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REVIEW ARTICLE

Of Man and Mouse: Leukocyte and Endothelial Adhesion Molecule Deficiencies

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"It is in her moments of abnormalities that nature reveals its secrets." (Goethe)

IMPORTANT INSIGHTS into a number of biological processes have come from studies of rare inherited diseases. Goethe's declaration is best exhibited by the leukocyte adhesion deficiency (LAD) syndromes, in which one of several molecules in the adhesion cascade is defective. Much has been learned from the study of LAD, yet the puzzle is far from being solved. Animal models have also been pivotal in understanding of biological events, and immunology has benefited tremendously from the investigation of various aspects of the immune response in mice. One of the most powerful techniques has been targeted gene deletion by homologous recombination.[1] This approach allows comparison of animals of similar genetic backgrounds that differ only in the absence of a single gene. Phenotypic differences between the knockout and wild-type littermates are presumed then to be due to the targeted gene deletion. Furthermore, various knockout mice can be interbred to produce deletions of several genes, providing animal models for more complex genetic defects.

Although gene targeting has many advantages, it is important to acknowledge that there are important differences in biology between the mice and humans. Indeed, comparisons between rare human disease and mice with deletion of the same gene have shown important differences as well as similarities. For example, the defect in Bruton's tyrosine kinase (BTK) in humans leads to severe hypogammaglobulinemia with almost no B cells. In contrast, mice with targeted deletion of the BTK gene produce some antibodies with up to 30% of normal B-cell number.[2] It is also important to recognize that comparisons may be confounded by the recruitment of alternative pathways in the human or mouse genetic deficiencies. In this regard, mice deficient in α_V-integrins exhibited no deficit in angiogenesis or vasculogenesis,[3] whereas $\alpha_V\beta_3$-integrin antagonists inhibit angiogenic responses in wild-type animals.[4] Whether such differences result from alternative pathways in the deficient animals or unexplained effects of the antagonists remains to be resolved.

In this brief review, we will compare 2 human LAD syndromes (Table 1) with gene-targeted mice with various adhesion molecule-deficiencies (Table 2), highlighting both disparities and similarities (Tables 3 and 4).

THE ADHESION CASCADE

Leukocytes must first adhere to the endothelium of blood vessels before they emigrate to tissue. The process of leukocyte emigration is a dynamic one involving multiple steps.[5,6] Several families of adhesion molecules mediate the interactions of leukocytes with endothelial cells, each involved in a distinct phase of emigration. The initial, rapidly reversible, adhesion of leukocytes to the vessel wall under conditions of flow produces rolling. This phase is mediated largely by the interaction of selectin receptors (E [CD62E], P [CD62P], and L [CD62L]) and their glycoconjugate ligands. The precise nature of the carbohydrate counter-structures for the various selectins has not been fully defined, but fucosylated, sialylated glycans such as Sialyl Lewis x (SLeX; CD15s) are clearly involved.[7]

In postcapillary venules of the systemic microcirculation, rolling is prerequisite for the subsequent steps in adhesion cascade of activation, firm adhesion, and transmigration. These latter events involve leukocyte integrins and their endothelial ligands of the Ig gene superfamily (IgSF). The β_2-subfamily comprises 4 α-subunits (CD11a-d) with the common β_2-integrins (CD18). CD11a/CD18 ($\alpha_L\beta_2$) and CD11b/CD18 ($\alpha_M\beta_2$) are the predominant β_2-subunits involved in leukocyte adhesion to endothelium. Other leukocyte integrins involved in emigration are VLA-4 ($\alpha_4\beta_1$; CD49d/CD29) and $\alpha_4\beta_7$. The leukocyte integrins interact with IgSF ligands on the endothelial cell. These include intercellular adhesion molecule-1 (ICAM-1; CD54) and ICAM-2 (CD102) for the β_2 integrins, vascular cell adhesion molecule-1 (VCAM-1; CD106) for VLA-4, and mucosal addressin cell adhesion molecule–1 (MAdCAM-1) for $\alpha_4\beta_7$.

Although adhesion molecule-deficient mice have been generated for nearly all of the molecules involved in leukocyte emigration (Table 2), the best characterized human LAD syndromes are due to defects in β_2-integrin (LAD I and LAD I

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Table 1. LAD Syndromes

	LAD I*	LAD II
Clinical manifestations		
Recurrent severe infections	Frequent	Not observed
Neutrophilia		
Basal	+	++
With infections	+++	++
Periodontitis	Common	Marked
Skin infections	Common	Not observed
Delayed separation of the umbilical cord	Common	Not observed
Developmental abnormalities	None	Marked
Laboratory findings		
CD18 expression	Marked decrease or absent	Normal
SLeX expression	Normal	Absent
Neutrophil rolling	Normal	Marked decrease
Neutrophil firm adherence	Marked decrease	Normal
T- and B-cell function	Decreased	Normal

Adapted and reprinted from Etzioni et al[8] in Ochs HD, Smith CIE, Puck JM (eds): Primary Immunodeficiency Diseases: A Molecular and Genetic Approach. New York, NY, Oxford, 1999.

*Severe phenotype.

variant) or selectin ligands (LAD II; Table 1).[8] However, because LAD I and LAD II affect different phases in the adhesion cascade, much can be learned about leukocyte-endothelial interactions from these rare human diseases.

β_2-INTEGRINS AND IgSF LIGANDS

LAD I. LAD I is a rare disease, with only approximately 200 patients reported. It results from heterogeneous mutations in the gene encoding the common β_2-subunit, CD18.[9,10] LAD I was described clinically in the late 1970s and early 1980s and is characterized by delayed separation of the umbilical cord, marked neutrophilia, and recurrent bacterial infections.[11] Two phenotypes have been reported.[9] In the severe form, there is no detectable expression of CD11/CD18 on leukocytes and the patients have a turbulent course, with death usually occurring from infection during the first few years of life. Consequently, if feasible, bone marrow transplantation is performed early in life. It is noteworthy that bone marrow transplantation has a high success rate in LAD I due to decreased graft rejection, even with haploidentical donors.[12] In the moderate phenotype, cells express 2% to 5% of the normal level of CD18, and the clinical course is much milder.[9] Recently, 2 LAD I variants have been described in which the β_2-subunits are expressed at adequate levels but are dysfunctional. In 1 patient, the CD18 alleles are normal, but may have an associated signaling defect.[13] The other patient has 2 mutated CD18 alleles, which are expressed but are nonfunctional.[14]

Table 2. Adhesion Molecule-Deficient Mice

Integrins and IgSF Ligands	Selectins
CD18	P-selectin (CD62P)
LFA-1 (CD11a)	E-selectin (CD62E)
Mac-1 (CD11b)	L-selectin (CD62L)
ICAM-1 (CD54)	E/P-selectin
ICAM-2 (CD102)	Fuc-TVII
VCAM-1 (CD106)	C2 GlcNAcT
VLA-4 (CD49d/CD29)	
ICAM-1 and P-selectin	

For reviews, see also Frenette and Wagner,[72] Hynes,[73] and Hynes and Bader.[74]

CD18-deficient mice. Early studies by Wilson et al[15] reported a mouse with partial CD18-deficiency, comparable to the mild-moderate LAD I phenotype. The CD18-hypomorphic mice were viable and fertile, without any gross anatomic or histologic abnormalities, and, in contrast to LAD I, exhibited only mild leukocytosis. Unlike LAD I patients,[16] these mice did not develop any spontaneous infections in the skin or other organs. However, they did show an impaired inflammatory response to chemical peritonitis and delayed rejection of cardiac transplants. The tolerance to allograft is consistent with the good results obtained after bone marrow transplantation in LAD I.

Recently, a murine model with complete absence of CD18 was reported.[17,18] In these animals, as in LAD I, marked neutrophilia was found (11- to 30-fold increase over wild-type), and there was almost no emigration of neutrophils into the skin (Table 3). In contrast, when compared with wild-type, the CD18-deficient animals exhibited comparable neutrophil emigration into inflamed peritoneum and increased emigration into inflamed lung. The lack of neutrophil emigration to the skin with normal emigration to the lungs was also described in 1 patient with the severe phenotype of LAD I.[19] The persistent emigration of neutrophils into inflamed peritoneum of the CD18-deficient mice contrasts with the nearly complete inhibition of peritoneal emigration by a CD18 monoclonal antibody (MoAb) in rabbits.[20,21] This apparent disparity may reflect differences between species, but may also result in part from the marked increase in circulating neutrophils in the CD18-deficient animals. Compared with the antibody studies in normal animals, the number of circulating neutrophils in the CD18-deficient animals is many fold higher. Because the number of emigrating neutrophils is, in part, dependent on the number of circulating neutrophils, the observation that the same numbers of neutrophils emigrate in the CD18-deficient animals as in the wild-type mice may actually reflect a large inhibition. However, studies in an LAD I patient showed an absence of neutrophils in infected peritoneum.[19] This discrepancy may reflect a true difference between mice and humans. Alternatively, it may be due to differences in sampling sites (peritoneal fluid in mice *v* tissue in humans) or to the duration of the inflammatory response (4 hours in mice *v* days in the patient).

CD11a- and CD11b-deficient mice. The roles of the CD11a and CD11b subunits in several aspects of neutrophil and lymphocyte function have also been examined in genetically deficient mice. In contrast to LAD I or CD18-deficient mice, CD11b-deficient mice did not exhibit any leukocytosis or marked increased incidence of bacterial infection.[22] In vivo studies of CD11b-deficient mice showed normal rolling but defective firm adhesion,[23] just as was observed with neutrophils from an LAD I patient.[24] Furthermore, like LAD I, neutrophils of CD11b-deficient mice exhibited in vitro defects of adhesion,

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Table 3. Phenotypes in Deficiencies of β2-Integrins and IgSF Ligands

	LAD I	CD18-Deficient	CD11b-Deficient	CD11a-Deficient	ICAM-1–Deficient	ICAM-2–Deficient
Spontaneous infections	Marked	Moderate-marked	None	None	None	None
Neutrophilia	Marked	Marked	Minimal	Minimal	Moderate	None
Neutrophil migration to						
Skin	Absent	Absent	NR	NR	NR	NR
Lung	Present	Present	NR	NR	Present	NR
Peritoneum	Absent	Present	Present	Reduced	Reduced	NR

Abbreviation: NR, not reported.

iC3b-mediated phagocytosis, phagocytosis-induced respiratory burst, and homotypic aggregation.[22] However, in contrast to LAD I, neutrophil accumulation in thioglycollate-induced peritonitis was normal or even increased in the CD11b-deficient mice,[22,23] a surprising result ascribed in part to impaired phagocytosis-induced apoptosis.[23] It is of interest that neutrophil emigration into inflamed peritoneum was markedly reduced in these animals when an anti-CD11a MoAb was administered, suggesting that CD11a/CD18 rather than CD11b/CD18 was primarily responsible for transendothelial migration of neutrophils.[22] Consistent with this observation, neutrophil accumulation in thioglycollate-induced peritonitis was modestly reduced in the CD11a-deficient mice.[25] The reduction in neutrophil emigration into inflamed peritoneum in CD11a-deficient animals[25] or CD11b-deficient animals treated with CD11a MoAb,[22] but not in CD18-deficient mice,[17] may reflect the relatively normal circulating neutrophil counts in the α-chain mutants versus the marked increase in circulating neutrophils in the CD18-deficient animals.

Based on studies in vitro and in vivo using blocking CD11a MoAbs, the CD11a/CD18 subunit has been implicated in a wide variety of immune functions, including delayed-type hypersensitivity (DTH) responses and cytolytic T-lymphocyte (CTL) effector functions. CD11a-deficient mice exhibited normal CTL responses to systemic virus infection[25]; LAD I patients also appear to mount adequate immune responses to viral challenge, because most infections and deaths have been due to bacterial and fungal infections rather than to viruses.[10] However, CD11a-deficient mice failed to develop a DTH response to 2,4 dinitro-fluorobenzene sensitization and challenge,[25] whereas LAD I patients mount normal skin reactions when challenged with antigen to which they have been sensitized.[10]

These 2 mouse models have provided important insights into the role of the CD11a/CD18 and CD11b/CD18 subunits in leukocyte functions. It will be of interest to determine CD11c and CD11d functions in knockout models and to compare double knockouts for CD11a and CD11b with CD18-deficient animals.

ICAM-1–deficient mice. ICAM-1 is a major ligand for both CD11a/CD18 and CD11b/CD18. Because ICAM-2 and -3 are also β_2-integrin ligands, it is expected that the phenotype of ICAM-1–deficient mice might differ from those CD18-deficient mice or the LAD I patients in whom multiple ICAM counter-receptors are deficient. Two groups reported ICAM-1–deficient mice.[26,27] The mutant animals generated by Sligh et al[26] were found to express novel isoforms of ICAM-1 due to alternative RNA splicing, although no in vivo function has yet been established for these isoforms.[28] Both ICAM-1–deficient murine lines developed normally, were fertile, and had moderate leukocytosis. The mice exhibited multiple abnormalities of inflammatory response, including impaired neutrophil emigration in response to chemical peritonitis, resistance to septic shock, and decreased contact hypersensitivity reaction.[26] Kumasaka et al[29] showed that neutrophil emigration during endotoxin-induced pneumonia was reduced substantially by anti–ICAM-1 MoAb or ICAM-1 antisense oligonucleotide, but was not altered in ICAM-1–deficient mice. Similarly, Qin et al[30] showed that *Pseudomonas aeruginosa*-induced pneumonia did not require ICAM-1 when studied using ICAM-1–deficient mice, whereas the blocking anti-ICAM-1 MoAb inhibited neutrophil emigration by 70% in wild-type mice (but not in the deficient mice). It is not clear whether these marked differences result from compensation in the deficient mouse or from effects of MoAb or antisense blockade apart from adhesion blockade (eg, signaling).[31]

Comparisons of ICAM-1–deficient mice with CD18-deficient mice should provide insights into the contributions of the other ICAM molecules or other potential CD18 ligands in addition to this subfamily in various inflammatory and immune responses.

ICAM-2–deficient mice. CD11a/CD18 binds to both ICAM-1 and ICAM-2. ICAM-2 is constitutively expressed at

Table 4. Phenotypes in Deficiencies of Selectins and Selectin Ligands

	LAD II	E/P-Deficient	Fuc-TVII–Deficient	C2 GlcNAcT-Deficient
Developmental defects	Marked	Absent	Absent	Absent
Neutrophilia	Marked	Marked	Moderate	Moderate
Periodontitis	Marked	Present	Absent	Absent
Dermal ulcerations	Absent	Present	Absent	Absent
Hypergammaglobulinemia	Absent	Present	NR	NR
Lymphadenopathy	Absent	Present	Absent	Absent
Rolling defect	Marked	Marked	Marked	Moderate
Peritoneal emigration of neutrophils	Unknown	Marked reduction	Marked reduction	Marked reduction
Lymphocyte homing	Unknown	NR	Marked reduction	Normal

Abbreviation: NR, not reported.

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high levels on all vascular endothelium, whereas ICAM-1 expression is strongly inducible by various cytokines, including tumor necrosis factor-α, interleukin-1, and interferon-γ. These expression patterns suggest that ICAM-2 may be important in leukocyte trafficking into uninflamed tissues, as occurs during lymphocyte recirculation, whereas ICAM-1 induction regulates leukocyte recruitment at inflammatory sites. However, the biologic functions of ICAM-2 in vivo have not been defined. Recently, ICAM-2–deficient mice were described.[32] Total leukocyte counts and leukocyte subset numbers were unaltered compared with wild-type mice. Although platelet counts were not reduced, there was a reduction in megakaryocyte progenitors in the bone marrow of the ICAM-2–deficient mice. Lymphocyte homing to peripheral nodes, mesenteric nodes, and spleen was unaffected by ICAM-2–deficiency.

Interestingly, during allergic lung inflammation, there was a delayed increase in eosinophils in the airway lumen and a prolonged presence of eosinophil infiltrates in lung tissue in the ICAM-2–deficient mice.[32] Notably, there was no effect on lymphocyte or monocyte accumulation in airway lumen. Studies using bone marrow chimeras showed that the alterations in eosinophil trafficking in vivo resulted from deficiency of ICAM-2 on nonhematopoietic cells. Also, migration of normal eosinophils across ICAM-2–null endothelial monolayers in vitro was reduced compared with migration across normal endothelium. Together, these results suggested that ICAM-2 expressed on vascular endothelium, alveolar walls, or large airway epithelium participated in the traffic of eosinophils from the blood stream to the airway lumen.[32]

β2-integrin–independent neutrophil emigration. The current multistep model of leukocyte-endothelial interactions was developed primarily from studies in the systemic circulation in which neutrophil emigration occurs predominantly in postcapillary venules. In the lung, leukocytes emigrate largely within capillaries, raising the possibility that adhesion pathways may differ in this organ. In studies with a blocking CD18 MoAb in rabbits with acute pneumonia, Doerschuk et al[20] first reported that there was a CD18-independent mechanism of neutrophil emigration in the lung during the acute response to certain stimuli. Studies in an LAD I patient confirmed neutrophil emigration into infected lung, whereas emigration to larynx, peritoneum, and esophagus was absent.[19] Stimuli that elicit CD11/CD18-independent neutrophil emigration into the distal airspaces of the lungs during the acute inflammatory process include *Streptococcus pneumoniae*, group B *Streptococcus*, *Staphylococcus aureus*, hydrochloric acid, hyperoxia, and complement protein C5a.[20,30,33-38] CD11/CD18-independent adhesion pathways were recruited during recurrent pneumonia induced by *Pseudomonas aeruginosa* in rabbits, although CD11/CD18 mediated acute neutrophil emigration in response to this organism.[39] CD11/CD18-independent emigration was also noted in peritonitis induced by glycogen or lipopolysaccharide at the 24-hour but not at the 4-hour time point in rabbits[21] and in the joints of rats after induction of inflammatory arthritis.[40] The molecular basis of this pathway has not been defined, but it does not appear to involve selectins.[41]

SELECTINS AND SELECTIN LIGANDS

LAD II. LAD II is a congenital defect in the selectin pathway that was first described in 1992.[42] To date, there are 4 known patients: the 2 males originally reported and a female and another male recently identified (A. Etzioni, manuscript submitted). All 4 are of Arabic origin, and the parents of each child are related. Although there is no consanguinity among the families, they likely share a common genetic background.

Clinically, LAD II is much a milder disease than LAD I. The 3 LAD II patients did not manifest delayed separation of the umbilical cord, a hallmark of LAD I. Although the children tended to suffer from an increased incidence of infections in early infancy,[42] compared with the severe form of LAD I, these episodes were quite mild, not requiring hospitalizations or intravenous antibiotics. Later in life, infections have been rare and the children are not on prophylactic antibiotics. The only persistent clinical symptom produced by neutrophil dysfunction is chronic, severe periodontitis, similar to that seen in LAD I.[43]

In contrast to LAD I, in which all clinical symptoms relate to the leukocyte adhesion defect, multiple other organ systems are affected in LAD II. The children have a rare blood group type, the Bombay phenotype, and suffer from profound mental and severe growth retardation.[44] The adhesion defect and other abnormalities result from a generalized defect in fucose metabolism.[45] Consequently, only 2% to 3% of normal fucosylated glycoproteins is expressed on the patients' leukocytes. Because fucose is essential for the biosynthesis of E-, P-, and L-selectin ligands such as SLeX (CD15s),[7] LAD II leukocytes are deficient in binding to endothelial E- and P-selectins.[46] The endothelium in these patients likely also exhibits reduced expression of fucosylated L-selectin ligands.[45] Thus, although the LAD II defect has no direct effect on the selectin genes themselves, the defect in fucose metabolism produces a deficiency of selectin ligands. With respect to leukocyte adhesion, the LAD II patients are therefore the human equivalent of mice with combined knockout of E- and P-selectin genes[47,48] and mice with knockout of the fucosyltransferase gene that directs biosynthesis of fucose-containing selectin ligands[49] (Table 4). The deficient selectin function accounts for the marked reduction of neutrophil rolling on inflamed mesenteric microvasculature observed by intravital microscopy.[24] Interestingly, the children have not shown any defect in immune function and responded to intradermal antigen with normal numbers of T cells.[50] In contrast, Th1 cells did not home to skin DTH sites in mice treated with anti–P- and anti–E-selectin antibody.[51]

The growth and mental retardation are most probably also due to the defect in fucose metabolism, establishing a heretofore unknown role for fucose in human growth and development. It is unlikely that deficient selectin function accounts for these abnormalities as no such defects are observed in the selectin-deficient mice (vide infra). Recently, it was found that the primary defect in LAD II is in the biochemical activity of GDP-D-mannose-4, 6 dehydratase (GMD), the enzyme that converts mannose to fucose.[45,52] However, cloning of GMD from an LAD II patient and a control showed normal amino acid sequence of patient GMD, suggesting that the LAD II defect results from a mutation(s) affecting some yet unidentified GMD-regulating protein(s).[52]

P-selectin–deficient mice. P-selectin–deficient mice were found to be viable, fertile, and without any anatomic abnormalities.[53] Whereas circulating neutrophil counts were 2 to 3 times higher than in wild-type animals, the numbers of progenitors in the bone marrow of the P-deficient mice were similar to the

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wild-type, suggesting a longer half-life of circulating neutrophils in the mutants. By injecting radiolabeled human neutrophils into the tail vein of mutant and wild-type animals, it was shown that neutrophils indeed survived longer in the P-selectin–deficient mice.[54] These findings in the mouse contrast with results in LAD II. Price et al[55] performed kinetic studies in 1 patient and showed a much reduced circulating half-life (<50% of normal), with a markedly increased marrow turnover rate. Although the increased turnover in the bone marrow could be explained in part by continuous stimulation (eg, the severe periodontitis), the reason for the markedly reduced half-life of the circulating neutrophils is not clear. In LAD I,[56] as in the P-selectin mutant mice,[54] the prolonged neutrophil half-life was ascribed to accumulation in the circulation due to the defect in emigration. It would be expected that this would also be the case in LAD II. It is possible that the defect in fucosylation of leukocyte membrane glycoproteins and glycolipids triggers their premature clearance by the reticulo-endothelial system.

Intravital microscopy in the P-selectin–deficient mice showed a marked reduction in the initial rolling phase, confirming the crucial role of P-selectin in the initial interaction of the leukocyte with the blood vessel.[53] Importantly, however, leukocyte rolling was observed at later time-points, despite the absence of P-selectin. Using neutrophils from an LAD II patient, a similar defect in neutrophil rolling was observed,[24] but this defect persisted for a longer time, indicating that fucosylated glycoconjugates are also involved in later events. Extravasation of neutrophils to the skin was diminished for several hours after insult in the P-selectin–deficient mice.[57] Using a skin chamber assay, neutrophil accumulation in an LAD II patient was markedly reduced over 24 hours.[55] P-selectin–deficient mice were also reported to have a mild defect in hemostasis,[58] but no bleeding tendency has been observed in the LAD II patients.

To determine the role of P-selectin in lymphocyte emigration, the contact hypersensitivity reaction was investigated in P-selectin–deficient mice. Accumulation of $CD4^{+}$ lymphocytes, monocytes, and neutrophils was reduced significantly, but there was no difference in vascular permeability or edema.[59] In a similar study, a DTH reaction was investigated in an LAD II patient. In contrast to the findings in the P-selectin–deficient mouse, normal numbers of T cells were found, whereas the clinical signs of redness and swelling were severely depressed compared with normal.[50]

E-selectin–deficient mice. The E-selectin mutant mouse was viable and exhibited no obvious developmental abnormalities. It displayed no significant change in trafficking of neutrophils in several models of inflammation.[60] More direct studies showed that, whereas the percentage of rolling neutrophils was not reduced in this model, the cells rolled much faster,[61] demonstrating a role for this selectin in the initial phase of the adhesion cascade. Blocking both endothelial selectins by treatment of the E-selectin–deficient mice with anti–P-selectin MoAb significantly inhibited neutrophil emigration to the skin and peritoneum, demonstrating that E- and P-selectin are functionally redundant in this regard.[60]

L-selectin–deficient mice. L-selectin–deficient mice develop normally but exhibit defects in lymphocyte homing and leukocyte rolling.[62] Lymphocytes from these mice did not bind to peripheral lymph node high endothelial venules (HEV), resulting in a marked reduction in the number of lymphocytes localized to peripheral lymph nodes. Other lymph nodes were similarly affected. The DTH reaction was impaired in L-selectin–deficient mice with 75% reduction in swelling,[63] similar to that seen in LAD II.[50] Recently, it was shown that the defective DTH reaction in these L-selectin knockout mice was restored by administration of activated platelets into the systemic circulation.[64] The activated platelets expressing P-selectin formed a bridge between lymphocytes and high endothelial venules, thereby enabling lymphocytes to undergo subsequent β_2-integrin–-dependent firm adhesion. Interestingly, as in LAD II,[50] T-cell–dependent antibody production to keyhole limpet hemocyanin was normal in the L-selectin–deficient mice.[65]

E/P-selectin–deficient mice. Whereas mice deficient in a single E- or P-selectin gene showed a relatively mild phenotype, mice deficient in both endothelial selectins (E/P-deficient) demonstrated extreme leukocytosis and elevated cytokine levels.[48] These mice developed a severe phenotype characterized by mucocutaneous infections, plasma cell proliferation, hypergammaglobulinemia, and severe deficiency of leukocyte rolling in cremaster venules with or without addition of tumor necrosis factor-α.[47,48]

To characterize the role of the endothelial selectins during bacterial sepsis in vivo, *Streptococcus pneumoniae* was inoculated into wild-type mice and mice with E-, P-, or E/P-selectin deficiency.[66] When compared with wild-type mice, all of these selectin-deficient mice showed greater morbidity, a significantly higher mortality associated with persistent bacteremia, and a higher bacterial load. During the first 5 days, mortality was higher in the E-selectin–deficient, and only later did the double mutant approach the mortality rate observed in E-selectin–deficient mice. It is possible that the presence of persistently high numbers of circulating leukocytes and plasma cells and higher serum levels of Igs in the E/P-selectin–deficient mice provided an advantage in the initial response to pneumococcal sepsis. Ultimately, however, the defect in emigration was detrimental for prolonged survival after untreated infection.

As opposed to the E/P-deficient mice, the 2 older LAD II patients have had no increase in systemic infections, and the few episodes of localized infection have responded to conventional treatment as in any immunocompetent child. The phenotype of the E/P-deficient animals thus appears to be much more severe than observed in LAD II. This might simply reflect differences between humans and mice. Alternatively, it is possible that nonfucosylated ligands participate in selectin interactions in vivo; thus, the absence of fucosylated ligands in LAD II would not impact all E- and P-selectin–dependent functions, whereas the null mice would be severely affected. Also, selectin receptors may serve other functions important for host defense, eg, signaling molecules for endothelium.[67] In this case, deficiency of the receptor proteins (in the deficient mice) would again have a greater impact than absence of their carbohydrate ligands (in the LAD II patients). In this regard, Ramos et al[68] reported that an MoAb to the consensus repeat region of murine E-selectin blocked neutrophil recruitment to inflamed peritoneum of Balb/c mice in vivo without affecting rolling in vivo or adhesion to E-selectin transfectants in vitro.

Fuc-TVII–deficient mice. The synthesis of the fucosylated glycans implicated in E-, P-, and L-selectin ligand activity is catalyzed by several glycosylation reactions. The final reaction

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is controlled by α(1,3) fucosyltransferase Fuc-TVII and, thus, deletion of the gene for this enzyme will result in a mouse deficient in SLeX and other fucosylated selectin ligands.[49] Consequently, the Fuc-TVII–deficient mice are perhaps the best animal model to compare with LAD II. Fuc-TVII–deficient mice yielded normal litter sizes, were vigorous, and were free of microbial infections, including the spontaneous bacterial dermatitis exhibited by the E/P-deficient mice.[48] The Fuc-TVII–deficient mice exhibited a phenotype reminiscent of the human LAD II, including marked leukocytosis, absent binding of leukocytes to E- and P-selectins, and compromised neutrophil trafficking to inflammatory sites. Absence of Fuc-TVII also yielded a deficit in expression of L-selectin ligands by high endothelial venules and a severe alteration in lymphocyte homing. However, the Fuc-TVII–deficient mice did not show any gross anatomic abnormalities, again implying that the growth and mental retardation in LAD II is due to the general defect in fucose metabolism and not to the adhesion deficiency.

Core 2 GlcNAcT–deficient mice. The core 2 β1-6 N-acetylglucosaminyltransferase (C2 GlcNAcT) is a key branching enzyme in the synthesis of serine/threonine-linked oligosaccharides (O-glycans). The core 2 branch of the O-glycans provides a scaffold for the subsequent production of lactosamine disaccharide repeats and, hence, sialylated and fucosylated selectin ligands such as sialyl Lewis X (CD15s).[7] As in LAD II and Fuc-TVII deficiency, the C2 GlcNAcT–deficient mice developed moderate neutrophilia. Moreover, like LAD II patients and Fuc-TVII–deficient mice, blood leukocytes from mice lacking C2 GlcNAcT were deficient in E- and P-selectin ligands.[69] Furthermore, C2 GlcNAcT–deficient neutrophils exhibited decreased rolling on immobilized E- and P-selectin Ig chimeras, although not as marked as observed with Fuc-TVII–deficient cells. Notably, neutrophil rolling on L-selectin appeared to be particularly dependent on core 2 oligosaccharide biosynthesis, because leukocytes from the deficient mice were unable to bind to L-selectin except at the lowest shear force. Neutrophil recruitment to inflamed peritoneum was markedly reduced, comparable to Fuc-TVII–deficient mice,[49] with only 20% of control numbers recovered 4 hours after thioglycollate instillation,[69] thereby demonstrating a critical role for C2 GlcNAcT in the biosynthesis of selectin ligands on myeloid cells. Interestingly, although a defect in L-selectin binding to peripheral lymph node HEV was observed in this model, lymphocyte homing to lymph nodes and spleen was unaltered.[69] Thus, in contrast to Fuc-TVII,[49] C2 GlcNAcT activity was not required for lymphocyte homing, suggesting either that core 2 O-glycans such as those expressed on CD34 and related mucins in HEV are not required for L-selectin–dependent lymphocyte rolling or that a second gene encoding a C2 GlcNAcT isozyme is expressed in HEV.

In contrast to the growth retardation and physical abnormalities observed in LAD II, C2 GlcNAcT–deficient mice, like Fuc-TVII–deficient mice, developed normally and lacked overt physical abnormalities.[69]

Selectin-independent neutrophil emigration. Just as with β_2-integrin, there are selectin-independent pathways of neutrophil emigration. When flow is reduced in postcapillary venules, shear force is diminished, and there is no longer a requirement for selectin-mediated tethering and rolling. Under these static conditions, integrin receptors can be directly engaged and can support firm adhesion and transmigration. This phenomenon was demonstrated by intravital microscopy in the microvasculature of rabbit mesentery using flourescein-labeled LAD II neutrophils.[24] Selectin-independent neutrophil emigration has also been reported in the microcirculation of the lung[41,41] and liver.[70] These selectin-independent pathways of neutrophil emigration may account for the relatively mild phenotype of LAD II patients with respect to infections.

CONCLUSION

The careful investigation of the LAD syndromes in humans and the adhesion molecule-deficient mice has dramatically increased our understanding of the physiology and the cell and molecular biology of leukocyte emigration. As we have indicated, these experiments have also generated a number of questions:

What accounts for the discrepancies observed between deficient animals and wild-type animals treated with blocking MoAbs?

Does deficiency of the molecule create a milieu in which alternative pathways are recruited?

Do MoAbs produce effects other than adhesion blockade?

What is the CD18-independent pathway of neutrophil emigration?

What role does fucose play in somatic and neurological growth and development?

What accounts for the intact cell-mediated immune responses and skin DTH reaction in LAD II versus the defects observed in the selectin-deficient mice or with MoAb blockade of selectin receptors?

What accounts for the markedly reduced circulating half-life of LAD II neutrophils?

What accounts for the minimal infectious problems in LAD II versus E/P-selectin mutant mice or LAD I?

Are there nonfucosylated ligands for the selectins?

Do selectins serve functions apart from rolling?

Are there HEV-specific C2 GlcNAcT isozymes?

Clearly, William Harvey's observation of more than 300 years ago holds true even today: ''Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces other workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to discovery of the usual law of nature by careful investigation of cases of rarer forms of disease'' (1657).[71]

NOTE ADDED IN PROOF

Marquardt et al[75] recently reported a fifth LAD II patient of Turkish descent. DeLisser et al[76] described loss of endothelial E-selectin surface expression in a patient with recurrent infections, potentially representing the first inherited dysfunction of an endothelial adhesion molecule.

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