-1[65].

Antibody Production

Although no humoral deficiency has been described in most of the patients, a deficiency in antibody synthesis polypeptidic antigens has been found after immunizations in a few patients totally lacking membrane LFA-1 on lymphocytes. Serum Ig concentrations are always normal or increased, as are antibody responses *in vivo* and *in vitro* toward polysaccharides[27,66]. The defective antibody production toward proteins such as influenza virus proteins is due to the absence of the LFA-1

molecule on helper T cells and monocytes, as shown by incubation experiments of LFA-1(+) cell populations with anti-LFA-1 antibodies and by cocultures of HLA identical LFA-1(+) and (−) cells (A. Fischer *et al.*, unpublished results).

Defective T-cell activation, T-cell cytotoxicity and T-cell help for antibody production are the consequences of diminished adhesion of T cells to antigen-presenting cells, target cells or B cells. This has been shown by the inhibition of cell conjugate formation by anti-LFA-1 antibodies[67-69] and by the abnormal number of conjugates formed using LFA-1(−) T-cells (A. Fischer *et al.*, unpublished results). It is worth noting that LFA-1(−) B-cells do normally bind LFA-1(+) T-cells, an observation that strengthens the idea that LFA-1 on B-cell surface is not involved in heteroconjugate formation. This is possibly due to different glycosylation of LFA-1 on B-cells[70]. Since defective T–B interaction affects B-cell activation more profoundly than defective APC–T interaction, LFA-1 dependent adhesive pathway could be a mandatory component of cognate T–B interaction.

Binding of lymphocytes to purified ICAM-1 incorporated into artificial membranes, its inhibition by anti-LFA-1 and anti-ICAM-1, and the failure of LFA-1(−) LAD patient lymphocytes to bind, demonstrate that ICAM-1 is a ligand for LFA-1[71]. ICAM-1 expression is induced on endothelial cells, dermal fibroblasts and epidermal keratinocytes by cytokines and LPS, and may influence lymphocyte and monocyte extravasation and localization *in vivo*[72].

IN VIVO RELEVANCE

T-cell function is thus suboptimal, each time an LFA-1-dependent cell-to-cell interaction is involved. There is, however, at least one other T-cell adhesive pathway involving CD2 and LFA-3 molecules[69,70]. Since this adhesive pathway is unaffected in the disease, it may partially compensate for the LFA-1 deficiency with a selection of T cells with high affinity for antigen.

This may contribute to normal T-cell functions *in vivo*, as shown by the paucity of opportunistic and viral infections, and by normal delayed type antigen-specific skin tests.

There may be some circumstances in which the lack of LFA-1 expression has some *in vivo* consequences. Kohl *et al.* have shown that the transfer into neonatal mice of human LFA-1(−) lymphocytes fails to protect them against herpes virus, whereas LFA-1(+) lymphocytes are efficient[64]. A few reports have mentioned that anti-LFA-1 antibody may alter lymphocyte migration, especially T-lymphocyte binding to endothelial cells, a step necessary for T-cell migration into lymphoid organs[73]. However, there is no convincing evidence from patient studies for an impairment in T-lymphocyte traffic.

Recently, Clayberger *et al.*[74] have suggested that a diminished expression of LFA-1 on some lymphomas may be associated with a poorer prognosis due to defective cytotoxic cell binding to lymphomas. One wonders whether a concomitant decrease in membrane expression of other adhesive proteins, i.e. LFA-3 and ICAM-1 as shown on Burkitt cells[75], could contribute to this phenomenon.

Finally, as discussed below, it is striking that 3/3 patients with LAD have not rejected HLA partially incompatible bone marrow, an observation that is unique to LAD[76]. This can likely be secondary to defective interaction of host cytotoxic cells with donor marrow cells.

It appears that LFA-1 deficiency of lymphocytes and of antigen-presenting cells may have variable consequences, depending on T-cell avidity for antigen and on the nature of cell-to-cell interaction.

THERAPY

In patients with the moderate phenotype, it is likely that the use of antibiotics as therapeutic and preventive means can prevent most of the risk of infections. Transfusion of granulocytes can help in the control of severe infections, since functional granulocytes migrate to sites of infection[10]. This approach is limited, however, by production of alloantibodies to the transfused granulocytes.

Bone marrow transplantation (BMT) is the logical treatment of LAD. Because of inherent risk and difficulties, this therapy is proposed only for patients with the severe phenotype. Eight patients have been transplanted so far[26,75,76]. Five have received HLA-identical bone marrow. In practice, a heavy conditioning regimen is required in order to ablate hyperactive myeloid elements in bone marrow. Failures of engraftment have been observed with protocols adequate for other immunodeficiencies[26]. Success has been obtained using high-dose Busulfan (16 mg/kg) with cyclophosphamide (200 mg/kg) or cyclophosphamide with total body irradiation. Major risk of infections requires transplantation in infection-free patients who are in good nutritional condition and are protected against infection by isolation, IV antibiotics and antifungal therapy. By this approach, we have been successful in 2/3 HLA-matched transplants and 3/3 mismatched transplants (Tables 3 and 4)[76]. One patient died from chronic graft-versus-host disease although he was cured of LAD. One patient accidentally died in Tunisia one year post transplant. The four other patients are doing well. In all four there is a mixed but stable chimerism between donor cells and recipient cells, allowing normal or subnormal

Table 3 Expression of adhesion molecules and recovery of leukocyte functions after haploidentical bone marrow transplantation (BMT).

	Patient 4		*Patient* 6	
	Before BMT	*After BMT* (36 *months*)	*Before BMT*	*After BMT* (9 *months*)
CR3 (%)[a] on PMN	9	62	0	92
LFA-1 (%)[a] on lymphocytes	0	72	0	100
Chemiluminescence opsonized zymosan (% of control)	0	50	0	75
NK (% lysis) effector: target 50:1	1	23	1	63

PMN = polymorphonuclear cells.
[a]% of positive cells.

phagocytic cell and lymphocyte functions. Transplantation is therefore a good choice for patients with the severe phenotype, and has to be proposed as early as possible in life because of the high incidence of early death (Figure 2). The fact that LFA-1(−)-deficient patients accept HLA partially incompatible bone marrow, in contrast to all other clinical conditions except patients with severe combined immunodeficiency (SCID) who lack T-cells, opens further possibilities for HLA-mismatched BMT (Tables 3 and 4)[78].

Table 4 Outcome of bone marrow transplantation (BMT) in six patients with LAD.

Patient	*Donor*	*Engraftment*	*Outcome*	*Follow-up*
1	Sister HLA=	Sustained[a] mixed chimerism	Alive and well	6 years
2	Mother HLA=	Full chimerism	Died from chronic GVHd	7 months
3	Brother HLA=	Mixed chimerism	Accidental death	15 months
4	Mother one haplotype†	Sustained[a] mixed chimerism	Alive and well	4 years
5	Father HLA A+DR†	Sustained mixed chimerism	Alive and well	30 months
6	Mother HLA B+DR†	Sustained mixed chimerism	Alive and well	12 months

[a]Following two attempts of BMT.

In most instances, HLA-mismatched BMT leads to either lethal GVHD or graft rejection due to residual host immunity provided that incompatibility of donor and recipient involves more than one HLA molecule[79]. Additional immunosuppression of the recipient is therefore needed to avoid graft rejection. Among other possible approaches, we reasoned that the infusion of anti-LFA-1 monoclonal antibody may reproduce transiently the LFA-1 deficiency and prevent graft rejection[78]. Heagy *et al.* have shown in the mouse that an anti-LFA-1 antibody limits the rejection of allogeneic or syngeneic tumors[80].

Using an antibody specific for the subunit of LFA-1, which exerts strong *in vitro* inhibitory effects on T-cell cytotoxic functions[81], we have treated recipients of HLA-incompatible bone marrow. They received either 0.1 mg/kg of antibody IV every other day from three days before to five days after transplantation, or 0.2 mg/kg daily in the same period. Thirty-four patients with either partial immunodeficiencies, metabolic diseases, Fanconi anemia or leukemia have likewise been treated. Sustained engraftment has been achieved in 79%, and 58% of patients are alive with a functional graft 3–31 months post transplant. These results can be compared with a historical control group treated similarly except for the use of anti-LFA-1 antibody. Only one out of 12 patients was successfully engrafted and none survived[78].

From the known *in vitro* effects of anti-LFA-1 antibody and from *in vivo* experimental and clinical data, one may envisage other applications of immunosuppression through the use of antibodies blocking T-cell adhesion.

PRENATAL DIAGNOSIS

Because of the potential severity of the disease, prenatal diagnosis of LAD can be proposed as for other severe immunodeficiencies[82]. Fetal blood can be drawn around the 20th week of gestation. Fetal polymorphonuclear and mononuclear cells can be investigated for leukocyte adhesion molecule expression, since they express these molecules.

Analysis of the gene by southern blot using the β-specific probe on trophoblastic cells would be feasible if a known RFLP were linked to the defect. Thus far, an RFLP associated with the mutation has been found only in one family (Kishimoto *et al.*, unpublished results)[83].

GENE THERAPY

Because a defect of a unique gene provokes the disease and because leukocyte adhesion molecule expression is corrected by the β-subunit in somatic hybrids, the introduction of a normal β-subunit encoding gene in patients' hematopoietic cells could correct the disease. As proposed for adenosine deaminase deficiency, defective retroviral vectors containing the β-subunit encoding gene are being made[36].

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