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DOCK8 (Dedicator of cytokinesis 8) deficiency

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Abstract

Purpose of the review—The purpose of this review is to describe a new combined primary immunodeficiency disease, previously known as autosomal recessive hyper-IgE syndrome, whose molecular basis was discovered in 2009.

Recent findings—Two groups identified homozygous and compound heterozygous loss-of-function mutations in the *DOCK8* (Dedicator of cytokinesis 8) gene in at least 30 patients who had been previously diagnosed with an atypical form of hyper-IgE syndrome. Absence of DOCK8 expression impairs T cell expansion in vitro, which could help explain the T cell lymphopenia and susceptibility to cutaneous viral infections observed in these patients. In mouse models of Dock8 deficiency, absence of DOCK8 expression also impairs the generation of a durable secondary antibody response to specific antigens, which could account for the functional antibody abnormalities and recurrent sinopulmonary infections observed in the patients. Two patients have been cured of infectious complications after myeloablative allogeneic hematopoietic cell transplantation.

Summary—The discovery of the molecular basis of this disease is expected to facilitate diagnosis and definitive treatment with hematopoietic cell transplantation. Further research is needed to understand how DOCK8 normally functions in lymphocytes and how DOCK8 deficiency leads to disease.

Keywords

DOCK8; combined immunodeficiency; lymphopenia; hyper-IgE; viral susceptibility

Introduction

The hyper-IgE syndrome, which was originally described in 1966, has recently been reviewed [1•,2,3]. Patients present with eczema, recurrent skin abscesses, pneumonias, and elevated serum IgE. Most patients have disease due to autosomal dominant *STAT3* mutations, which are associated with increased susceptibility to certain fungal infections and non-immune abnormalities including pneumatoceles [4,5]. However, some patients with hyper-IgE syndrome instead present with increased susceptibility to viral infections and an autosomal recessive pattern of disease inheritance [6]. Among this latter group, *TYK2* mutations were found in one patient who had the additional unusual feature of BCG infection [7,8]. Thus, the responsible mutations in the majority of patients with autosomal recessive hyper-IgE syndrome remained unaccounted for, until the discovery in 2009 of mutations in the *DOCK8* (Dedicator of cytokinesis 8)gene.

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In this review, I describe the discovery of *DOCK8* mutations, what is known about this gene, and the clinical and laboratory data that provide insight into disease pathogenesis. Contrary to its initial description as a form of hyper-IgE syndrome, DOCK8 deficiency can alternatively be regarded as a combined immunodeficiency that features eczema and elevated IgE, much like the Wiskott-Aldrich syndrome.

Discovery of *DOCK8* mutations in immunodeficiency disease

Work from the International HapMap project has shown that the human genome varies considerably from one person to the next. These differences reflect not only single nucleotide polymorphisms (SNP), but also copy number variations (CNV) that include large deletions or duplications of genes [9]. Because CNV are enriched in genes of the immune system, CNV can contribute to diseases of the immune system, as is the case for systemic lupus erythematosus or HIV progression. Indeed, by using high-resolution oligonucleotide array-based comparative genomic hybridization, Zhang *et al*. found large deletions in the *DOCK8* gene in patients who had been previously diagnosed with autosomal recessive hyper-IgE syndrome or unknown combined immunodeficiency disorders [10••]. Using a similar approach, Engelhardt *et al*. also detected *DOCK8* deletions in a cohort of mostly Turkish patients from consanguineous families [11••]. The latter study also revealed loss of homozygosity of chromosome 9p in those patients who lacked large deletions in the *DOCK8* gene but who instead turned out to have point mutations in the *DOCK8* gene.

At present, there are 32 DOCK8-deficient patients from 23 families published in the literature, who have either homozygous or compound heterozygous *DOCK8* mutations confirmed on both alleles [10••,11••,12•]. The 30 different genomic mutations appear unique to each family and are distributedas follows: 19 (63%) are large deletions, 5 (17%) are point mutations that alter splicing to cause out-of-frame nonsense mutations, 3 (10%) are point mutations that are also in-frame nonsense mutations, and 3 (10%) are small indels that cause out-of-framenonsense mutations. Because the large deletions in *DOCK8* are non-recurrent and have different breakpoints, they are probably generated during fork stalling and template switching/microhomology-mediated break-induced replication [9]. These mutations result in loss of DOCK8 expression, in many cases through nonsense-mediated decay of mRNA.

The human *DOCK8* gene, which consists of 46 to 48 exons, depending upon the isoform, is spread over ~250 kb on chromosome 9p24.3. DOCK8 was originally shown by Northern blot hybridization analysis to be expressed in various non-immune tissues such as placenta, kidney, lung, and pancreas [13]. However, DOCK8 is also highly expressed within the immune system, especially by lymphocytes, suggesting crucial functions in these cell types [10••,14].

DOCK8 structure and biochemical function

DOCK8 is a member of the DOCK180-related family of atypical guanine nucleotide exchange factors (GEF) [15,16]. Unlike the classical Dbl homology-pleckstrin homology (DH-PH) domain-containing GEF, DOCK180-related family members each have two related conserved protein domains. These protein domains are termed Dock homology regions (DHR), or sometimes CDM (for Ced5, Dock180, Myoblast city) zizimin homology (CZH) domains. Whereas DHR2 contains the actual catalytic site for GEF activity, DHR1 is required for downstream signaling and biological function, probably through its ability to localize the enzyme complex to the plasma membrane. The presence of additional structural domains allows the 11 mammalian DOCK180-related family members to be grouped into four subfamilies [16]. The DOCK-C (Zir) subfamily, which contains DOCK6, DOCK7, and DOCK8, is defined by the absence of additional domains besides DHR1 and DHR2.

The DOCK180-related family members activate Rho GTPases by facilitating the removal of GDP to allow GTP binding to the Rho GTPases, the most familiar of which are RAC and CDC42. Recent X-ray crystallographic structures of DOCK9 in complex with CDC42 suggest that this process is accomplished through a DHR2-containing nucleotide sensor, which can distinguish between GDP- and GTP-bound forms of CDC42 to induce appropriate conformational changes [17•]. DOCK8 was shown by a yeast two-hybrid system to bind to the Rho GTPases CDC42, RAC1, RHOJ (TCL), and RHOQ (TC10) [13]. However, stable interaction between DOCK8 and either CDC42 or RAC1 could not be demonstrated in pull-down experiments. Although the substrate specificity of DOCK8 remains uncertain, many of the DOCK180-related family members activate RAC and/or CDC42 to initiate signaling for reorganization of the cytoskeletal architecture. Because of this, the DOCK180 family members are involved in diverse biological processes that include cell migration, polarization, phagocytosis, fusion, and morphogenesis.

Role of DOCK180-family members in the immune system

Prior to the discovery of DOCK8 mutations in the patients, DOCK8 had not previously been known to play a role within the immune system. Intriguingly, though, mice deficient in a related DOCK180-family member, Dock2, were already known to have prominent immunological abnormalities. Dock2-deficient mice have T cell lymphopenia, decreased cellularity of thymus and secondary lymphoid organs, loss of marginal zone B cells, decreased lymphocyte chemotaxis and migration, and decreased T cell proliferation due to impaired immunological synapse formation [18,19,20,21]. When backcrossed onto an allergy-prone genetic background, the Dock2-deficient mice spontaneously develop elevated serum IgE [22]. However, the Dock2-deficient mice also have impairments in migration and other functions of neutrophil and plasmacytoid dendritic cells, including the ability of the latter to produce antiviral IFN-α in response to stimulation through toll-like receptors-7 and -9 [23,24,25,26]. Thus, although the Dock2-deficient mice are similar to the DOCK8-deficient humans in their T cell lymphopenia and hyper-IgE, myeloid cell abnormalities seen in the mice are not obviously suggested by the clinical presentation of the patients.

Finally, two other DOCK180-related family members may also have roles in the immune system given their expression profiles. Both DOCK10 and DOCK11 are highly expressed in peripheral blood leukocytes, including both T and B cells, and to a lesser degree in lymphoid organs [27,28]. Moreover, DOCK10 is upregulated in IL-4 stimulated B cells, whereas Dock11 expression is enriched in germinal center vs. non-germinal center B cells. These expression profiles suggest that these two members of the DOCK-D (Zizimin) subfamily might play complementary roles in B cell activation and differentiation.

Clinical features of DOCK8 deficiency

DOCK8 deficiency exhibits an unusual constellation of clinical features, but diagnosis can be confusing when some features are absent (Table 1). Both DOCK8 deficiency and classical hyper-IgE syndrome due to *STAT3* mutations typically present with signs of atopic dermatitis, *Staphylococcus aureus* skin abscesses or soft tissue infections, pneumonias, elevated serum IgE, and eosinophilia. These two conditions may not be easily distinguished from each other during early childhood, as the non-immune manifestations unique to *STAT3* mutant hyper-IgE syndrome, such as the characteristic facial appearance, pneumatoceles, delayed exfoliation of primary teeth, and pathological fractures, can take years to become evident [1•]. As with hyper-IgE syndrome, other combined immunodeficiencies, such as the Wiskott-Aldrich syndrome, can be associated with eczematous rash, infectious susceptibility, and high IgE [29]. However, only DOCK8 deficiency is typically associated with asthma and severe allergies including anaphylaxis to foods.

The most distinctive clinical feature useful in distinguishing DOCK8 deficiency from hyper-IgE syndrome and other conditions is the cutaneous viral infections. These infections are extensive, difficult to control, and often occur concurrently. The most common viruses involved are herpes simplex virus (HSV), human papillomavirus (HPV), molluscum contagiosum virus (MCV), and varicella-zoster virus (VZV). Chronic orolabial or ulcerative anogenital HSV infections, as well as herpes simplex keratitis and eczema herpeticum, are typically observed, but systemic HSV infections including herpes simplex encephalitis are not. Patients have disfiguring flat and verrucous warts from HPV infections, although it is unclear whether they are also at increased risk for genital warts. MCV lesions are often confluent, and VZV can present as severe primary infection or recurrent zoster. By contrast, sporadic cases of progressive multifocal leukoencephalopathy (PML) due to JC virus, and one case of systemic human cytomegalovirus (CMV) viremia, have rarely been reported [11••].

DOCK8 deficiency is associated with a variety of other types of infections. Patients have recurrent upper and lower respiratory tract infections, including otitis media, mastoiditis, sinusitis, pneumonia, and bronchitis. Unlike *STAT3*-mutant hyper-IgE syndrome, the pneumonias in DOCK8 deficiency are not primarily due to *Staphylococcus aureus*, but rather a wide spectrum of gram-positive and gram-negative bacteria and fungi. These include not only *Streptococcus pneumoniae* and *Haemophilus influenzae*, but also *Pneumocystis jirovecii* and Histoplasmosis. Aspergillosis, as occurs in *STAT3*-mutant hyper-IgE patients after parenchymal lung damage, has not been observed. Mucocutaneous candidiasis can occur in both conditions, although the overall frequency appears lower in DOCK8 deficiency. Cryptococcal, *Listeria*, pneumococcal, and *Haemophilus influenzae* meningitis, as well as *Acinetobacter baumanii*, *Klebsiella*, and *Neisseria meningitides* sepsis, have been reported and can cause death. DOCK8-deficient patients can also have recurrent infections of the gastrointestinal tract, such as *Salmonella* enteritis and Giardiasis. Together, the wide spectrum of infections and pathogens support deficits in both adaptive and innate immunity.

In addition to atopy and increased susceptibility to infections, DOCK8 deficiency is associated with the development of malignancies in childhood or young adulthood. Squamous cell carcinomas, in the setting of chronic cutaneous viral infections, as well as Burkitt or other lymphomas, predominate and contribute to fatalities [30]. Microcystic adnexal carcinoma and leiomyoma have also been reported [30]. The occurrence of these cancers suggests a deficit in immune surveillance functions.

Finally, several other unusual clinical features have been reported, including autoimmune hemolytic anemia and central nervous system (CNS) vasculitis [11••]. Although heterozygous *DOCK8* deletions were reported in several cases of mental retardation, developmental delay, and autism spectrum disorder, these features are only rarely observed in DOCK8 deficiency [31,32]. Thus, it appears that DOCK8 plays no significant role in development of the nervous system, in contrast to other DOCK180-family members, such as Dock3 and Dock7 in the mouse [33].

Immunological features of DOCK8 deficiency

DOCK8-deficient patients exhibit multiple abnormalities of the immune system (Table 1). The most striking findings, besides high serum IgE and eosinophilia, include lymphopenia and antibody abnormalities (discussed below). The lymphopenia, which seems to progress with age, affects both CD4 and CD8 T cells, especially the CD4 T cells, and to a lesser extent NK cells and B cells. Because of the known importance of T cells in antiviral defense, we examined their responses in vitro after T cell receptor (TCR) stimulation of

peripheral blood mononuclear cells [10••]. Under these conditions, CD8 T cells from DOCK8-deficient patients fail to activate, divide, and expand. Furthermore, their production of the antiviral cytokines IFN-γ and TNF-α is decreased, although cytotoxic function on a per cell basis, as assessed by perforin content and cytotoxic granule exocytosis, appears intact. Other studies have corroborated the decreased T cell activation and proliferation in the DOCK8-deficient patients [11••,12•], although a convincingly reproducible defect in CD4 T cells has not been established in vitro [10••,11••].

The lymphopenia in the DOCK8-deficient patients is recapitulated in the spleens of recently discovered Dock8-deficient mice [34••]. These mice have decreases in naïve CD8 and CD4 T cells, as well as of certain B cell subsets (described below). As shown by competitive adoptive transfer experiments, the decreased T cell numbers reflect an intrinsic T cell defect. Besides effects on T cell responses after TCR stimulation, another explanation for the lymphopenia is that DOCK8 may play a role in T cell migration in vivo. This explanation is suggested by the known roles of DOCK180-related family members in chemotaxis, and might help to account for the increased susceptibility to cutaneous but not systemic viral infections in most DOCK8-deficient patients.

In addition to their lymphopenia, DOCK8-deficient patients have antibody abnormalities. Besides their elevated serum IgE, which could reflect a selection bias, patients have low IgM. They also can have high or normal IgG, as well as high, normal, or low IgA. Their antibody responses to previously encountered protein- or polysaccharide- conjugated vaccines are variable, with antigens unpredictably eliciting a response in some individuals but not others. When tested, antibody responses to previously encountered viruses such as HSV and VZV have been normal. In two patients who were immunized with the neoantigen bacteriophage φ174, secondary challenge failed to elicitisotype class switching or memory responses, suggesting possible defects in T cell help for B cell functions [10••].

The defective antibody titers observed in the DOCK8-deficient patients are consistent with observations in Dock8-deficient mice, although isotype abnormalities including hyper-IgE were not noted in the mice [34••]. Two separate lines of Dock8-deficient mice, generated by *N*-ethyl-*N*-nitrosourea (ENU)-mutagenesis, were identified after functional screening showed that the mice are unable to make long-lived and mature antibody responses after secondary challenge. Splenic marginal zone and germinal center B cells are decreased in the mice. Despite a possible contribution of decreased CD4 T cell help, the decreased survival and selection of germinal center B cells primarily reflect an intrinsic B cell defect, as shown by competitive adoptive transfer experiments. This defect is likely to result from the demonstrated disrupted organization of the B cell immunological synapse.

Finally, reanalysis of two older studies shows that DOCK8-deficient patients may have decreased CD4 T helper type 17 (Th17) cells [35,36•]. These studies originally found that decreases in Th17 cells, which are important for defense against extracellular bacteria and fungi, could account for the infectious susceptibilities seen in *STAT3*-mutant hyper-IgE patients. However, the control groups in these studies also included several hyper-IgE patients who lacked STAT3 mutations, but who are retrospectively now known to be DOCK8-deficient (two patients in [10••,35]; six patients in [11••,36•]). These groups of *STAT3*-wildtype hyper-IgE patients had mildly to moderately decreased percentages of Th17 cells, as measured by their ex vivo ability to both produce IL-17 and express the Th17 master transcription factor RORγτ. However, naïve CD4 T cells could be differentiated in vitro into RORγτ-expressing cells but not IL-17-expressing cells, suggesting a defect in late differentiation or survival of Th17 cells [36•]. The individual results were not linked to each DOCK8-deficient patient, so these analyses need further confirmation. If confirmed, the

findings could explain an increased susceptibility of some DOCK8-deficient patients to mucocutaneous candidasis.

Treatment and outcome

The viral infections of the skin are extremely difficult to manage in DOCK8-deficient patients. Because *Staphylococcus aureus* skin infections can worsen the eczema and trigger eczema herpeticum, patients benefit by decreasing colonization through the use of bleach baths, topical antiseptics, or antimicrobials. Corticosteroids can also be used to control eczema, but can potentially worsen viral infections, and when discontinued the eczema can flare. Valacyclovir or acyclovir is usually given to contain herpes simplex virus outbreaks. Topical imiquimod, cidofovir, and other conventional treatments for warts and molluscum contagiosum may be tried but are usually unsuccessful. Interferon-α has anecdotally helped to control warts and molluscum contagiosum in some patients [10••]. Those patients who have impaired functional antibodies may benefit from intravenous immunoglobulin infusions to decrease the frequency of sinopulmonary infections. However, the immunoglobulin infusions do not affect the viral infections, which is consistent with findings that patients already have protective titers to HSV or VZV.

DOCK8 deficiency is associated with high morbidity and mortality. Of the 32 reported patients confirmed to have *DOCK8* mutations on both alleles, 7 died between the ages of 6 and 21 [10••,11••,12•]. Of these, 3 died from malignancy (squamous cell carcinomas, T cell leukemia-lymphoma), and 4 died from either infections (sepsis, encephalitis, PML) or CNS vasculitis. The difficulty in controlling viral infections – and their likely contribution to increased risk of skin cancers – has been an argument for hematopoietic cell transplantation. Indeed, two DOCK8 patients were retrospectively found to have undergone myeloablative and reduced intensity conditioning followed by allogeneic hematopoietic cell transplantation (HCT) [12•]. They are now up to four years out of transplantation with complete and stable engraftment, as well as near normalized lymphocyte functions and completely resolved molluscum contagiosum and recurrent herpes zoster infections. Nonetheless, DOCK8 is expressed at low levels in non-immune tissues and its loss in various cancers suggests that DOCK8 could act as a tumor suppressor molecule, apart from its probable role in CD8 T cells for tumor surveillance [37,38,39,40,41]. Therefore, it remains to be seen in long-term follow up whether transplantation is completely curative in preventing malignancies. Furthermore, as is the case for other combined immunodeficiencies, the variable outcome makes it is difficult to predict natural history in less severely affected individuals. For example, two patients who have only had infectious complications of their disease, without malignancy, are still alive in their 40's [11••]. Together, these results indicate that HCT should be strongly considered in severe cases of DOCK8 deficiency, but it remains unclear as to its place in less severely affected individuals.

Conclusion

Although DOCK8 deficiency was initially discovered in patients who had been diagnosed with atypical hyper-IgE syndrome, the clinical and immunological features of DOCK8 deficiency suggest that this clinical entity may in many respects more closely resemble other combined immunodeficiencies. For instance, the Wiskott-Aldrich syndrome also presents with eczema, hyper-IgE, infectious susceptibility, and lymphocyte dysfunction including lymphopenia. The Wiskott-Aldrich syndrome results from deficiency of the Wiskott-Aldrich syndrome protein (WASp), which is an effector of the Rho GTPase CDC42 that presumably acts downstream of DOCK8. Thus, the overlapping clinical phenotypes may reflect overlapping signaling pathways. Further mechanistic studies will help to clarify the

molecular pathogenesis of DOCK8 deficiency, the relationship of this disease to other combined immunodeficiencies, and how DOCK8 regulates normal immune cell functions.

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Table 1

Clinical and laboratory features of DOCK8 deficiency

Clinical or laboratory feature	Patients affected (%)
Atopic dermatitis	91
Asthma	41
Allergies	66
Bacterial skin infections	78
Mucocutaneous candidiasis	72
Any viral infection	88
HSV	47
HPV	28
MCV	38
VZV	22
Respiratory tract infections	97
Gastrointestinal tract infections	6
Sepsis	9
Meningitis	13
Central nervous system vasculitis	6
Autoimmune hemolytic anemia	6
Any malignancy	19
Squamous cell carcinoma	13
Lymphoma	9
Serum IgE, high	100
Eosinophilia	90
Lymphopenia	44
T cell	72
CD4 T cell	75
CD8 T cell	52
NK cell	34
B cell	19
Serum IgM, low	78
Serum IgG, high	41
Serum IgA, high	19
Serum IgA, low	25

Patients with DOCK8 deficiency (confirmed on both alleles) were analyzed [10••, 11••,12•]. Laboratory values were compared against expected values for age.