HHS Public Access

Author manuscript

Clin Immunol. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

Clin Immunol. 2017 August ; 181: 75–82. doi:10.1016/j.clim.2017.06.003.

DOCK8 Deficiency: Insights into Pathophysiology, Clinical Features and Management

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Abstract

Dedicator of Cytokinesis 8 (DOCK8) deficiency is a combined immunodeficiency that exemplifies the broad clinical features of primary immunodeficiencies (PIDs), extending beyond recurrent infections to include atopy, autoimmunity and cancer. It is caused by loss of function mutations in *DOCK8*, encoding a guanine nucleotide exchange factor highly expressed in lymphocytes that regulates the actin cytoskeleton. Additional roles of DOCK8 have also emerged, including regulating MyD88-dependent Toll-like receptor signaling and the activation of the transcription factor STAT3. DOCK8 deficiency impairs immune cell migration, function and survival, and it impacts both innate and adaptive immune responses. Clinically, DOCK8 deficiency is characterized by allergic inflammation as well as susceptibility towards infections, autoimmunity and malignancy. This review details the pathophysiology, clinical features and management of DOCK8 deficiency. It also surveys the recently discovered combined immunodeficiency due to DOCK2 deficiency, highlighting in the process the emerging spectrum of PIDs resulting from DOCK protein family abnormalities.

Keywords

Actin; CDC42; Combined Immunodeficiency; Dedicator of Cytokinesis; DOCK2; DOCK8; Hyper IgE Syndrome; Primary Immunodeficiency; RAC1; STAT3

1. Introduction

Increased recognition of primary immunodeficiencies (PIDs) through advancements in genetic screening and diagnosis of these disorders has revealed surprisingly broad clinical

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spectra with which they may present. It is now appreciated that infectious susceptibility is just one manifestation of PID among others that include atopic disease, autoimmunity and malignancy [1–4]. Dedicator of Cytokinesis 8 (DOCK8) deficiency is a combined immunodeficiency that illustrates this paradigm, with clinical features ranging from recurrent infections, allergic diseases including eczema and food allergy, autoimmunity and virally-driven cancers [5–7]. First reported in 2009, DOCK8 deficiency was identified as the underlying abnormality in the majority of patients with autosomal recessive Hyper IgE Syndrome (AR-HIES) [8,9]; the autosomal dominant form of this syndrome (AD-HIES) caused by signal transducer and activator of transcription 3 (*STAT3*) mutations [10,11]. Despite sharing some similarities with AD-HIES, such as eosinophilia, elevated serum IgE levels, and recurrent staphylococcal infections, it is now appreciated that DOCK8 deficiency is a unique entity with distinct immunological and clinical features. This review will examine our current understanding of DOCK8 function in immune cells, including its role in the remodeling of the actin cytoskeleton in response to activation signals, as well as more recent findings on its role in amplifying signaling via STAT3. We will detail the pathophysiology and clinical features of DOCK8 deficiency, and highlight the emergence of a family of DOCK-related immune deficiencies, with the recent identification of DOCK2 as a cause of combined immunodeficiency.

2. Epidemiology

DOCK8 deficiency is a rare autosomal recessive primary immunodeficiency seen predominantly in consanguineous populations. Its exact prevalence is unknown, with approximately 230 cases described to date [5,6,8,9,12–49] (Supplemental Table 1). The majority of patients with DOCK8 deficiency are of Turkish and Arabic descent, populations in which consanguinity rates are high [50–52]. However, the condition has been identified in other populations throughout the world, including North and South America, Europe, and China [8,19,38].

3. Genetics of DOCK8 Deficiency

First identified in 2004, *DOCK8* is a large gene located on chromosome 9, comprising 48 exons that span over 200 kilobases [53]. The majority of mutations affecting *DOCK8* are deletions that can range in size from a small number of base pairs to ones spanning the entire locus, most often resulting in absent protein expression [6,8,9,54]. The high frequency of deletions may be attributed to the repetitive genomic sequences around and within *DOCK8*, leading to abnormal recombinations [7,8]. Other mutations described in DOCK8-deficient patients include nonsense and splice site mutations, as well as single and 2 base pair insertions [6,37,38,43]. Missense mutations are rare, with only two patients reported to date (discussed below) [7,47]. One possible source of phenotypic variation amongst patients is somatic reversion of *DOCK8* mutations, which has been described in some affected patients [22,43]. Through genetic analysis of T cells compared to neutrophil genomic DNA, somatic reversions were identified in T cells of affected patients with certain germline mutations, and were found to occur through compensatory point mutations and reversions. While patients with reversions suffered less severe allergic manifestations, their infectious risk persisted, and hematopoietic stem cell transplantation was still necessary to cure the disease [22].

Particular mutant alleles are enriched in certain geographical areas, suggesting founder effects. For example, the IVS16 splice acceptor site mutation: c.[1869 –1 G>C][21] has been identified as a recurring allele in the Konya area of Turkey, and a large deletion spanning exons 1 through 27 traces to the Turkish city of Izmir [8]. Other common mutations reported in unrelated Saudi families, such as the mutation at position 5625 T>G; Y1875X also suggest a founder effect [13]. Although heterozygous carriers of mutant *DOCK8* alleles appear clinically normal, extensive longitudinal studies on their phenotypes and outcomes have not been reported. It is therefore unknown if heterozygosity for DOCK8 is associated with long-term health risks, such as increased risk of malignancy, atopy or other chronic diseases [7].

4. DOCK8 Structure and Function

DOCK8 belongs to the DOCK180 superfamily of atypical Guanine Exchange Factors (GEFs) involved in actin cytoskeleton regulation [53,55]. There are 11 DOCK proteins, of which DOCK8 is a member of the DOCK-C family [53,55] (Figure 1). DOCK proteins activate members of the Ras homolog gene family (Rho) of small guanine triphosphate binding proteins (GTPases), such as CDC42 and RAC, which integrate signals from the cell membrane to control pathways involved in actin polymerization and cytoskeletal rearrangement [56] (Figure 2). DOCK proteins each contain a Dock homology region-1 (DHR1) domain that localizes GEF activity to cell membrane compartments via phosphoinositide binding, as well as a DHR2 domain containing the catalytic subunit that exchanges GDP for GTP on Rac or CDC42 [53,57–59] (Figure 3). Failure of CDC42 activation is sufficient to cause disease manifestations of DOCK8 deficiency. This was revealed in a patient carrying a missense mutation (c.5956A>T) in the GEF catalytic loop, impairing CDC42 activation while preserving protein expression. The patient presented with clinical and immunologic features in keeping with DOCK8 deficiency [47].

DOCK8 encodes a large protein approximately 190 kDa in size [53]. DOCK8 is expressed primarily in hematopoietic tissues, but has also been found in various non-immune tissues such as placenta, kidney, lung, and pancreas [53,60]. DOCK8 specifically binds to and activates CDC42 without binding to RAC1 or to RhoA [61]. DOCK protein selectivity for Rho GTPases is primarily conferred by DHR2 domain interactions with residue 56 as well as the switch I region of the Rho GTPase [56]. DOCK8 specificity for CDC42 has been supported by structural studies comparing the DHR2 domains of DOCK8 complexed with CDC42 to that of DOCK2 complexed with RAC1 [61]. These revealed that the tryptophan 56 residue of RAC1 is larger than the analogous phenylalanine found on CDC42, and would therefore be unable to interface with tyrosine 2043 of DOCK8. Additionally, lobe B of the DOCK8 DHR2 domain binds to the switch I region of CDC42 in a manner similar to DOCK9, a protein that is also known to be CDC42 specific [61].

5. Immunological Features of DOCK8

The immune abnormalities seen in patients with DOCK8 deficiency reflect the importance of DOCK8 in controlling both actin cytoskeleton-dependent and -independent immune responses (Figure 4). DOCK8 plays a prominent role in both innate and adaptive immunity.

DOCK8 function in innate immunity was revealed in murine studies, which showed that dendritic cells rely on DOCK8 for trafficking from the skin to nearby lymph nodes. Migrating dendritic cells deficient in DOCK8 cannot activate CDC42 at the leading edge membrane, leading to severe impairments in amoeboid polarization and migration in 3-D space [61]. In addition, DOCK8-deficient patients have decreased plasmacytoid dendritic cells in circulation with very poor IFN-alpha production [21]. DOCK8 is important in other aspects of innate immunity, such as the function and survival of ROR$\gamma\tau^+$ innate lymphoid cells (ILCs). DOCK8-deficient mice have decreased numbers of ROR$\gamma\tau^+$ ILCs in their GI tract. These ILCs display decreased IL-7 responsiveness and IL-22 production, as well as a predisposition to apoptosis. The defect in ILCs reflects the importance of DOCK8 for optimal STAT3 activation and IL-22 production [62].

DOCK8 enables adaptive immune responses by several mechanisms. Through its regulation of the actin cytoskeleton, it facilitates the accumulation of adhesion molecules and cytotoxic granules at immunologic synapses [58,63]. Deficiency of these interactions may contribute to impaired B, T and NKT cell survival and long-lived memory responses in DOCK8-deficient patients. DOCK8 also regulates filamentous actin, LFA-1 and cytolytic granule accumulation in the cytotoxic synapse, processes critical for NK-cell mediated cell death [64]. When DOCK8 is suppressed in human NK cells, they demonstrate defects in natural cytotoxicity as well as specific activating receptor-mediated NK cytotoxicity [64]. Without DOCK8 present to coordinate the actin cytoskeletal network, DOCK8-deficient T and NK cells undergo a form of cell death termed cytothripsis when migrating through confined shapes, such as collagen-dense tissues like the skin [65]. The predisposition of cytotoxic cells to undergo this form of cell death during migration through these tissues prevents the generation of skin-resident memory $CD8^+$ T cells. This represents an additional factor that may contribute to the susceptibility of DOCK8-deficient patients to herpetic viral skin infections [65].

DOCK8 augments humoral immunity in a multifaceted manner, functioning as an adaptor in Toll-like Receptor 9-driven B cell signaling, and contributing to ICAM-mediated intercellular connections [26,66]. Loss of DOCK8 impairs antibody production, as well as the generation of memory B cells [26]. Antibody levels in DOCK8 deficiency are variable, and may include elevated, normal or decreased levels of IgG, IgA and IgM. IgE levels are nearly always elevated, however, a case of DOCK8 deficiency with a normal IgE level has also been reported [6]. Although total antibody levels vary, impaired memory B cell survival leads to compromised serologic memory, resulting in failure to generate long-lived specific antibody responses to vaccine antigens [26].

T lymphocytes have widespread defects, including a decreased number of naïve T cells in peripheral blood [34]. The low number of T cell receptor excision circles (TRECs) found in patients with DOCK8 deficiency points towards decreased thymic output as a contributor to their low naïve T cell numbers [17]. $CD8^+$ T cells display an exhausted phenotype with decreased survival and low memory response [63]. Proliferation to mitogens may be normal or decreased [35]. A higher proportion of activated cells producing T_H2 cytokines has been observed in DOCK8-deficient patients when compared to controls [12,34,47]. When cultured under T_H2-polarizing conditions in vitro, naïve DOCK8-deficient $CD4^+$ T cells

display increased differentation towards the T_H2 cell lineage [47]. The predilection towards a T_H2 phenotype is reflected by the significant eosinophilia and elevated IgE seen in DOCK8-deficient patients.

Recent work has also revealed a role for DOCK8 in STAT3 function and T_H17 cell immunity. STAT3 is critical for T_H17 cell polarization and function, as evidenced by the impairment of this T helper subset in patients with AD-HIES caused by STAT3 deficiency [67]. It has recently been shown that DOCK8 mediates STAT3 translocation to the nucleus and transcription of STAT3-dependent genes [47]. While DOCK8 interacts with STAT3 independent of its GEF activity, it regulates STAT3 phosphorylation in a GEF activity-dependent fashion. In accordance with DOCK8′s role in STAT3 function, naïve $CD4^+$ T cells deficient in DOCK8 show impaired T_H17 cell differentiation [47]. Regulation of STAT3 function and T_H17 differentiation by DOCK8 may explain some of the overlapping features of AD-HIES and DOCK8 deficiency.

Complementary roles in T cell receptor-driven actin polymerization contribute to the phenotypic similarities between DOCK8 deficiency and Wiskott-Aldrich Syndrome (WAS) [68]. WAS is a primary immunodeficiency caused by defects in the WAS protein (WASp), a critical regulator of actin cytoskeleton-dependent T cell functions [69]. DOCK8 forms a complex with WASp and WASp-interacting protein (WIP). Upon T cell receptor stimulation, DOCK8 activates CDC42, which in turn activates nearby WASp. Activated WASp leads to downstream actin polymerization, mediating important T cell functions such as immune synapse formation, mechanotransdunction, and transendothelial T cell migration into secondary lymphoid organs. DOCK8 thus serves a critical role in mediating T cell receptor-driven changes in the actin cytoskeleton network through its interactions with WASp and WIP [68].

Impaired lymphocyte tolerance contributes to the immune dysregulation seen in DOCK8 deficiency. Affected patients have increased levels of autoreactive antibodies, primarily directed against cytosolic antigens [70]. While central B cell tolerance remains intact, peripheral B cell tolerance is defective in the absence of DOCK8. This was demonstrated by DOCK8-deficient patients maintaining a normally low percentage of polyreactive new/transitional B cells, however, an enrichment of autoreactive B cells in the mature naïve B cell compartment [70]. In addition, affected patients have both qualitative and quantitative regulatory T (Treg) cell defects, exhibiting decreased Treg frequency and impaired suppressive activity [70].

6. Clinical Features of DOCK8 Deficiency

DOCK8 deficiency generally presents at a young age, ranging from the first months to early years of life [35]. It is a combined immunodeficiency characterized by eczema, recurrent respiratory as well as persistent viral infections largely affecting the skin [5]. The predisposition towards atopic disease is a defining feature of DOCK8 deficiency. Although eczema and markedly elevated IgE levels are seen in nearly all cases, patients may suffer from a number of atopic conditions, including food and environmental allergies, asthma, eosinophilic esophagitis, idiopathic anaphylaxis (unpublished observation), and allergic

rhinitis [5,6,8,9,12,13,35]. Both DOCK8-deficiency and AD-HIES cause dermatitis, elevated IgE levels and eosinophilia, however, patients with AD-HIES do not suffer from environmental or food allergies [7]. This distinction may be explained by impaired mast cell degranulation in AD-HIES secondary to profoundly impaired STAT3 activation [71].

Patients with DOCK8 deficiency frequently suffer from cutaneous viral infections, including Varicella zoster, Molluscum contagiosum, Herpes simplex, and Human Papilloma viruses; these infections may be severe, persistent, and refractory to treatment [6,21,28]. Viral infections may also be systemic or involve deeper tissues. There have been several reports of polymultifocal leukoencephalopathy (PML) secondary to JC virus [5,6,24,37]. Other noncutaneous viral infections include meningitis, encephalitis, keratitis, retinitis, blepharoconjunctivitis, periodontitis, pneumonia, hepatitis and enteritis with many implicated viruses, such as cytomegalovirus, Epstein Barr Virus, rotavirus, Herpes simplex virus, as well as hepatitis A, B and C viruses [6,13,29,40].

The infectious spectrum of DOCK8 deficiency includes both superficial and/or localized as well as invasive bacterial infections. Patients often experience recurrent sinopulmonary bacterial infections that can lead to bronchiectasis [5,6]. Cutaneous bacterial infections, in particular with *Staphylococcus aureus*, are a common feature of DOCK8 deficiency [72]. Bacterial or fungal abscesses have been identified in the skin, liver, kidney, lung and brain [6,12,13,25,30]. Fungal infections range from mucocutaneous candidiasis to invasive disease with organisms such as *Aspergillus*, and less commonly, *Cryptococcus neoformans* [5,6,72]. Sclerosing cholangitis secondary to chronic infection has also been reported in DOCK8-deficient patients [15]. Similar to what is seen in patients with CD40 ligand deficiency, hepatobiliary infection with *Cryptosporidium* can be particularly damaging and difficult to treat [12]. Other reported parasitic infections include *Entamoeba histolytica* and *Giardia lamblia* [6,15,42].

DOCK8-deficient patients may suffer from significant autoimmune sequelae. These include autoimmune hemolytic anemia, chorioretinitis/uveitis, hypothyroidism, as well as cytopenias and vasculitis [5,12,13,44]. Systemic lupus erythematosus (SLE) was reported in one patient with DOCK8 deficiency who developed purpuric and necrotic skin lesions, arthritis, and glomerulonephritis along with the presence of anti-nuclear, anti-DNA and antiphospholipid antibodies [16].

The immune defects caused by DOCK8 deficiency also lead to an increased risk of cancer, and affect up to 17% of patients [5]. Malignancies are typically virally-driven, such as squamous cell carcinomas related to Human Papillomavirus infection, as well as EBV-driven smooth muscle tumors and lymphomas [6,13,35,37,72,42]. Patients have also been diagnosed with cancers that are not conventionally associated with viral infections, such as micro-cystic adnexal carcinoma as well as rapidly progressive cutaneous T cell lymphoma [72].

Intestinal complications can lead to failure to thrive and growth stunting [6]. Malabsorption resulting in failure to thrive may be caused by allergic or autoimmune enteropathy, as well as by intestinal infections. Chronic diarrhea caused by enteropathy can be a prominent feature

to the degree that the condition may present as IPEX-like disease (unpublished observations).

The central nervous system is another organ system commonly affected in DOCK8 deficiency. Infectious complications include meningitis, bacterial or fungal abscesses, as well as viral encephalitis [5,6,13]. Non-infectious complications affecting the nervous system have also been described in DOCK8 deficiency. These include CNS vasculitis, aneurysms, tumor infiltration, as well as strokes and hemiparesis [6,13,44].

DOCK8 deficiency is associated with high morbidity and mortality. A recent large retrospective review showed a decline in overall probability of survival from 87% to 37% at 10 and 30 years, respectively [5]. Cumulative incidence of life-threatening infections, cerebral events and malignancies was 88%, 32% and 48% at 30 years of age. Death in patients with DOCK8 deficiency has been reported to occur from infection, malignancies and less commonly vasculitis [5].

7. Diagnosis and Management of DOCK8 Deficiency

DOCK8 deficiency is diagnosed based on clinical features in combination with suggestive immunologic laboratory findings and confirmatory genetic analysis. The clinical findings of atopic disease with a history of recurrent infections, malignancy or autoimmunity should raise concern for DOCK8 deficiency [5]. Supportive findings on laboratory evaluation include eosinophilia and an elevated IgE level. Further immune evaluation may reveal impaired vaccine titer responses, low naïve $CD4^+$ T cell count, an exhausted cytotoxic T cell panel with elevated percentages of effector memory RA $(T_{EMRA})^+$ $CD8^+$ T cells, as well as low switched and unswitched memory B cells [67]. DOCK8 protein expression can be evaluated through flow cytometry or western blot analysis [27]. Obligate carriers display intermediate expression of DOCK8 protein on flow cytometry, however overlap of values with normal controls indicates that carrier status should be confirmed by appropriate genetic analysis [27]. Flow cytometry has also demonstrated utility in differentiating DOCK8 deficiency from severe atopic dermatitis, with DOCK8-deficient patients exhibiting significantly lower percentages of $CD3^+$, $CD4^+$, and $CD8^+CD45RA^+CCR7^+$ naïve T cells [73]. In patients with mutations that allow for somatic reversion, DOCK8 may be expressed up to normal levels in the majority of T cells, with minimal reversion in B cells. DOCK8 expression should therefore be assessed in a range of immune cell types, and in cases where there is a strong suspicion for DOCK8 deficiency, confirmatory sequencing of DNA from non-lymphoid sources (e.g. saliva, neutrophils or fibroblasts) should be performed [22].

The differential diagnosis for DOCK8 deficiency includes other primary immunodeficiencies that may present with eosinophilia and elevated serum IgE levels. As mentioned previously, DOCK8 deficiency shares some clinical features with STAT3 deficiency, including staphylococcal skin infections, candidiasis, respiratory tract infections, as well as elevated eosinophil blood counts and serum IgE levels. The two conditions also have distinguishing characteristics, with STAT3 deficiency carrying non-immune features such as connective tissue and bone abnormalities as well as retained primary teeth, and DOCK8 deficiency presenting with hallmarks of allergic diseases and cutaneous viral

infections [60]. Recently, a modified weighted HIES score was developed that helps clinicians in determining whether a patient is more likely to carry mutations in STAT3 or DOCK8 [6]. It was found that most cases could be distinguished by a linear classifier examining the following 5 items from the 20-item HIES clinical scoring sheet: parenchymal lung abnormalities, sinusitis/otitis, eosinophilia, retained primary teeth, and fracture with minor trauma [6].

Management of DOCK8 deficiency includes screening for and treatment of complications, administration of immunoprophylaxis, and definitive therapy with hematopoietic stem cell transplantation. Patients should be evaluated for indolent infections as well as malignancies. Screening measures often include sending blood PCR levels of herpes viruses, such as herpes simplex virus (HSV), cytomegalovirus, and Epstein-Barr virus (EBV), as well as obtaining baseline imaging studies to evaluate for occult cancer and/or complications of chronic viral infections. Pulmonary and liver function should be assessed, and impairments in either warrant aggressive workup and treatment in order to preserve their function prior to transplantation.

The high prevalence of atopic disease warrants a careful evaluation for these conditions in DOCK8-deficient patients [6]. Patients should be evaluated for underlying atopic diseases that may contribute to inflammation and thus, their risk of infection. As many suffer from multiple food allergies as well as failure to thrive, nutritional evaluation is critical. Aggressive management of atopic dermatitis is paramount to maintaining a protective skin barrier and limiting viral and bacterial super-infection.

Antibacterial and antiviral prophylaxis is recommended, and prophylaxis against fungal and *Cryptosporidial* infections should also be considered. Although total IgG levels may be normal, immunoglobulin prophylaxis is nonetheless recommended based on impaired long-lived antibody responses in DOCK8-deficient patients [26]. Subcutaneous pegylated interferon alpha has shown efficacy for rescue therapy of severe viral infections such as HSV and human papilloma virus [21,28,29].

Hematopoietic stem cell transplantation (HSCT) represents the only curative treatment for DOCK8 deficiency, and is recommended based on the high morbidity and mortality associated with this disease. Multiple reports of successful allogeneic HSCT for treatment of DOCK8 deficiency have been described [31–33,49,48]. One study of 6 patients demonstrated that a uniform myeloablative conditioning regimen followed by transplantation with either matched-related or -unrelated donors was associated with immunologic reconstitution and reversal of clinical phenotype in DOCK8-deficient patients [18]. Improvements in both infections and atopy have been described post-transplant. IgE levels decline post-transplant, and in some patients is accompanied by resolution of food allergies, while in others food allergies may persist [42,45,46]. A recent review of 11 patients who received allogeneic HSCT showed that even in the setting of significant pre-transplant morbidity, survival post-transplant was high (91%), and associated with improvement in both atopic and infectious complications [42]. In addition, 3 of 11 patients underwent mismatched transplant, and despite having mixed chimerism still demonstrated robust cellular and humoral immunity.

8. DOCK2 Deficiency

The spectrum of DOCK protein-related immune disease expanded with the identification of a novel form of combined immunodeficiency caused by biallelic mutations in DOCK2 [74]. Five unrelated children presented with early onset invasive bacterial and viral infections. Two patients died early in childhood, and the remaining three were cured by hematopoietic stem cell transplantation. Analogous to DOCK8 activation of CDC42, DOCK2 functions as an atypical GEF to activate the small GTPase RAC1. Immune evaluation of affected patients revealed impaired RAC1 activation in T cells, and defective chemokine-induced migration and actin polymerization in T, B and NK cells. Interferon immunity was also notably impaired in both hematopoietic and non-hematopoietic cells. Comparing the phenotypes of DOCK2 and DOCK8 deficiency reveals the overlapping functions as well as the unique roles of DOCK proteins in actin cytoskeleton regulation and immune function. Both conditions are associated with T cell lymphopenia and impaired lymphocyte migration and NK cell cytotoxicity. Patients affected by DOCK2 deficiency, however, appear to be more severely affected by invasive viral infections, and unlike DOCK8 deficiency, were not found to suffer from allergic or autoimmune disease. Definitive therapy for DOCK2 deficiency is HSCT [74].

9. Summary and future directions

In conclusion, DOCK8 deficiency leads to a combined immunodeficiency with broad and devastating clinical sequelae, including infections, atopy, autoimmunity and cancer. The importance of DOCK8 in immune cell function arises from its role in actin cytoskeleton regulation as well as in STAT3 activation. Curative therapy with hematopoietic stem cell transplantation is advised based on the high morbidity and mortality associated with DOCK8 deficiency, and has been associated with successful immune reconstitution and reversal of infectious and atopic complications [42]. Since its discovery in 2009, our knowledge of the DOCK8 protein and its role in actin cytoskeleton regulation has greatly expanded, however many questions remain. In particular, characterization of the protein itself, as well as its interacting partners is needed. Defining the DOCK8 interactome and signalosome could uncover key regulatory mechanisms behind the development of atopy as well as the predisposition towards infections and cancer. The literature thus far has described patients with biallelic mutations or deletions encompassing DOCK8. Future directions may seek to identify and characterize individuals with hypomorphic or heterozygous mutations, as it is possible these individuals may also have a clinical phenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by National Institutes of Health grant 2R01AI065617 (to T.A.C.). C.M.B. received support from NIH grant T32AI007512 and is currently supported by the CAAIF/AllerGen Research Fellowship and the AllerGen Emerging Clinician-Scientist Research Fellowship.

Abbreviations

AR-HIES	Autosomal recessive hyper IgE syndrome
AD-HIES	Autosomal dominant hyper IgE syndrome
CDC42	Cell division control protein 42 homolog
DHR-1	Dock homology region-1
DOCK8	dedicator of cytokinesis 8
EBV	Epstein-Barr virus
GEF	Guanine exchange factor
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
ILC	Innate lymphoid cell
PML	polymultifocal leukoencephalopathy
RAC1	Ras-related C3 botulinum toxin substrate 1
Rho	Ras homolog gene family
SLE	Systemic lupus erythematosus
STAT3	Signal transducer and activator 3
Treg	regulatory T cell
WAS	Wiskott-Aldrich Syndrome

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Highlights

- DOCK8 deficiency is a rare combined immunodeficiency with high morbidity and mortality
- Clinical features include atopy, recurrent infections, risk of autoimmunity and cancer
- DOCK8 regulates actin cytoskeleton organization and STAT3 nuclear translocation
- Defects in DOCK8 have far-reaching effects on innate and adaptive immune cell function and survival
- Hematopoietic stem cell transplantation can be curative for DOCK8 deficiency

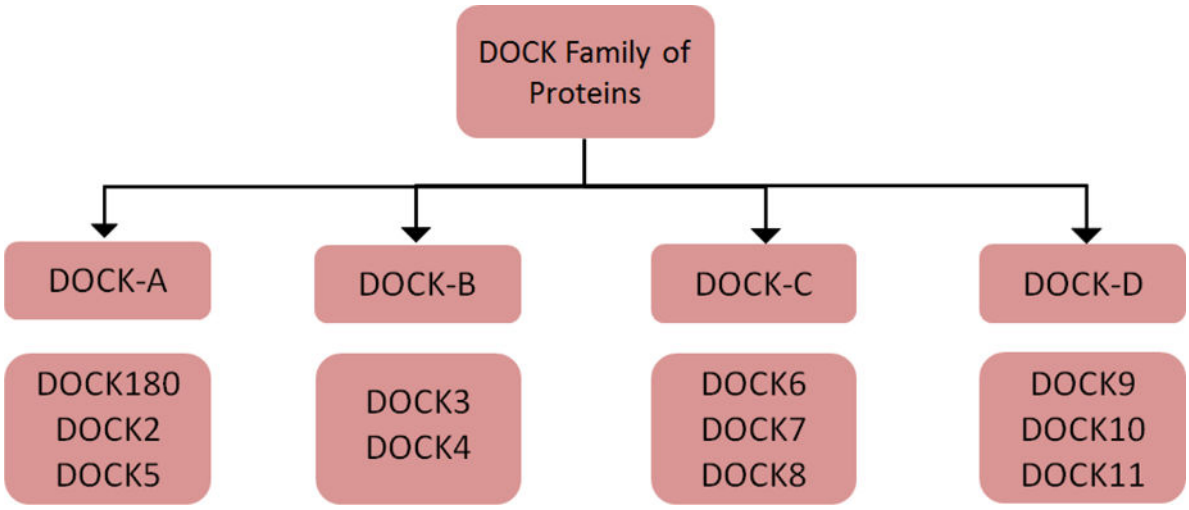

Figure 1.

The DOCK family of proteins. There are 4 subfamilies of the DOCK proteins, divided based on substrate specificity and sequence homology [55,75].

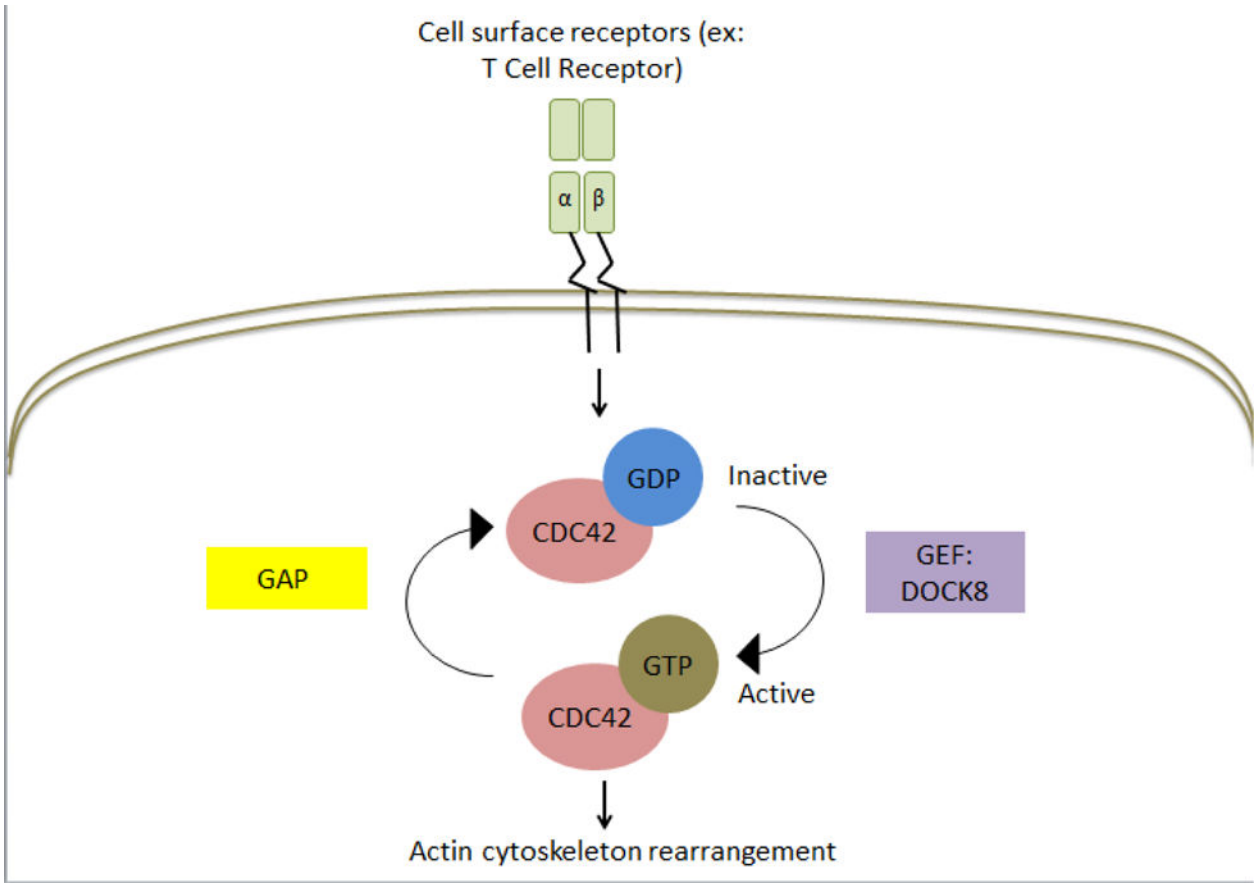

Figure 2.

DOCK8 activates the small GTPase CDC42. DOCK8 exchanges GDP for GTP on CDC42, which integrates signals from the cell membrane to control pathways involved in actin polymerization and cytoskeletal rearrangement [56].

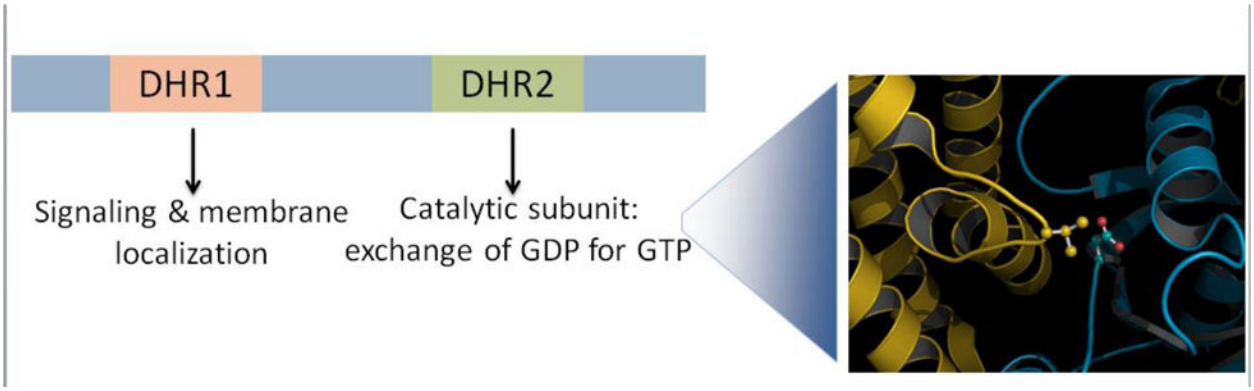

Figure 3.

DOCK8 protein structure. DOCK8 contains a DHR1 domain that localizes GEF activity to cell membrane compartments via phosphoinositide binding, and a DHR2 domain that contains the catalytic subunit responsible for exchanging GDP for GTP on CDC42 [53,57–59].

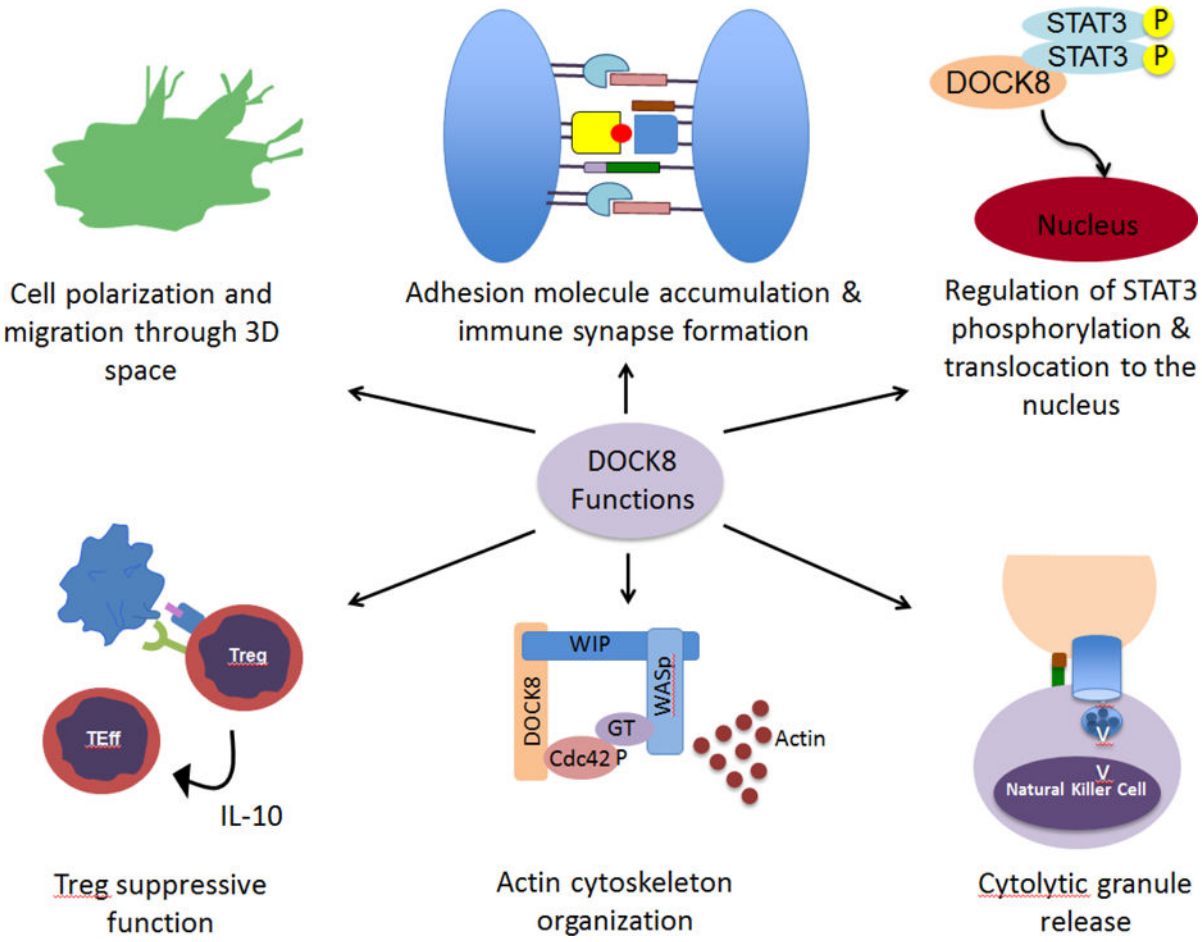

Figure 4.

DOCK8 is important for numerous cellular processes. The identified roles of DOCK8 include cell polarization and migration through 3 dimensional space, adhesion molecule accumulation & immune synapse formation, regulation of STAT3 phosphorylation and nuclear translocation, Treg suppressive function, actin cytoskeleton organization, as well as cytolytic granule release [25,47,61,66,70].