Leukocyte LFA-1, OKM1, p150,95 deficiency syndrome: functional and biosynthetic studies of three kindreds[1,2]

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ABSTRACT

Three patients (2 female, 1 male) with recurrent infection, granulocytosis, impaired pus formation, and/or delayed umbilical cord separation were identified. Assessments of polymorphonuclear leukocytes (PMN)/monocyte function in each patient revealed profound abnormalities of adherence and adherence-dependent functions. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) of their PMN lysates demonstrated a deficient or absent protein(s) of 138 kilodaltons (gp138). Na^3HB_4 labeling demonstrated the absence of a major cell surface glycoprotein complex in each patient. Among parental and sibling PMN suspensions, functional assessments revealed no consistent abnormalities, although variably diminished gp138 was identified by SDS-PAGE and Na^3HB_4 labeling. Analysis by fluorescence-activated cell sorting and monoclonal antibodies (MAb) to LFA-1 α, OKM1 α, and their common β subunit demonstrated a severe or total deficiency of PMN/monocyte surface expression of each protein among all patients; intermediate values were observed for parental and affected sibling suspensions, findings consistent with an autosomal recessive mode of inheritance for this disorder. Cell surface labeling (^{125}I) and immunoprecipitation with the same MAb demonstrated the absence of these glycoproteins in addition to a 150-kilodalton protein (p150,95). Identical abnormalities of surface expression of patient lymphocytes blast-transformed with phytohemagglutinin (PHA) or Epstein-Barr virus were demonstrated. Further, significantly diminished natural killer cell cytotoxicity was observed for each patient tested. PHA blast-transformed patient lymphocytes labeled with [^{35}S]methionine demonstrated a total absence of the β molecule but indicated the presence of an LFA-1 α precursor. These findings indicate that LFA-1 α synthesis and surface expression require β association. It is concluded that impaired inflammatory function in this disorder is casually related to a heritable deficiency of critical "adhesive" leukocyte glycoproteins.—**Anderson, D. C.; Schmalstieg, F. C.; Shearer, W.; Becker-Freeman, K.; Kohl, S.; Smith, C. W.; Tosi, M. F.; Springer, T.** Leukocyte LFA-1, OKM1, p150,95 deficiency syndrome: functional and biosynthetic studies of three kindreds. *Federation Proc.* 44: 2671–2677; 1985.

The critical role of cell adherence in allowing expression of normal leukocyte functions and the pathogenic importance of adhesive abnormalities in clinical disorders characterized by dysfunction of phagocytic leukocytes have been increasingly recognized (1–3, 5–7, 10, 14). Workers in several laboratories have recently recognized a new heritable clinical syndrome characterized by impaired inflammation and associated infectious susceptibility (1–3, 5–8, 10). We have identified eight patients (four male and four female) with a clinical syndrome characterized by recurrent bacterial or fungal soft tissue infections, progressive periodontitis, persistent granulocytosis, poor wound healing, and/or delayed umbilical cord separation (gp138 deficiency syndrome). Profound abnormalities of leukocyte motility in vitro and tissue mobilization (Rebuck skin window) have been recognized in all cases. In this paper we shall summarize assessments of polymorphonuclear leukocyte (PMN)/monocyte and natural killer (NK) cell function in three representative patients with this disorder, and shall describe the identification in each case of a severe deficiency or absence of surface expression of LFA-1 and OKM1, two structurally and functionally related "adhesive" glycoproteins normally expressed on human myeloid cells (4, 13). The latter findings provide a molecular basis for understanding many normal cellular adhesive properties as well as complex functional abnormalities observed in this disorder. Further, the use of specific subunit monoclonal antibodies

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TABLE 1. Assessments of adherence-dependent PMN leukocyte functions among three gp138-deficient kindreds

PMN function tested	5-year-old female	17-year-old male	14-month-old female	Parents and siblings[a]	Healthy adults
Directed migration[b]	69 ± 4	70 ± 6	47 ± 3	106 ± 7	103 ± 6
Orientation[c]	6.5 ± 3	2.0 ± 1	10 ± 3	57 ± 8	59 ± 6
Adherence[d]					
Baseline	11.0 ± 3	14.1 ± 2.0	13 ± 7	24 ± 11	38 ± 6
Stimulated	10.0 ± 3	14.4 ± 4.0	14 ± 5	68 ± 14	63 ± 6
Aggregation[e]	6 ± 6	7 ± 3	7 ± 1	94 ± 8	100 ± 6
Spreading[f]	34	75	55	85 ± 7	82 ± 6
Phagocytosis[g]					
Paraffin ORO-(C3)	0.65	3.7	1.1	8.1 ± 2.4	7.0 ± 3.1
Paraffin ORO-(IgG)	1.8	1.35	0.8	1.7 ± 0.6	1.7 ± 0.4
Antibody-dependent cellular cytotoxicity[h]					
100:1	6.8	7.1	2.1	21 ± 9	25 ± 12
30:1	3.0	0	5.7	—	16 ± 6

[a] Included are three mothers, two fathers, and one female sibling (all heterozygotes). [b] Values represent the mean ± SD of "leading front" Boyden assays with f-Met-Leu-Phe (10 nM, 40 min). [c] Values represent the mean ± SD percent of PMNs accurately orienting toward a gradient of f-Met-Leu-Phe established in Zigmond chambers. [d] Values represent the mean ± SD percent of PMNs adhering to serum-coated (6%) glass substrates at 1 g for 500 s in Smith-Hollers chambers under baseline (phosphate-buffered saline) or f-Met-Leu-Phe-stimulated (10 nM) conditions. [e] Values represent the mean ± SD percent of two to six individual determinations of PMN aggregation in response to zymosan-activated plasma (ZAP) expressed as ZAP units. [f] Values represent the mean of two experiments expressed as the percent of PMNs anchoring on plastic substrates (5 min, 37 C). [g] Values represent the mean ± SD of Oil Red O (ORO) paraffin ingestion expressed as dionylphthalate uptake (micrograms per 10^7 PMNs per 10 min) for particles selectively preopsonized with endotoxin-activated antibody-deficient serum or human serum albumin–anti-human serum albumin. [h] Values represent the mean ± SD of ^{51}Cr release determinations (n = 2–6) for PMN-to-target cell ratios of 100:1 or 30:1.

(MAb) to these surface glycoproteins has allowed phenotypic analyses of gp138-deficient kindreds, which have confirmed an autosomal recessive mode of transmission for this disorder.

As shown in Table 1, directed migration of patients' PMNs was profoundly diminished in each case whereas values for all parental or sibling suspensions were entirely normal. Observations by means of an Optimax image analyzer of the distributions of entire PMN populations in Boyden assays confirmed these findings and revealed no "slow" cell subpopulations. To understand the basis for impaired cell motility, studies of formylmethionylleucylphenylalanine (f-Met-Leu-Phe) receptor-ligand binding, investigations of cell activation and shape change in suspension, and evaluations of cell orientation in chemotactic gradients (Zigmond chambers) were performed. Entirely normal specific and saturable binding of f-Met-Leu-[^{3}H]Phe (7000–10,000 receptors/PMN) was observed for all patients and family members. With respect to both C5a and f-Met-Leu-Phe, comparable threshold concentrations (C5a, 1.2 μg/ml; f-Met-Leu-Phe, 0.1 nM) effected cell activation (membrane ruffling) of patients' and control PMNs (2). At maximally effective concentrations (C5a, 4 μg/ml; f-Met-Leu-Phe, 2 nM), the percentage of patients' PMNs demonstrating bipolar morphology was comparable to that of control suspensions. Patients' cells also demonstrated a normal capacity to form uropods under all test conditions (12).

The capacity of patients' cell suspensions to orient accurately toward gradients of f-Met-Leu-Phe is summarized in Table 1. For each patient tested, the percentage of their PMNs demonstrating a capacity to orient in Zigmond chambers was significantly diminished at all times. At peak time intervals, mean patient values (6.1 ± 2.1%) were significantly ($P < 0.001$) diminished compared with values of 57 ± 8% and 59 ± 6% for parental plus sibling and healthy adult controls, respectively. An apparent discrepancy between findings of normal shape change by patients' cells in suspension and their impaired orientation while attached to surfaces in chemotactic gradients was further evaluated with scanning electron micrographs of patients' cells processed while undergoing orientation and migration in Zigmond chambers. Patients' adherent cells were clearly activated and bipolar in a plane perpendicular to the substrate after exposure to chemotactic factors, but they were unable to initiate new adhesion sites to the substrate, which would allow the normal sequence of cell orientation and migration.

These findings suggested an intrinsic defect of cell adhesive properties, which were then evaluated. Serum-coated glass substrates in Smith-Hollers chambers (14) were used to study adherence of patients' or control PMNs under a variety of experimental conditions. As shown in Table 1, mean baseline adherence of patients' cell suspensions (9.1 ± 4%) was significantly diminished compared with sibling plus parental (24 ± 11%) or healthy adult (38 ± 6%) values. More dramatic abnormalities were observed

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when patients' cells were exposed to chemotactic factors, A23187 or phorbol myristate acetate (PMA). Although expected enhancement of adherence was observed under these conditions among control suspensions, patients' PMNs demonstrated essentially no enhancement of adherence above baseline values. For both baseline and stimulus conditions, all maternal, paternal, and sibling cell suspensions demonstrated normal values. Adherence was also assessed with an albumin-coated latex bead (ACLB) binding assay (14), which quantitates the initiation of adhesion sites by chemotactic stimuli. After exposure to f-Met-Leu-Phe (10 nM, 5 min, 21 C), or PMA (10 μg/ml, 5 min, 21 C), binding of ACLB by patients' PMNs was profoundly diminished compared with control suspensions. The percentage of nonbinding patients' PMNs (54–85% f-Met-Leu-Phe; 22–67% PMA) was significantly ($P < 0.001$) increased compared with a range of values of 0–12% for all maternal, paternal, or healthy adult PMN suspensions. Further, the number of ACLB bound per cell by a small proportion of patients' PMNs capable of ACLB binding was also significantly diminished compared with most control suspensions.

To further characterize adhesive properties of patients' PMNs, aggregometry studies were performed (Table 1). PMNs of each patient suspension demonstrated a profoundly diminished capacity to aggregate in response to stimulation with zymosan-activated plasma (ZAP), f-Met-Leu-Phe (10 nM), or PMA (10 μg/ml). Further, as shown by immunofluorescence microscopy, patients' PMNs failed to adhere to one another but not to control PMNs when test mixtures of control PMNs and FITC-stained patients' PMNs were employed (1). Mean ± 1 SD values (ZAP units) for patient suspensions (ZAP, 14 ± 7; f-Met-Leu-Phe, 16 ± 4; and PMA; 17 ± 6) were significantly ($P < 0.001$) diminished compared with individual or mean group values for maternal, paternal, sibling, or healthy adult control suspensions tested. Patients' and control cells were allowed to undergo irreversible anchorage, or spreading on plastic or glass substrates under a variety of experimental conditions. With respect to untreated plastic and glass substrates, spreading values for patients' PMNs were significantly ($P < 0.001$) diminished. Diminished spreading values were also observed when glass substrates were pretreated with 5% human serum albumin (HSA). However, relatively normal spreading by patients' cells was observed on substrates treated with HSA-anti-HSA immune complexes. These findings suggested that PMN Fc receptors of patients' cells facilitated a normal attachment and spreading sequence under these conditions.

Further insight into the structural and functional bases for impaired cell adherence in this clinical model was found in phagocytosis experiments (Table 1). Considerable heterogeneity of ingestion by patients' PMN suspensions was observed with respect to the test particle and opsonic substrate employed. Patients' PMNs uniformly demonstrated severely diminished ingestion of paraffin Oil Red O particles selectively opsonized with C3-derived ligands compared with maternal, paternal, sibling, or healthy adult suspensions. Further, uptake of radiolabeled staphylococci opsonized with normal human serum or zymosan particles opsonized in antibody-deficient serum was also significantly diminished. However, uptake by patients' PMNs of IgG-opsonized Oil Red O emulsions was moderately reduced in only one of three patients' suspensions and was slightly diminished or comparable to control PMNs in two of three patients' suspensions tested. Further, as assessed with a phagocytosis-associated chemiluminescence assay, the rate of uptake and/or binding of IgG-opsonized ACLB by PMN suspensions from two patients tested was comparable to or increased compared with healthy adult control suspensions (data not shown). These findings further suggested that impaired ingestion by patients' PMNs was related to functional abnormalities of the iC3b receptor complex but was unrelated to membrane Fc receptors.

Extensive evaluations of antibody-dependent cellular cytotoxicity (ADCC) and NK cytotoxicity by patients' leukocyte populations were performed. For ADCC experiments, herpes simplex virus (HSV)-infected Chang liver effector cells were reacted with PMN or mononuclear cells (effector-to-target cell ratio 100:1 to 30:1) in the presence of anti-HSV human immune serum. Patients' PMNs demonstrated essentially nonreactive ADCC by use of a ^{51}Cr release technique. Individual and mean paternal and maternal ADCC values were similar to those of normal adult controls. To allow a further understanding of the basis for these abnormalities, an agarose single-cell cytotoxicity assay was designed to selectively evaluate the role of cell adhesion with respect to this cytotoxic defect. In this assay, 5–6% of maternal, paternal, or adult control PMNs bound to target cells in the presence of antibody, in contrast to only 0.5 ± 0.2% of patients' cells ($P < 0.001$). As shown by trypan blue exclusion, so few target cells were bound by patients' PMNs that the calculation of the percent killed was considered to be unreliable. Thus, impaired ADCC would appear to be causally related to impaired target cell binding in this experimental system. Our findings provide new evidence that this Fc receptor-mediated function appears to be also dependent on an adhesive event unrelated to Ig-PMN Fc receptor linkage. In addition, this model represents the first clinical example of pathologic ADCC caused by impaired PMN-target cell binding (12).

Studies of mononuclear cell NK cytotoxicity of these patients was also assessed and shown to be significantly diminished compared with all control suspensions. At an effector-to-target cell ratio of 30:1, the mean mononuclear cell NK cytotoxicity of patients' cells (10.0 ± 4.3) was significantly ($P < 0.05$) lower than that of controls (39.5 ± 9.4). In further assessments of mononuclear cell NK cytotoxicity, a second target cell, K562, was used. In a 4-h ^{51}Cr release assay with cells from three patients, NK cytotoxicity for K562 cells was shown to be significantly diminished compared with normal controls ($P < 0.05$ at all effector-to-target cell ratios for each patient's suspension).

In contrast to the severe abnormalities of adhesion-dependent cell functions described above, adhesion-independent leukocyte functions of these patients and their families were shown to be generally normal. Specific and saturable binding of f-Met-Leu-[^3H]Phe by patients' PMNs was normal as was cell shape change in

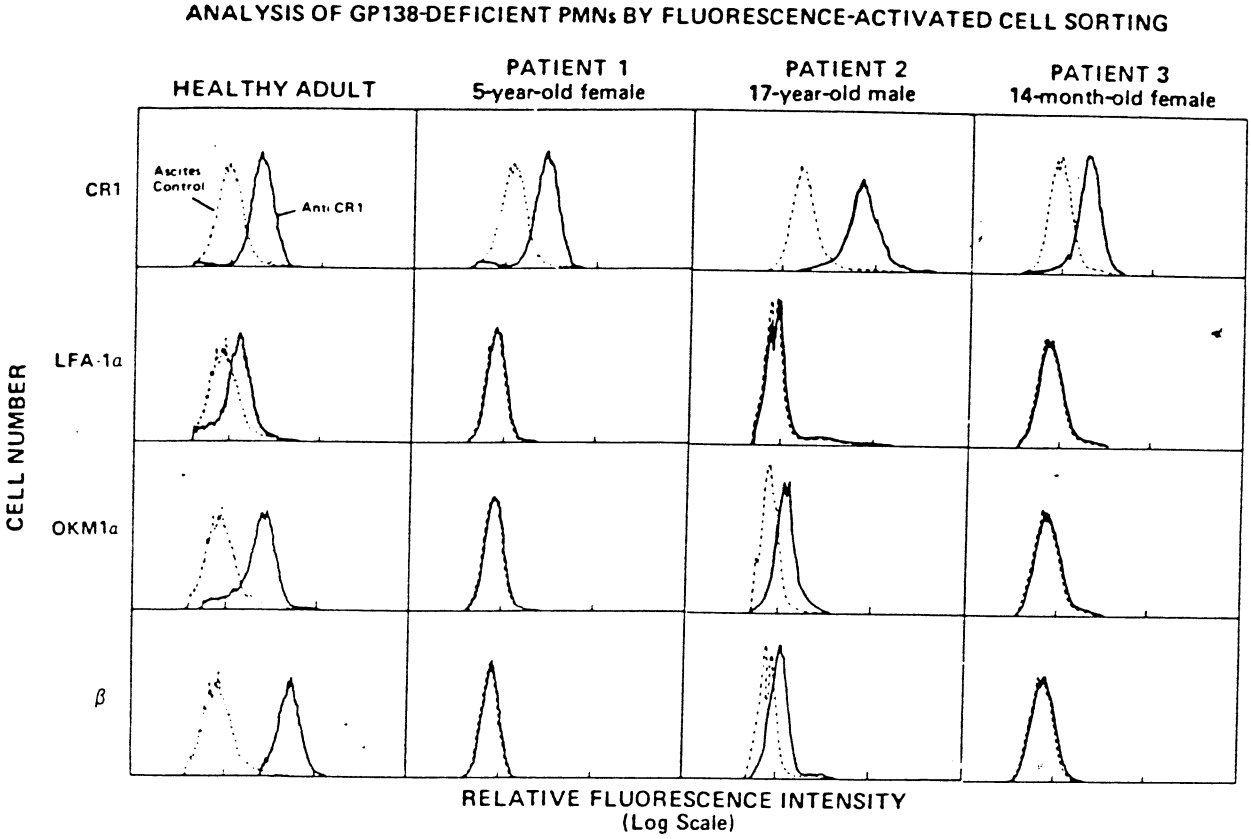


Figure 1. The surface expression of CR1, LFA-1, and OKM1 on patient or control PMNs is shown. Cells were indirectly stained with a $F(ab')_2$ fragment of rabbit IgG anti-CR1 or maBS directed at LFA-1 α, OKM1 α, or their common β subunit and were reacted with FITC-anti-mouse IgG or anti-goat $F(ab')_2$ (——). PMNs initially reacted with nonimmune ascites controls are also shown (-----). Paired histograms demonstrate relative fluorescence intensity (log_{10}), on the x axis and cell number on the y axis (10^4 cells/histogram). Patients' PMNs demonstrate a severe or total deficiency of surface OKM1 α and LFA-1 α and β, but express CR1 normally.

response to chemotactic factors or secretagogues. Soluble stimuli including PMA, A23187, and chemotactic factors elicited normal superoxide generation, chemiluminescence evolution, and secretion of lysozyme, β-glucuronidase, and lactoferrin (7). In contrast to the latter findings, phagocytosis-associated degranulation was significantly diminished in all patients. In all cases, cytochalasin B pretreatment of patients' PMNs significantly enhanced secretion mediated by a soluble or particulate stimulus, findings that are consistent with normal behavior of microfilament dissassembly by patients' PMNs. Therefore, diminished secretion by patients' PMNs during phagocytosis suggests a diminished kinetics of ingestion resulting from abnormalities of particle-cell interaction rather than abnormalities of degranulation per se.

In further assessments of selected biophysical properties of patients' PMN membranes, the spin label 5-doxyl stearic acid and electron spin resonance spectroscopy were used to measure membrane fluidity. The order parameters (S) of unstimulated control or patients' PMNs were equivalent to those of healthy adult controls before and after f-Met-Leu-Phe stimulation. Further, as assessed by cell electrophoresis, the mean cell mobilities of patient, maternal, or paternal PMNs were comparable to those of healthy adult controls before and after f-Met-Leu-Phe stimulation (2). Thus, no evidence for abnormalities of cell surface charge have been detected with respect to this model. Further quantitative and functional assessments of cytoplasmic microtubules were performed with tubulin immunofluorescence. Both the mean number of microtubules per cell (patient, 31.9 ± 4.0; healthy adult, 34.8 ± 4.5; $P < 0.05$) and the mean length of individual microtubules of f-Met-Leu-Phe-stimulated patients' PMNs (patient, 10.1 ± 3.1 μm; healthy adult, 9.7 ± 2.4 μm; $P < 0.05$) were comparable to adult control cells and expected normal laboratory values. Additional evidence of normal PMN/monocyte microtubular function in this disorder was supported by studies demonstrating normal concanavalin A capping by patient suspensions.

Collectively, functional analyses of patients' cell suspensions indicated the absence or dysfunction of a cell surface moiety, in part, related to receptors that react with C3-derived ligands. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) analysis of patients' PMN lysates revealed the absence or severe deficiency of an identical protein or protein complex of approximately 138 kilodaltons. To confirm that the deficient protein was a glycoprotein and that it was expressed on the cell surface, a galactose oxidase-NaB^3H_4 technique (11) was employed. Patients' PMNs demonstrated the absence of a major glycoprotein complex that was routinely observed on healthy adult or age-matched control PMNs. By both SDS-PAGE and NaB^3H_4 labeling techniques, variable deficiencies were observed among paternal, maternal, and sibling suspen-

sions. Previous work in other laboratories suggested certain candidate adhesive proteins deserving specific assessments in these patients including a family of structurally and functionally related glycoproteins variably expressed in human myeloid cells (4, 13). Specifically, these include the lymphocyte function-associated antigen 1 (LFA-1); the OKM1 molecule (otherwise termed the complement receptor 3, Mo1, or Mac-1), which is identical to or closely associated with the iC3b receptor of human myeloid cells; and a third molecule termed p150,95. Each molecule contains a high-molecular-weight α subunit noncovalently bound to a common β subunit.

Employing subunit-specific MAb we assessed PMN/monocyte surface expression of these proteins on all patients' cell suspensions in fluorescence-activated cell sorting (FACS) and ^{125}I-labeled immunoprecipitation experiments. Representative FACS histograms of experiments performed on three patients are shown in Fig. 1. For these experiments, purification procedures were employed to avoid up-regulation of cell surface protein expression. All of these patients demonstrated normal surface expression of the C' receptor 1 (CR1) (9). However, in each case the LFA-1 α, OKM1 α, and β proteins were severely deficient or totally absent from the cell surface. Most patients are >99% deficient in surface expression, although some (e.g., the 17-year-old male in Fig. 1) demonstrate as much as 10% of normal surface expression. The relatively mild clinical features in this patient in addition to the identification of relatively modest functional deficiencies in selected assays of his cell suspensions (e.g., ADCC and NK cytotoxicity) suggest functional and clinical heterogeneity among individuals with this disorder. Studies performed in collaboration with M. A. Arnaout demonstrated severely diminished rosette formation by PMNs of patient number 1 reacted with iC3b-coated sheep erythrocytes. Analysis of mononuclear cell suspensions with the same MAb demonstrated a total or severe deficiency of the same cell surface proteins among the patients shown.

Because functional analyses failed

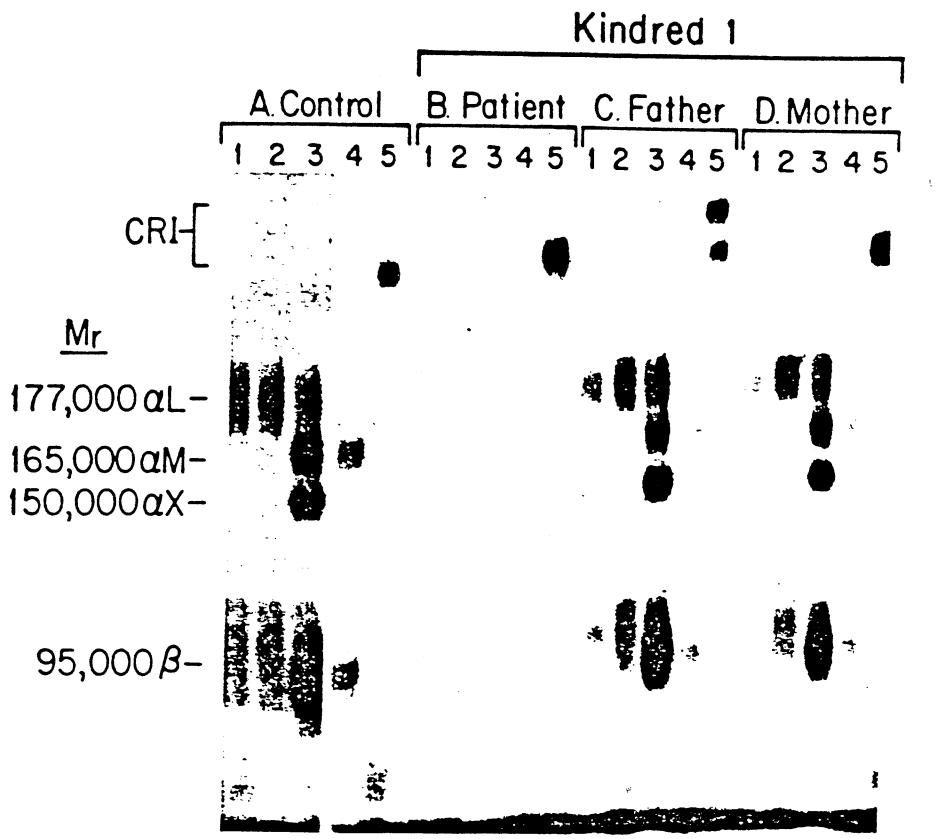
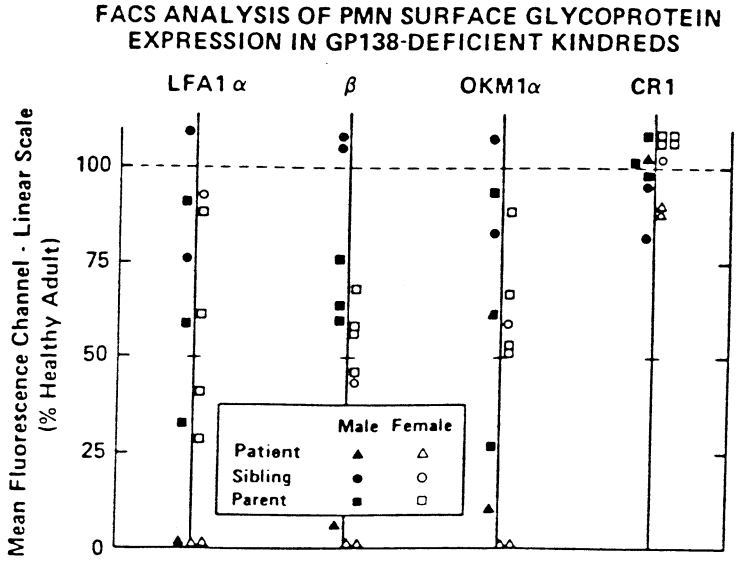


Figure 3. Immunoprecipitation of ^{125}I-labeled surface proteins from PMNs of kindred number 1. PMNs were surface labeled with ^{125}I by using lactoperoxidase. Triton X-100 lysates of each suspension were immunoprecipitated with a mixture of five different anti-LFA-1 α MAb (lane 1), anti-LFA-1 α TS1/22 MAb-Sepharose CL-4B (lane 2), anti-β TS1/18 MAb-Sepharose (lane 3), anti-OKM1 MAb (lane 4), and anti-CR1 44D MAb (kindly provided by Dr. V. Nussenzweig) (lane 5). Immunoprecipitates for lanes 1, 4, and 5 were formed with antimouse IgG and *Staphylococcus aureus*, and were subjected to SDS-7% PAGE and autoradiography. Patients' PMNs demonstrate totally deficient LFA-1 α, β, and OKM1 α but normal expression of CR1.

Figure 2. PMN surface expression of LFA-1, OKM1, or CR1 of four patients and their kindreds was assessed by FACS as in Fig. 1 experiments. Two female patients demonstrate a total absence of LFA-1 and OKM1, whereas the male patient demonstrates ~7–9% OKM1 α and β compared with healthy adult PMNs. Intermediate maternal and paternal values are evident as are those for a female sibling carrier. Two unaffected male siblings demonstrate normal surface expression of LFA-1 and OKM1. All members of each kindred tested demonstrated normal CR1 expression.



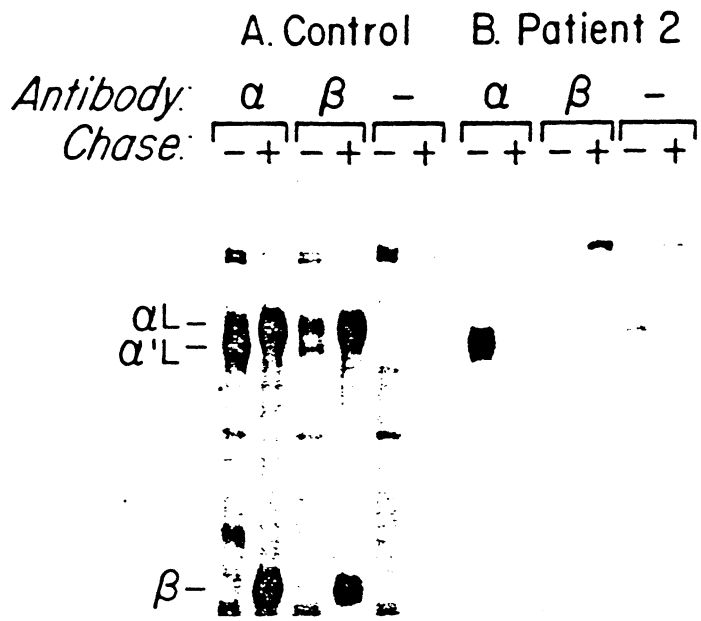


Figure 4. LFA-1 biosynthesis in lymphocytes from patients and normal individuals. Lymphocytes of patient number 2 were blast-transformed with PHA. They were then labeled with [^{35}S]methionine for 2 h, and either harvested immediately or chased for 22 h with complete medium as indicated. Cell lysates prepared with Triton X-100 and sodium deoxycholate were immunoprecipitated with purified antibodies coupled to Sepharose CL-4b(10): TS1/22 anti-LFA-1 α or TS1/18 anti-β. Activated, quenched Sepharose was used as a negative control. Precipitates were subjected to SDS-PAGE and fluorography.

to adequately delineate heterozygotes for gp138 deficiency, we again employed FACS analysis to phenotype all parents and siblings of the patients. As shown in Fig. 2, data obtained from four kindreds (including the three patients discussed) indicate absent or severely diminished LFA-1 α, β, and OKM1 α among the patients. Intermediate deficiencies were observed among maternal and paternal suspensions and for a female sibling of the 17-year-old male patient. In addition, two male siblings of an affected female patient (number 3) demonstrated normal values with respect to each of these surface molecules. As shown, the entire kinships of all patients demonstrate normal surface expression of CR1. Similar relationships were observed when chemotactic or secretory stimuli were employed to up-regulate surface expression of these proteins before FACS analysis. Thus, these findings clearly indicate an autosomal recessive mode of inheritance for this disorder. Our findings of four male and four female individuals among eight patients identified in the Houston and Galveston, Texas, referral area as well as the relatively equivalent number of male and female patients reported by other investigators further confirm these findings.

Observations by FACS analysis were confirmed by ^{125}I-labeling and immunoprecipitation experiments as illustrated by the autoradiographs in Fig. 3. Representative experiments with ^{125}I-labeled PMNs of patient number 1 demonstrated a total absence of four proteins corresponding to LFA-1 (177 kilodaltons), OKM1 (165 kilodaltons), p150,95 (150 kilodaltons), and the β subunit (95 kilodaltons) shared by each of these proteins. These studies provide the first evidence that the cell surface expression of p150,95 in addition to LFA-1 and OKM1 is profoundly abnormal in this clinical pathologic model.

Biosynthetic studies have also been performed in a limited number of patients as illustrated in Fig. 4. Phytohemagglutinin (PHA) blast-transformed lymphocytes of patient number 2 were pulsed with [^{35}S]-methionine, with or without a 22-h chase, before immunoprecipitation of cell lysates with anti-LFA-1 α or β. Control cells clearly demonstrated the presence of labeled LFA-1 α and β subunits after the chase. In contrast, no β' was detectable in the patients' lymphocytes studied under the same conditions. However, a normal LFA-1 α precursor designated α'L was identifiable. These findings suggest that impaired biosynthesis of the β molecule represents a fundamental molecular lesion in the gp138 deficiency syndrome, and that complete processing and surface expression of LFA-1 α requires β association.

Finally, the use of the specific MAb to LFA-1 and OKM1 subunits has been employed in blocking experiments in an attempt to reproduce the functional abnormalities observed in our patients. Independent and additive inhibitory influences of each MAb on normal PMN adherence and other adherence-dependent functions including directed migration, phagocytosis, and antibody-dependent cytotoxicity have been demonstrated. In contrast, adherence-independent functions including f-Met-Leu-[^{3}H]Phe binding, shape change in suspension, degranulation, and oxidative metabolic activity mediated by soluble stimulants are entirely unaffected by preincubation with these MAb. Binding controls, including those directed at the CR1 receptor and the HLA framework antigen, have shown no inhibition of cell adherence or related functions.

In conclusion, these studies indicate that recurrent infection and impaired inflammatory functions in patients with the gp138 deficiency syndrome are causally related to a heritable absence or deficiency of a family of leukocyte glycoproteins that is clearly required for multiple adhesion-dependent functions. Definition of the molecular lesion in this disorder has allowed a conceptual integration of many leukocyte functions based on an adhesive common denominator.

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