Current Status of Dedicator of Cytokinesis-Associated Immunodeficiency
DOCK8 and DOCK2

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KEYWORDS

• Immunodeficiency • Dedicator of cytokinesis 8 • Dedicator of cytokinesis 2 • Atopic dermatitis • Cutaneous viral infection • Malignancy

KEY POINTS

- DOCK8 deficiency is an autosomal recessive hyper–immunoglobulin E syndrome associated with atopy, recurrent sinopulmonary and cutaneous viral infections, and malignancies.
- The DOCK8 protein plays an important role in cytoskeletal organization, impacting dendritic cell transmigration.
- DOCK8 deficiency leads to persistence of B cells in germinal centers, early T-cell death, and lowered natural killler cell cytotoxicity.
- DOCK2 deficiency has been recently described in several patients with early-onset invasive bacterial and viral infections.

INTRODUCTION

Dedicator of cytokinesis 8 (DOCK8) deficiency is an autosomal recessive combined immunodeficiency syndrome characterized by recurrent sinopulmonary and cutaneous viral infections, as well as an increased immunoglobulin (Ig)E level and atopy. Although patients with an autosomal recessive variant of hyper-IgE syndrome had been described as early as 2004, a genetic basis involving bi-allelic mutations often with large deletions was not established until 2009.[1–3] In the intervening years, definitive treatment with early hematopoietic stem cell transplantation (HSCT) has gained prominence, and advances have been made in understanding the functions of DOCK8 in dendritic cell and lymphocyte activity. Recently, another syndrome with differing phenotype but similar immunopathogenic basis, dedicator of cytokinesis 2 (DOCK2) deficiency, has been described.[4]

CLINICAL PRESENTATION OF DEDICATOR OF CYTOKINESIS 8 DEFICIENCY

Atopy

Patients with DOCK8 deficiency demonstrate atopy early on. Nearly all patients exhibit atopic dermatitis (AD), which ranges from mild to very severe and difficult to treat (**Fig. 1**). Unlike patients with autosomal dominant hyper-IgE syndrome from Signal transducer and activator of transcription 3 (STAT3)

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Abbreviations and acronyms

Cdc42	G protein activated by DOCK guanine exchange factors.
DOCK2	Dedicator of cytokinesis 2, one of a class of guanine nucleotide exchange factors whose role is to activate the G protein Rac.
DOCK8	Dedicator of cytokinesis 8, one of a class of guanine nucleotide exchange factors whose role is to activate G proteins such as Rac and Cdc42. Deficiency leads to impaired cytoskeletal organization and a phenotype of combined immunodeficiency with eczema, elevated IgE, and malignancy.
HSCT	Hematopoietic stem cell transplantation, a treatment for primary immunodeficiencies that result from genetic defects in hematopoietic cells.
ICAM-1	Intercellular adhesion molecule 1, a ligand for LFA-1 necessary for leukocyte endothelial transmigration.
LFA-1	Lymphocyte function–associated antigen 1, binds to ICAM-1 and functions as an adhesion molecule.
MST1	Macrophage-stimulating 1 (also known as STK4). Deficiency results in a rare form of immunodeficiency with a phenotype similar to DOCK8 deficiency.
MyD88	Myeloid differentiation primary response 88, a protein used by Toll-like receptors to activate the transcription factor NF-κB.
PGM3	Phosphoglucomutase 3, which mediates glycosylation. Deficiency results in a phenotype of severe atopy, hypergammaglobulinemia, leukopenia, and developmental delay.
Rac	G protein activated by DOCK guanine exchange factors.
Rho GTPase	G protein such as Cdc42 and Rac, activated by DOCK guanine exchange factors. These proteins regulate various aspects of cytoskeletal dynamics.
STAT3	Signal transducer and activator of transcription 3, a transcription factor. Deficiency leads to autosomal dominant hyper-IgE syndrome.
TLR9	Toll-like receptor 9, important for activation of innate immunity via MyD88.
Tyk2	Tyrosine kinase 2, a protein involved in IL-10 and IFN-α signaling. Deficiency has been associated with a variable phenotype that includes susceptibility to mycobacterial infection.
WAS	Wiskott-Aldrich syndrome is a rare X-linked recessive disease classically characterized by a triad of recurrent sinopulmonary infections, eczema, and thrombocytopenia with small platelets. Many patients do not exhibit the classic triad and may have autoimmune disease among other manifestations.
WASp	Wiskott-Aldrich syndrome protein, a protein that coordinates cytoskeletal reorganization. Deficiency leads to WAS.

mutations, many have food allergies with anaphylaxis, as well as asthma. Eosinophilic esophagitis also has been seen with increased frequency.[3,5–7]

Infections

Cellulitis and skin abscesses are common, as is mucocutaneous candidiasis. There is a striking susceptibility to cutaneous infections by viruses, such as human papillomavirus (HPV) leading to widespread and recalcitrant warts, extensive and disfiguring molluscum contagiosum, herpes simplex virus (HSV) with recurrent or persistent lesions or herpes keratitis, and varicella zoster virus (VZV) with severe primary infection or recurrent zoster (**Fig. 2**). Chronic Epstein-Barr virus (EBV) viremia is frequent, and may be associated with transformation to malignancy. Interestingly, severe systemic viral infections are less common, although several patients have suffered from cytomegalovirus (CMV) disease, encephalitis, and progressive multifocal leukoencephalopathy.[3,5–7]

Most patients have a history of recurrent sinusitis and otitis media requiring tympanostomy tubes. Most also have had multiple pneumonias, with development of bronchiectasis in more than a third but infrequent pneumatocele formation (**Fig. 3**).[3,5–7]

Malignancy

Increased risk of neoplasms, especially hematological and epithelial, is an important feature of DOCK8 deficiency, and malignancy is often particularly aggressive and has early onset. In one large cohort of 136 patients, 17% of patients were diagnosed with malignancy at a median age of 12 years.[6] Malignancy most frequently arises from poor control of viruses including squamous cell carcinomas from HPV infection and EBV-related lymphomas. Microcystic adnexal carcinoma, aggressive cutaneous T-cell lymphoma, and diffuse large B-cell lymphoma have been described.[3,8] Of note, not all tumors have been associated with viral infection.