ORIGINAL ARTICLE

Inherited DOCK2 Deficiency in Patients with Early-Onset Invasive Infections

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ABSTRACT

BACKGROUND

Combined immunodeficiencies are marked by inborn errors of T-cell immunity in which the T cells that are present are quantitatively or functionally deficient. Impaired humoral immunity is also common. Patients have severe infections, autoimmunity, or both. The specific molecular, cellular, and clinical features of many types of combined immunodeficiencies remain unknown.

METHODS

We performed genetic and cellular immunologic studies involving five unrelated children with early-onset invasive bacterial and viral infections, lymphopenia, and defective T-cell, B-cell, and natural killer (NK)–cell responses. Two patients died early in childhood; after allogeneic hematopoietic stem-cell transplantation, the other three had normalization of T-cell function and clinical improvement.

RESULTS

We identified biallelic mutations in the dedicator of cytokinesis 2 gene (*DOCK2*) in these five patients. RAC1 activation was impaired in the T cells. Chemokine-induced migration and actin polymerization were defective in the T cells, B cells, and NK cells. NK-cell degranulation was also affected. Interferon-α and interferon-λ production by peripheral-blood mononuclear cells was diminished after viral infection. Moreover, in DOCK2-deficient fibroblasts, viral replication was increased and virus-induced cell death was enhanced; these conditions were normalized by treatment with interferon alfa-2b or after expression of wild-type *DOCK2*.

CONCLUSIONS

Autosomal recessive DOCK2 deficiency is a new mendelian disorder with pleiotropic defects of hematopoietic and nonhematopoietic immunity. Children with clinical features of combined immunodeficiencies, especially with early-onset, invasive infections, may have this condition. (Supported by the National Institutes of Health and others.)

COMBINED IMMUNODEFICIENCIES COM-prise a heterogeneous group of inherited defects of the immune system that are characterized by quantitative or qualitative defects of T lymphocytes. These defects are associated with primary or secondary defects of B lymphocytes.[1] In patients with combined immunodeficiencies, impairment of adaptive immunity causes increased susceptibility to early-onset, severe infections with a variety of viruses, bacteria, fungi, and parasites.[1,2] Autoimmune manifestations, allergies, and cancers can also occur.[2]

Identification of gene defects that cause combined immunodeficiencies has helped patients considerably, provided new and important insights into mechanisms governing T-cell development and function in humans,[2] and led to an understanding of the molecular and cellular basis of common conditions, including autoimmunity, allergy, inflammation, and cancer. However, the specific molecular, cellular, and clinical features of many combined immunodeficiencies remain poorly defined.

Next-generation sequencing has revolutionized studies of human genetic diseases, enabling the identification of new causative genetic variations in an increasing number of patients with primary immunodeficiencies.[3-7] Here we report on human dedicator of cytokinesis 2 (DOCK2) deficiency as a combined immunodeficiency in five unrelated patients of various ethnic origins. These patients presented with a distinctive clinical phenotype of early-onset, invasive infections that were associated with a broad spectrum of defects in hematopoietic and nonhematopoietic immunity.

METHODS

STUDY OVERSIGHT

The study was approved by the institutional review boards of the Kuwait Ministry of Health, INSERM, Rockefeller University, the Medical University of Vienna, Ankara University Medical School, Boston Children's Hospital, and Duke University School of Medicine. Written informed consent was obtained from the patients' parents or guardians.

CASE PATIENTS

Pedigrees of the five unrelated index patients are shown in Figure 1A, and Figure S1 in the Sup-

Figure 1 (facing page). Identification of *DOCK2* Mutations in Patients with Combined Immunodeficiency.
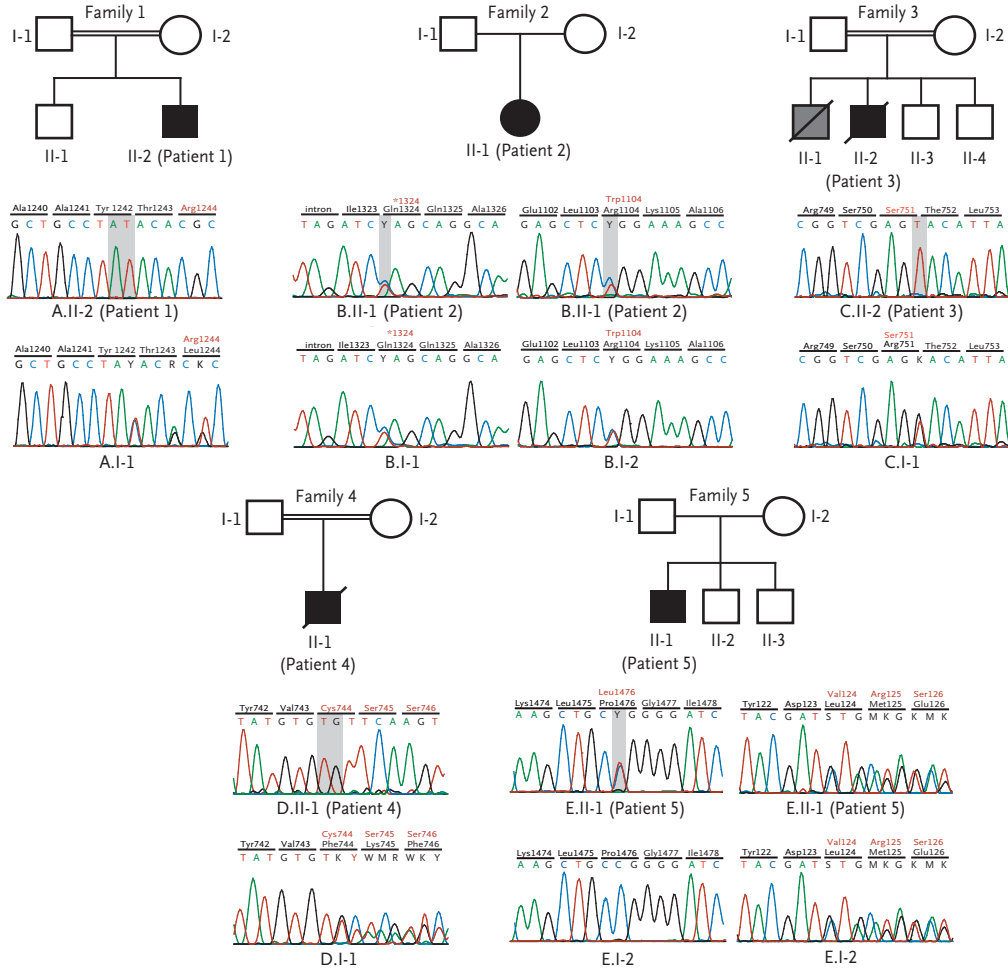
Panel A shows the pedigrees of the five families of the patients with *DOCK2* mutations in the study (Patients 1 through 5, solid symbols). Circles represent female family members, and squares male family members. A slash through a symbol represents a deceased person. Chromatograms corresponding to the identified *DOCK2* mutations in these patients and heterozygous carriers for each family are shown. Panel B shows the clinical spectrum of DOCK2 deficiency (from left to right): pneumonia requiring intubation in Patient 2, rash with vesicular lesions due to varicella in Patient 3, and neutrophil infiltrate in colonic lamina propria and crypt epithelium consistent with focal active colitis in Patient 4 (hematoxylin and eosin, low magnification). Panel C shows the distribution of the identified mutations relative to the DOCK2 protein structure depicting the SRC homology 3 (SH3) domain, the DOCK homology region 1 (DHR-1) domain, and the DOCK homology region 2 (DHR-2) domain. Panel D shows the immunoblot analysis of protein lysates from Epstein–Barr virus (EBV)–transformed B-cell lines from Patient 3 and two healthy controls and protein lysates from T-cell lines from Patients 1 and 2 and a control. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as protein-loading control.

plementary Appendix, available with the full text of this article at NEJM.org. Clinical and laboratory data are summarized in Table 1.

Patient 1, a boy born to consanguineous Lebanese parents, presented at 3 months of age with respiratory syncytial virus bronchiolitis, followed by recurrent episodes of pneumonia. At 5 months of age, severe T-cell lymphopenia and markedly reduced in vitro T-cell proliferation were observed (Table 1). At 9 months of age, after myeloablative conditioning with busulfan and fludarabine, he underwent T-cell–depleted haploidentical hematopoietic stem-cell transplantation (HSCT) from his father. He was well and was not receiving intravenous immune globulin replacement therapy 13 months after undergoing HSCT.

In the first 2 years of life, Patient 2, a girl born to nonconsanguineous Finnish parents, had recurrent otitis media, pneumonia, diarrhea, and three episodes of thrombocytopenia that resolved spontaneously. At 2.5 years of age, vaccine strain–related varicella developed, with liver and lung involvement and multiple pulmonary infiltrates, and the patient required ventilatory support (Fig. 1B). Several months later, computed tomog-
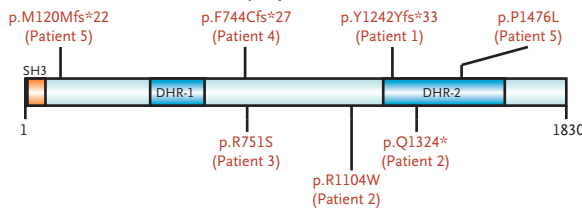
A Family Pedigrees and Identification of *DOCK2* Mutations

A.II-2 (Patient 1) — Ala1240 Ala1241 Tyr 1242 Thr1243 Arg1244 / GCTGCCTATACACGC

A.I-1 — Ala1240 Ala1241 Tyr 1242 Thr1243 Arg1244 Leu1244 / GCTGCCTAYACRCKC

B.II-1 (Patient 2) — intron Ile1323 *1324 Gln1324 Gln1325 Ala1326 / TAGATCYAGCAGGCA

B.I-1 — intron Ile1323 *1324 Gln1324 Gln1325 Ala1326 / TAGATCYAGCAGGCA

B.II-1 (Patient 2) — Glu1102 Leu1103 Trp1104 Arg1104 Lys1105 Ala1106 / GAGCTCYGGAAAGCC

B.I-2 — Glu1102 Leu1103 Arg1104 Lys1105 Ala1106 / GAGCTCYGGAAAGCC

C.II-2 (Patient 3) — Arg749 Ser750 Ser751 The752 Leu753 / CGGTCGAGTACATTA

C.I-1 — Arg749 Ser750 Ser751 Arg751 The752 Leu753 / CGGTCGAGKACATTA

D.II-1 (Patient 4) — Tyr742 Val743 Cys744 Ser745 Ser746 / TATGTGTGTTCAAGT

D.I-1 — Tyr742 Val743 Cys744 Phe744 Ser745 Lys745 Ser746 Phe746 / TATGTGTKYWMRWKY

E.II-1 (Patient 5) — Lys1474 Leu1475 Leu1476 Pro1476 Gly1477 Ile1478 / AAGCTGCYGGGGATC

E.I-2 — Lys1474 Leu1475 Pro1476 Gly1477 Ile1478 / AAGCTGCCGGGGATC

E.II-1 (Patient 5) — Tyr122 Asp123 Val124 Leu124 Arg125 Met125 Ser126 Glu126 / TACGATSTGMKGKMK

E.I-2 — Tyr122 Asp123 Val124 Leu124 Arg125 Met125 Ser126 Glu126 / TACGATSTGMKGKMK

B Clinical Features in Patients with DOCK2 Deficiency

C DOCK2 Protein Domains and Synopsis of DOCK2 Mutations

p.M120Mfs*22 (Patient 5)
p.F744Cfs*27 (Patient 4)
p.Y1242Yfs*33 (Patient 1)
p.P1476L (Patient 5)
p.R751S (Patient 3)
p.Q1324* (Patient 2)
p.R1104W (Patient 2)

SH3 · DHR-1 · DHR-2 · 1 — 1830

D DOCK2 Protein Expression

EBV-transformed B cells — Control, Control, Patient 3
T cells — Control, Patient 1, Patient 2
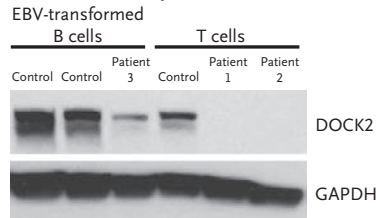
DOCK2
GAPDH

Table 1. Immunologic Characteristics of Patients with DOCK2 Deficiency.*

Variable	Patient 1 Value	Patient 1 Reference Range	Patient 2 Value	Patient 2 Reference Range	Patient 3 Value	Patient 3 Reference Range	Patient 4 Value	Patient 4 Reference Range	Patient 5 Value	Patient 5 Reference Range
Age at evaluation	5 mo		2.5 yr		6.3 yr		1 yr		4 mo	
Absolute lymphocyte count (cells/mm³ ×10⁻³)	1.22	3.9–9.0	1.24	2.3–5.4	1.1	1.9–3.7	2.3	3.6–8.9	4.4	3.9–9.0
Lymphocyte subset										
CD3+ T (cells/mm³)	114	2500–5600	548	1400–3700	341	1200–2600	1173	2100–6200	830	2500–5600
CD4+ T (cells/mm³)	57	1800–4000	305	700–2200	176	650–1500	129	1300–3400	511	1800–4000
CD45RA+CCR7+ (%)	4.0	76.7–91.4	0.4	65.2–84.8	NA		NA		4.5	76.7–91.4
CD45RA−CCR7+ (%)	16.0	6.7–15.6	19.2	10.5–23.2	NA		NA		33.8	6.7–15.6
CD45RA−CCR7− (%)	78.0	1.1–5.3	79.8	2.9–9.8	NA		NA		44.5	1.1–5.3
CD45RA+CCR7− (%)	12.0	0.1–1.9	0.6	0.2–3.0	NA		NA		17.2	0.1–1.9
CD8+ T (cells/mm³)	24	590–1600	133	490–1300	187	370–1100	763	620–2000	319	590–1600
CD45RA+CCR7+ (%)	8.5	62.1–94.0	1.6	39.0–89.0	NA		NA		22	62.1–94.0
CD45RA−CCR7+ (%)	14.7	0.9–5.6	5.2	0.9–5.7	NA		NA		26.3	0.9–5.6
CD45RA−CCR7− (%)	72.1	1.3–19.5	74.0	3.4–28.2	NA		NA		9.8	1.3–19.5
CD45RA+CCR7− (%)	4.7	1.5–22.7	19.2	4.8–30.0	NA		NA		41.9	1.5–22.7
CD19+ B (cells/mm³)	646	430–3000	146	390–1400	473	270–860	299	720–2600	1857	430–3000
CD3−CD56+/CD16+ (cells/mm³)	191	170–830	489	130–720	187	100–480	138	180–920	1539	170–830
Immunoglobulin										
IgG (mg/dl)	350	172–814	788	424–1051	559	633–1280	821†	217–904	413	164–558
IgA (mg/dl)	77	8.1–84.0	422	14–123	131	33–202	192†	11–90	50	4.4–73.0
IgM (mg/dl)	24	33–108	37	48–168	82	48–207	31†	34–126	170	27–101
IgE (IU/ml)	NA		2704	0.3–29.5	41	1–161.3	5.28†	0.8–7.3	26†	0.4–3.8
Serum antibody responses	NA		Nonprotective against tetanus toxoid, PRP, Streptococcus pneumoniae		No response to VZV		Response to HBV not detectable		Response to KLH not detectable	

TRECs at birth (copies/μl)	NA	<252‡	NA	<252‡	NA
T-cell response to phytohemagglutinin	2.6 (38.4)§	0.1 (278.2)§	9 (46–89)¶	18 (52–94)¶	6.04 (289.49)§

* Listed are reference ranges or laboratory values for the patient's age group. To convert values for IgE to micrograms per liter, multiply by 2.40. HBV denotes hepatitis B virus, KLH keyhole limpet hemocyanin, NA not assessed, PRP polyribosylribitol phosphate, TREC T-cell–receptor excision circle, and VZV varicella–zoster virus.
† This immunoglobulin level was measured when the patient was 9 months of age.
‡ The cutoff value for newborn screening for severe combined immunodeficiency in Massachusetts is shown. Normal amplification of the RNaseP reference gene was detected in dried blood spots obtained from both Patient 2 and Patient 4.
§ Stimulation index units (i.e., a response to phytohemagglutinin in counts per minute of radiolabeled thymidine incorporated minus counts per minute of background incorporation, divided by counts per minute of background incorporation) are shown. The T-cell response stimulation index units from a healthy control are shown in parentheses.
¶ The percentage of CD25+ cells after immunization with 10-valent pneumococcal protein-conjugate vaccine is shown. The range of the percentage of CD25+-expressing T cells in healthy controls is shown in parentheses.

raphy of the chest showed a new pulmonary infiltrate (Fig. S2A in the Supplementary Appendix). A lung biopsy revealed granulomatous inflammation (Fig. S2B in the Supplementary Appendix) with acid-fast bacilli. *Mycobacterium avium* was cultured from the biopsy specimen, and human herpesvirus-6 DNA was detected. Immunologic investigations revealed T-cell and B-cell lymphopenia, defective in vitro T-cell proliferation, and a lack of specific antibody responses (Table 1), all of which were consistent with combined immunodeficiency. At the age of 3.8 years, after reduced-intensity conditioning with the use of treosulfan, fludarabine, and alemtuzumab, she underwent HLA-matched unrelated-donor HSCT. She was well 8 months after HSCT.

Patient 3, a boy born to consanguineous Turkish parents, had recurrent respiratory tract infections from the age of 3 months. At 6 years of age, he had two episodes of meningoencephalitis. On the basis of examination of the cerebrospinal fluid (1000 leukocytes per cubic millimeter, 74% of which were lymphocytes), high serum amylase levels (762 U per liter), and detection of mumps-specific IgM, this condition was presumed to be due to mumps virus infection that was concurrent with an outbreak of mumps at the child's school. At the age of 6.3 years, severe varicella (Fig. 1B) with alveolar infiltrates developed, and child's illness rapidly progressed to multiorgan failure and death. Laboratory studies during the patient's hospitalization showed severe T-cell lymphopenia, impaired T-cell activation, and a lack of antibody responses to varicella–zoster virus (Table 1). A postmortem examination of the patient's liver and lungs revealed coagulation necrosis, apoptosis, inflammatory infiltrates with neutrophils and monocytes, and nuclear inclusion bodies within pneumocytes; the latter findings were consistent with viral pneumonitis (Fig. S2C and S2D in the Supplementary Appendix).

Patient 4, a boy born to consanguineous Turkish parents, had neonatal-onset chronic diarrhea with mucus and recurrent episodes of fever and oral moniliasis. A liver biopsy, performed at 3 months of age because of persistently elevated aminotransferase levels, revealed macrovesicular steatosis, nonnecrotic eosinophilic granuloma-like lesions, and lobular inflammation (Fig. S2E in the Supplementary Appendix). During hospital admission when the boy was 1 year of age,

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growth failure (body weight, 4.5 kg [3.5 kg below the 3rd percentile] and length, 64 cm [9 cm below the 3rd percentile]), a nodular erythematous lesion at the site of bacille Calmette–Guérin vaccination, and hepatomegaly were detected. In addition, histopathological analysis of the colon revealed focal active colitis (Fig. 1B) that was associated with a paucity of B cells, plasma cells, and to a lesser extent T cells in the lamina propria of the colon. Immunologic investigations (Table 1) revealed T-cell lymphopenia and defective T-cell activation in response to phytohemagglutinin. Subsequently, multiple episodes of pneumonia due to parainfluenza virus type 3 and adenovirus developed. The patient had several episodes of cytomegalovirus reactivation and died from *Klebsiella pneumoniae* sepsis at 20 months of age.

Patient 5, a Hispanic boy born to nonconsanguineous parents from Honduras and Nicaragua, presented at the age of 4 months with interstitial pneumonia that responded to high-dose trimethoprim–sulfamethoxazole. Immunologic findings were consistent with combined immunodeficiency (Table 1). At 2 years of age, a rectal fistula developed. At 3 years of age, he received an HSCT from his HLA-identical brother after conditioning with myeloablative doses of busulfan and cyclophosphamide. This patient was well and was not receiving intravenous immune globulin replacement therapy 17.5 years after transplantation.

GENETIC, IMMUNOLOGIC, AND BIOCHEMICAL ANALYSES

Details of the methods for whole-exome sequencing, genomewide linkage analysis, homozygosity mapping, and sequencing analysis are provided in the Supplementary Appendix. In addition, the generation of T-cell, B-cell, and natural killer (NK)–cell lines are described in detail in the Supplementary Appendix, as are immunologic and biochemical studies of hematopoietic and nonhematopoietic cells.

RESULTS

IMMUNOLOGIC ABNORMALITIES

In all five patients, T-cell lymphopenia and impaired in vitro T-cell activation in response to phytohemagglutinin were detected (Table 1). Maternal T-cell engraftment was ruled out in all the patients. More detailed immunologic analyses

that were performed in Patients 1, 2, and 5 revealed a markedly reduced proportion of naive (CD45RA+CCR7+) CD4+ and CD8+ T lymphocytes that were associated with an increased proportion of effector memory (CD45RA–CCR7–) CD4+ T lymphocytes and of either effector memory or CD45RA+CCR7– T_{EMRA} CD8+ T lymphocytes (Table 1). B-lymphocyte counts were reduced in Patients 2 and 4 (Table 1). Despite relatively normal serum levels of IgG and IgM, Patients 2, 4, and 5 had defective antibody production to T-cell–dependent immunization antigens (Table 1). Finally, in Patients 2 and 4, levels of T-cell–receptor excision circles, a marker of active thymopoiesis, were markedly reduced in dried blood spots obtained at birth (Table 1).

IDENTIFICATION OF BIALLELIC DELETERIOUS MUTATIONS IN *DOCK2*

Whole-exome sequencing was performed to elucidate the genetic basis of the patients' combined immunodeficiencies. Linkage analysis or homozygosity mapping were also performed in Patients 3 and 4, who were born to consanguineous parents. In Patients 1, 3, and 4, we selected genes harboring previously unreported homozygous variants, and in Patients 2 and 5 (for whom no parental consanguinity was known) we selected genes bearing two or more variants (Table S1 in the Supplementary Appendix). Biallelic mutations in *DOCK2* were identified and confirmed by means of Sanger sequencing in all five patients (Fig. 1A). No other gene harbored biallelic mutations in two or more patients. Patients 1 and 4 were homozygous for *DOCK2* dinucleotide insertions leading to frameshift and premature termination, Patient 3 was homozygous for a missense mutation, and Patients 2 and 5 were compound heterozygotes for different missense and nonsense *DOCK2* mutations (Fig. 1A). Multiple sequence alignment showed that all of the three missense mutations affect evolutionarily conserved residues (Fig. S3 in the Supplementary Appendix). Intrafamilial segregation was consistent with autosomal recessive inheritance with complete penetrance (Fig. S1 in the Supplementary Appendix). Collectively, we identified seven distinct rare mutations in *DOCK2* in five patients of various ethnic origins; four of these mutations led to premature termination, and three were predicted deleterious missense mutations affecting conserved residues of DOCK2 (Fig. 1C,
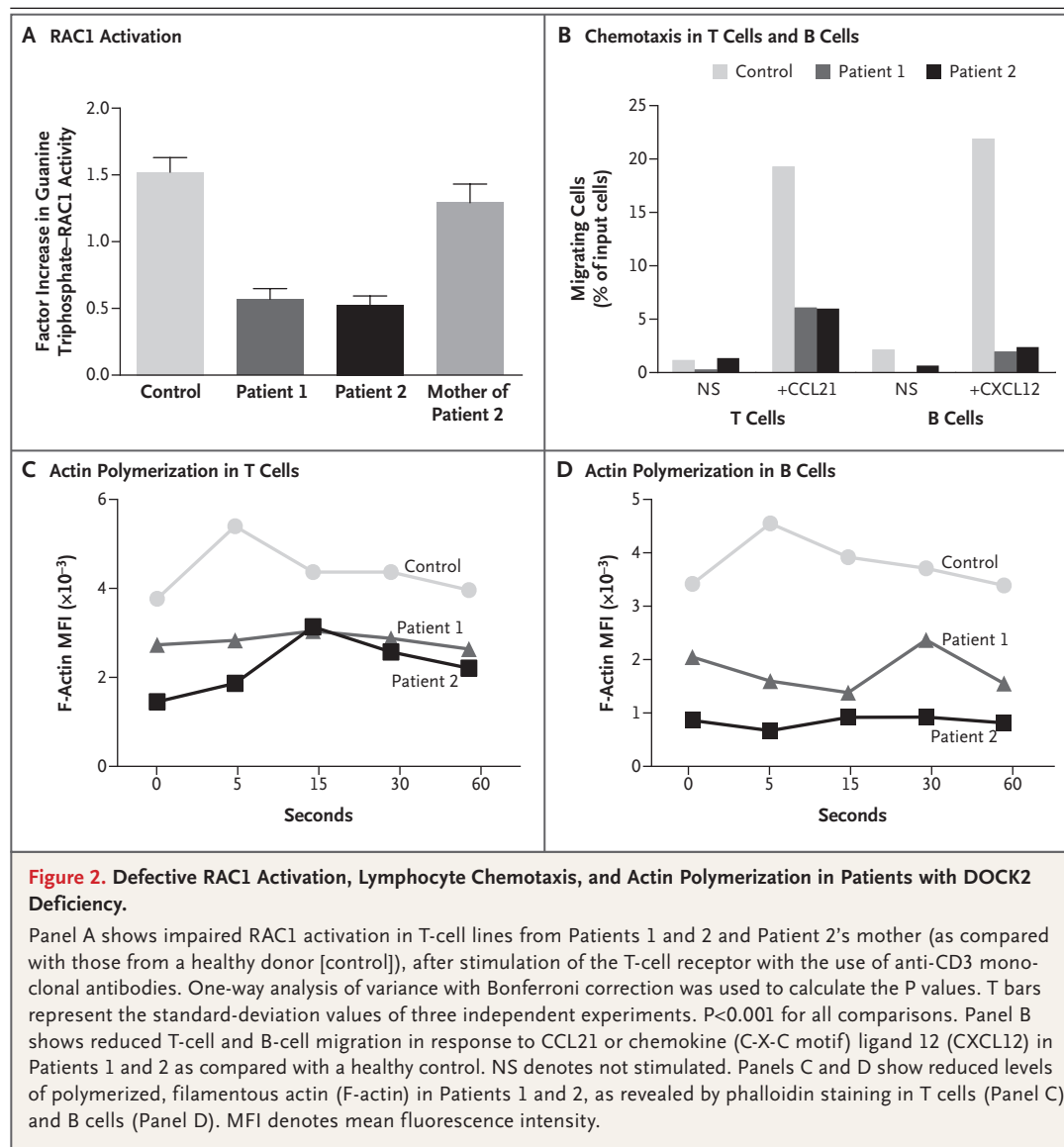
Figure 2. Defective RAC1 Activation, Lymphocyte Chemotaxis, and Actin Polymerization in Patients with DOCK2 Deficiency.

Panel A shows impaired RAC1 activation in T-cell lines from Patients 1 and 2 and Patient 2's mother (as compared with those from a healthy donor [control]), after stimulation of the T-cell receptor with the use of anti-CD3 monoclonal antibodies. One-way analysis of variance with Bonferroni correction was used to calculate the P values. T bars represent the standard-deviation values of three independent experiments. $P < 0.001$ for all comparisons. Panel B shows reduced T-cell and B-cell migration in response to CCL21 or chemokine (C-X-C motif) ligand 12 (CXCL12) in Patients 1 and 2 as compared with a healthy control. NS denotes not stimulated. Panels C and D show reduced levels of polymerized, filamentous actin (F-actin) in Patients 1 and 2, as revealed by phalloidin staining in T cells (Panel C) and B cells (Panel D). MFI denotes mean fluorescence intensity.

and Table S2 and Fig. S3 in the Supplementary Appendix).

EFFECT OF *DOCK2* MUTATIONS ON PROTEIN EXPRESSION AND T-CELL AND B-CELL SIGNALING

Immunoblot analysis revealed no DOCK2 protein expression in T-cell lines obtained from Patient 1 and trace amounts in Patient 2; markedly reduced levels of protein were detected in Epstein–Barr virus–transformed B cells obtained from Patient 3 (Fig. 1D, and Fig. S4A in the Supplementary Appendix). No biologic specimens from Patients 4 and 5 were available; however, overexpression of streptavidin–hemagglutinin–tagged DOCK2 bearing the p.F744Cfs*27 mutation (present in Patient 4) showed expression of a truncated DOCK2 protein (Fig. S4B in the Supplementary Appendix) that lacks the DOCK homology region 2 domain that is critical for the DOCK2 guanine nucleotide exchange factor function.

Previous studies involving mice have shown that Dock2 is essential for Rac1 activation downstream of the T-cell receptor.[8,9] In our study, after activation of polyclonal human T-cell lines with an anti-CD3 monoclonal antibody, guanine triphosphate–bound RAC1 was clearly detected in T cells from a healthy control and from Patient 2's

mother, but not from Patients 1 and 2 (Fig. 2A, and Fig. S5 in the Supplementary Appendix).

Chemokine-mediated cell migration is critically important during lymphocyte development, immune surveillance of lymph nodes, and recruitment of immune cells to sites of inflammation. Previous experimental data suggested a role for DOCK2 in actin polymerization and chemotactic responses of T lymphocytes and B lymphocytes after chemokine stimulation.[9,10] Indeed, the chemotactic response of T cells and B cells obtained from Patients 1 and 2 was profoundly impaired (Fig. 2B). Furthermore, chemokine (C-X-C motif) ligand 12 (CXCL12)–induced actin polymerization in T cells and B cells from Patients 1 and 2 was impaired and delayed (Fig. 2C and 2D). Baseline levels of polymerized actin (filamentous actin [F-actin]) were also reduced in DOCK2-deficient T lymphocytes and B lymphocytes from Patients 1 and 2 (Fig. 2C and 2D).

DEFECTS IN NK CELLS AND NK T CELLS IN PATIENTS WITH DOCK2 DEFICIENCY

Invasive viral infections were a prominent clinical feature in Patients 2, 3, and 4. Patients with DOCK2 deficiency had normal numbers of CD3–CD56+/CD16+ NK cells (Table 1), and NK cells from Patient 2 had a normal immunophenotype (Fig. S6 in the Supplementary Appendix). However, NK cells from Patients 1 and 2 showed impaired degranulation after stimulation with the human erythroleukemia cell line K562 (Fig. 3A).

The ability of NK cells to lyse virus-infected and tumor-target cells correlates with the functionality of a variety of activating NK receptors interacting with distinct adaptor (DAP10 and DAP12) and signaling (CD3ζ, FcεRIγ) molecules.[11-13] The triggering of activating NK receptors induces actin polymerization, activation of phosphatidylinositol-3-OH kinase, and phosphorylation of extracellular signal-regulated kinase (ERK) and mitogen-activated protein–ERK (MEK), ultimately promoting NK-cell cytotoxicity.[14]

We analyzed NK-cell degranulation after engagement of CD16, NKp30 (NK-cell p30-related protein), or NKp46 (NK-cell p46-related protein) — all of which use CD3ζ and FcεRIγ — or NKG2D (which recruits the DAP10 adaptor). We observed severely impaired degranulation in Patient 1 (Fig. 3B) and moderately impaired degranulation in Patient 2, probably corresponding to residual amounts of DOCK2 protein in Patient 2's hema-

topoietic cells (Fig. S4A in the Supplementary Appendix). Degranulation was also impaired in Patient 2's interleukin-2–activated polyclonal NK cells after engagement of NKp44 (NK-cell p44-related protein) (which uses DAP12) (Fig. S7 in the Supplementary Appendix). Furthermore, we observed reduced levels of F-actin in Patient 2's NK cells after stimulation with anti-CD16 and anti-NKp46 monoclonal antibodies (Fig. 3C); these findings were reminiscent of observations in *Dock2*^{−/−} mice.[15] These reduced levels possibly reflected impaired tonal signaling through antigen and chemokine receptors. Reduced phosphorylation of ERK1/2 and MEK and impaired actin polymerization were also detected in polyclonal NK cells from Patient 2 after cross-linking of NKp30, NKp44 (Fig. 3D), CD16, and NKp46. NK cells are also involved in cytokine production.[16] After overnight stimulation with interleukin-12 and interleukin-18, the proportion of NK cells expressing interferon-γ was markedly reduced in Patient 2 (Fig. 3E).

Finally, the number of circulating NK T cells was severely reduced in Patients 1 and 2 (Fig. S8 in the Supplementary Appendix). Altogether, these data show that DOCK2 serves an essential role in NK and NK T-cell biology; these findings are consistent with similar observations in mice.[17,18]

IMPAIRED ANTIVIRAL INTERFERON RESPONSES IN PATIENTS WITH DOCK2 DEFICIENCY

Human interferon-α/β and interferon-λ immunity has been suggested to be essential in host defense against viral infections.[19] Plasmacytoid dendritic cells are the major source of interferon-α in human blood in response to enveloped viruses and synthetic toll-like receptor 7 and toll-like receptor 9 agonists.[20] Previous studies involving mice have shown that Dock2 serves an essential function in regulating interferon-α production in plasmacytoid dendritic cells without perturbing development of these cells.[15,21]

Although a normal proportion of circulating plasmacytoid dendritic cells was detected in Patient 2 (Fig. S9 in the Supplementary Appendix), the production of interferon-α and interferon-λ in the peripheral-blood mononuclear cells (PBMCs) in Patients 1, 2, and 3 after stimulation with herpes simplex virus type 1 (HSV-1) or vesicular stomatitis virus (VSV) was markedly impaired (Fig. 4A, and Fig. S10 in the Supplementary Appendix). By contrast, similar amounts of inter-
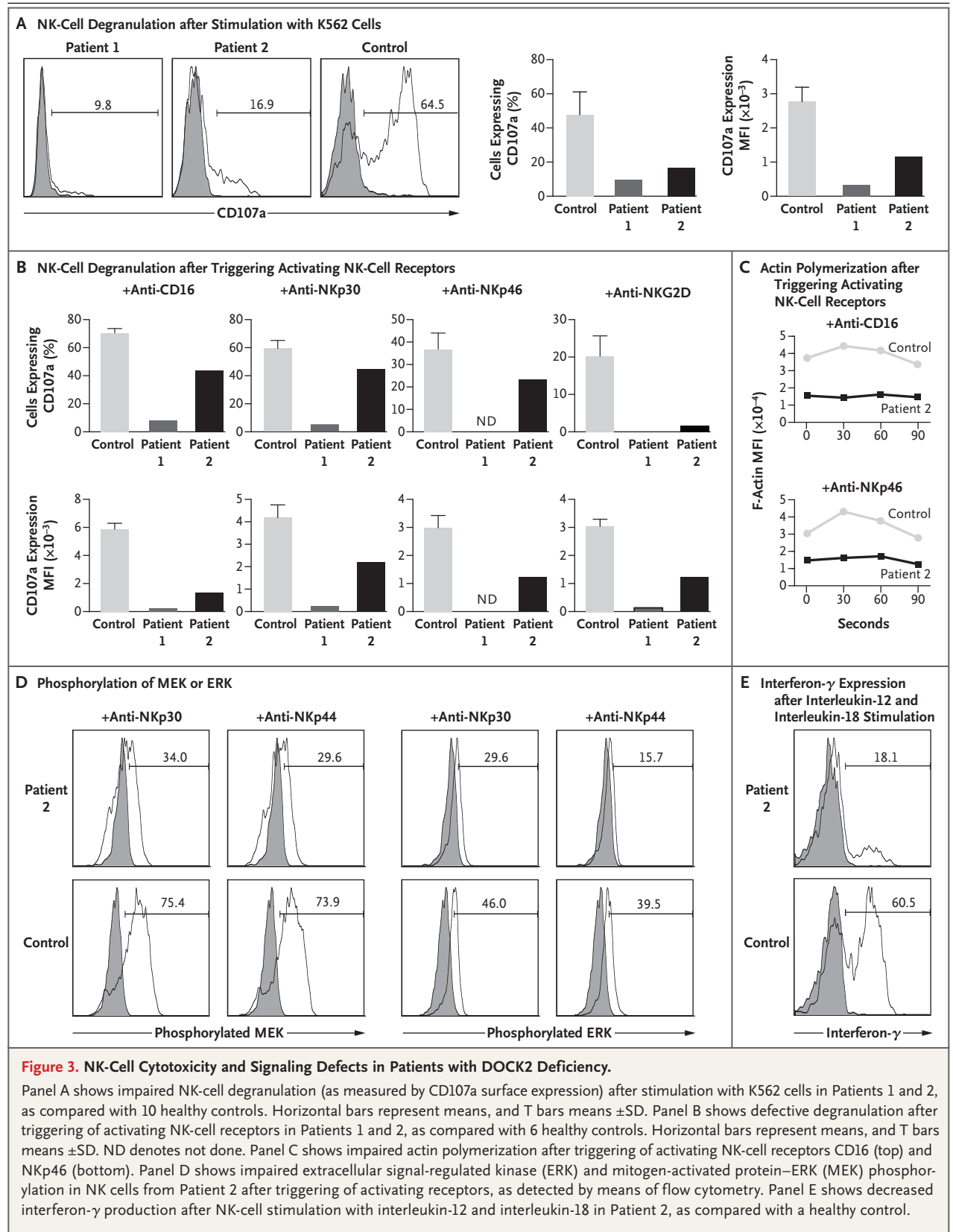
Figure 3. NK-Cell Cytotoxicity and Signaling Defects in Patients with DOCK2 Deficiency.

Panel A shows impaired NK-cell degranulation (as measured by CD107a surface expression) after stimulation with K562 cells in Patients 1 and 2, as compared with 10 healthy controls. Horizontal bars represent means, and T bars means ±SD. Panel B shows defective degranulation after triggering of activating NK-cell receptors in Patients 1 and 2, as compared with 6 healthy controls. Horizontal bars represent means, and T bars means ±SD. ND denotes not done. Panel C shows impaired actin polymerization after triggering of activating NK-cell receptors CD16 (top) and NKp46 (bottom). Panel D shows impaired extracellular signal-regulated kinase (ERK) and mitogen-activated protein–ERK (MEK) phosphorylation in NK cells from Patient 2 after triggering of activating receptors, as detected by means of flow cytometry. Panel E shows decreased interferon-γ production after NK-cell stimulation with interleukin-12 and interleukin-18 in Patient 2, as compared with a healthy control.
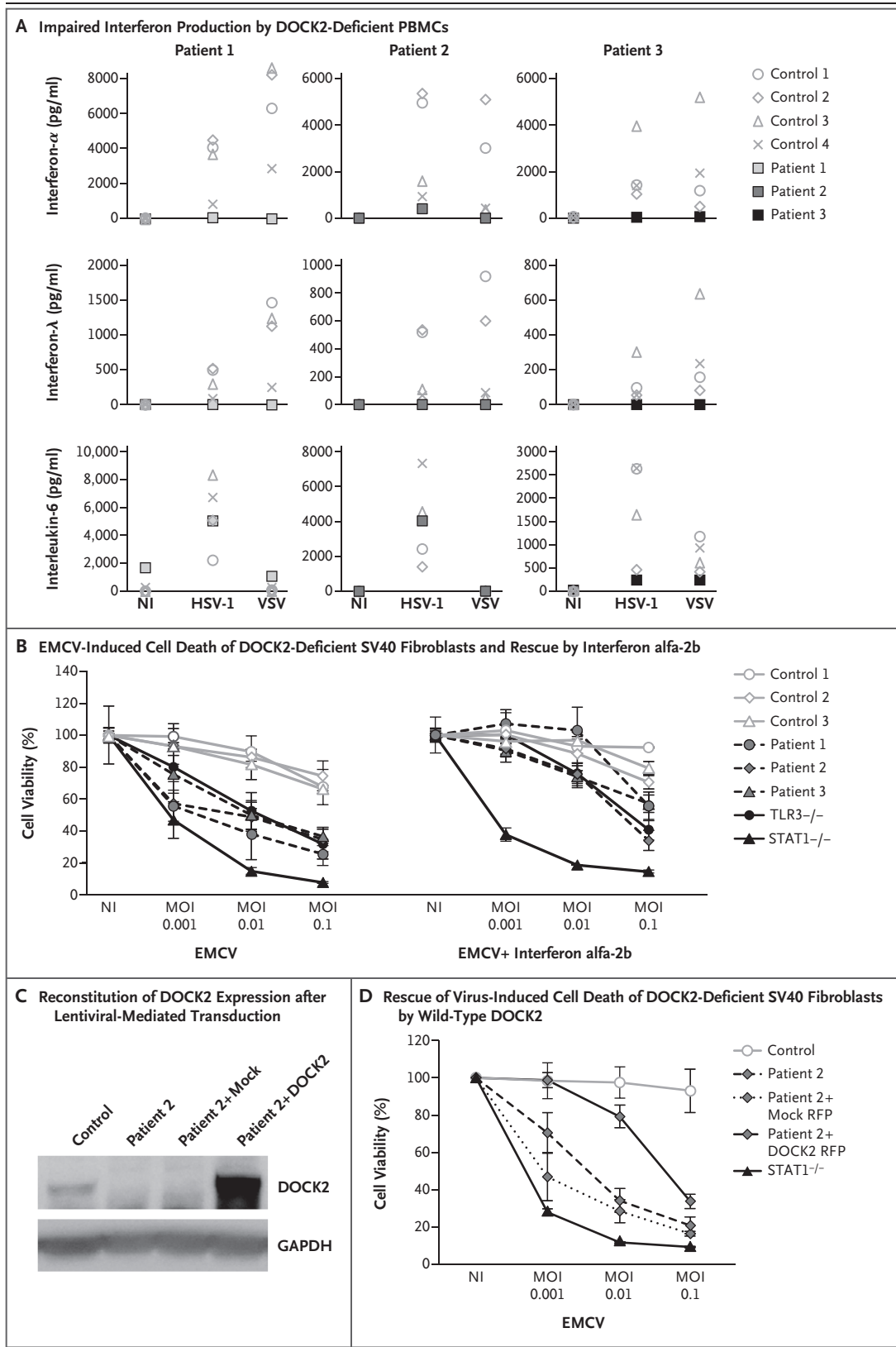
A Impaired Interferon Production by DOCK2-Deficient PBMCs

B EMCV-Induced Cell Death of DOCK2-Deficient SV40 Fibroblasts and Rescue by Interferon alfa-2b

C Reconstitution of DOCK2 Expression after Lentiviral-Mediated Transduction

D Rescue of Virus-Induced Cell Death of DOCK2-Deficient SV40 Fibroblasts by Wild-Type DOCK2

Figure 4 (facing page). Impaired Interferon Responses to Viruses in DOCK2-Deficient Leukocytes and Fibroblasts.

Panel A shows impaired interferon-α and interferon-λ production by DOCK2-deficient peripheral-blood mononuclear cells (PBMCs) after exposure to either herpes simplex virus 1 (HSV-1) or vesicular stomatitis virus (VSV) for 24 hours each. By contrast, production of interleukin-6 by the patients' PBMCs was similar to that in the PBMCs of the healthy donors (controls) and served as an assay control. NI denotes not infected. Panel B shows increased encephalomyocarditis virus (EMCV)–induced cell death of DOCK2-deficient simian virus 40 (SV40) fibroblasts (left) and rescue by the addition of interferon alfa-2b (right). Toll-like receptor 3 (TLR3)–deficient and signal transducer and activator of transcription 1 (STAT1)–deficient SV40 fibroblast cell lines served as examples of defective interferon-dependent antiviral immunity. I bars represent the standard-deviation values of triplicate measurements from one representative experiment of three experiments performed. MOI denotes multiplicity of infection. Panel C shows immunoblot analysis of protein lysates obtained from SV40 fibroblasts from a healthy donor (control) and Patient 2, as well as from mock-transduced (Mock) and DOCK2-transduced fibroblasts from Patient 2. Panel D shows rescue of EMCV-induced cell death of SV40 fibroblasts from Patient 2 by exogenous expression of wild-type *DOCK2*. STAT1-deficient fibroblasts were used as a negative control. The data in Panels B and D show one representative experiment of three independent experiments with technical triplicates carried out in each experiment.

leukin-6 were produced by PBMCs in samples obtained from patients with DOCK2 deficiency and from healthy donors (Fig. 4A, and Fig. S10 in the Supplementary Appendix). Altogether, these data indicate that in addition to T cells, NK cells, and NK T cells, plasmacytoid dendritic cells may also be defective in patients with DOCK2 deficiency; this may also contribute to the patients' viral susceptibility.

Although DOCK2 is preferentially expressed in hematopoietic cells,[22] low levels of expression were detected in fibroblasts from healthy controls, but not from Patients 1 and 2 (Fig. S4A in the Supplementary Appendix). Only minimal expression was detected in fibroblasts from Patient 3 (Fig. S4A in the Supplementary Appendix). To investigate whether DOCK2 contributes to cell-intrinsic antiviral responses in nonhematopoietic tissues, we studied simian virus 40 (SV40)–immortalized fibroblasts from Patients 1, 2, and 3 and from healthy controls. After infection with VSV or encephalomyocarditis virus, we

found enhanced levels of viral replication and decreased viability of DOCK2-deficient SV40 fibroblasts (Fig. 4B, and Fig. S11 in the Supplementary Appendix); similar results were observed in SV40 fibroblasts from patients with toll-like receptor 3 or signal transducer and activator of transcription 1 deficiency (Fig. 4B, and Fig. S11 in the Supplementary Appendix), which affect the production of or the response to interferon-α/β and interferon-λ, respectively.[23]

Both treatment with recombinant interferon alfa-2b (Fig. 4B) and lentiviral-mediated wild-type DOCK2 expression (Fig. 4C) protected DOCK2-deficient fibroblasts from virus-induced cell death (Fig. 4D). The *DOCK2* mutations may therefore also impair cell-intrinsic, nonhematopoietic immunity, at least in fibroblasts and in response to some viruses.

DISCUSSION

In this study, we showed that biallelic mutations in *DOCK2* were the molecular cause of a distinctive type of combined immunodeficiency that is characterized by early-onset, invasive bacterial and viral infections; T-cell lymphopenia; impaired T-cell, B-cell, and NK-cell function; and defective interferon immunity in both hematopoietic and nonhematopoietic cells. Our results also indicate that this disease can be detected at birth with newborn screening for severe combined immunodeficiency (Table 1) and can be cured by means of HSCT (Fig. S12 in the Supplementary Appendix).

The observation that DOCK2 deficiency in humans leads to impaired RAC1 activation and to defects in actin polymerization, T-cell proliferation, chemokine-induced lymphocyte migration, and NK-cell degranulation confirms and extends similar observations in *Dock2*^{−/−} mice.[9,10,17,24] It also highlights the essential role of regulated actin dynamics for immune-cell function, a role that is also evident with respect to other combined immunodeficiencies involving defective actin polymerization such as the Wiskott–Aldrich syndrome,[25] as well as with respect to deficiency of Wiskott–Aldrich syndrome protein–interacting protein (WIP),[26] DOCK8 protein,[27] the protein encoded by the Ras homologue family member H (RHOH),[28] and macrophage-stimulating 1 growth factor (MST1) protein.[29,30]

The occurrence of invasive viral infections, including disseminated vaccine-strain varicella,

was a prominent feature in patients with DOCK2 deficiency. Human antiviral immunity is critically dependent on intact T-cell function as well as on innate immune responses, as observed in patients with genetic defects affecting T-cell, NK-cell, NK T-cell, and dendritic-cell development, function, or both,[1,31] or with mutations affecting production of (or response to) interferon-α, interferon-β, and interferon-λ in both hematopoietic and nonhematopoietic cells.[32] We observed defective interferon-α/β and interferon-λ responses in both hematopoietic and nonhematopoietic cells in patients with DOCK2 deficiency. Plasmacytoid dendritic cells are the most potent interferon-α–producing cells.[33] Severe reduction of splenic and lymph-node plasmacytoid dendritic cells and of their capability for interferon-α production were observed in $Dock2^{-/-}$ mice.[15,21] Here we show impaired interferon-α and interferon-λ production in DOCK2-deficient PBMCs after stimulation with HSV-1 or VSV, possibly reflecting a defect of plasmacytoid dendritic cells. Therefore, we speculate that treatment with interferon alfa-2b might be beneficial in patients with DOCK2 deficiency who have severe viral infections.

Furthermore, our study suggests a role for DOCK2 in antiviral responses in nonhematopoietic cells. DOCK2 deficiency in nonhematopoietic cells may contribute to the pathogenesis of severe viral infections. Normalization of immunologic abnormalities and resolution of infections were observed in Patients 1, 2, and 5 after HSCT (Fig. S12 in the Supplementary Appendix). This finding implies that correction of hematopoietic cells may be sufficient to rescue the clinical phenotype, possibly by providing a source of cells producing interferon-α/β (e.g., plasmacytoid dendritic cells) and therefore complementing the defect in nonhematopoietic tissues.

K. pneumoniae sepsis was the cause of death in Patient 4. Susceptibility to invasive bacterial infections in patients with DOCK2 deficiency may reflect impaired function of neutrophil granulocytes in addition to impaired antibody production. Defective neutrophil chemotaxis has been reported in $Dock2^{-/-}$ mice.[34] Because of a lack of primary material, we could not test whether a similar defect existed in the patients in our study.

Mutations in *DOCK8*, another member of the DOCK family of proteins, have been identified in patients with another form of combined immunodeficiency.[35,36] Similarities and important differences have been observed between patients with DOCK2 deficiency and those with DOCK8 deficiency. Both conditions are characterized by recurrent bacterial and viral infections[36] and are associated with T-cell lymphopenia,[36] defective NK-cell function,[37] aberrant NK T-cell survival and function,[38] and impaired antibody responses.[39] However, the natural course of DOCK2 deficiency appears to be more severe than that of DOCK8 deficiency. Although DOCK8 deficiency is characterized mostly by cutaneous viral infections,[36] patients with DOCK2 deficiency have early-onset, life-threatening, invasive viral and bacterial infections. Furthermore, severe food allergies, eczema, and autoimmunity are commonly observed in patients with DOCK8 deficiency,[36,40,41] whereas none of the patients with DOCK2 deficiency had such manifestations.

In summary, we have identified DOCK2 deficiency as a pleiotropic immunodeficiency leading to early-onset, invasive bacterial and viral infections. The broad spectrum of infections observed in patients with DOCK2 deficiency highlights the effect of DOCK2 function on several aspects of immunity and arouses possible concern about the application of new immunosuppressive agents targeting DOCK2.[42] Our observations indicate that HSCT can provide a cure for this immunodeficiency.

APPENDIX

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