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Insights into immunity from clinical and basic science studies of DOCK8 immunodeficiency syndrome

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Summary:

DOCK8 immunodeficiency syndrome (DIDS) is a progressive combined immunodeficiency that can be distinguished from other combined immunodeficiencies or hyperimmunoglobulinemia E syndromes in featuring 1) profound susceptibility to virus infections of the skin, with associated skin cancers, and 2) severe food allergies. The *DOCK8* locus has many repetitive sequence elements that predispose to the generation of large germline deletions as well as recombination-mediated somatic DNA repair. Residual DOCK8 protein contributes to the variable disease phenotype. The severe virus infections of the skin, and probably also VZV-associated vasculopathy, reflect an important function of DOCK8, which is normally required to maintain lymphocyte shape integrity as the cells migrate through dense tissues. Loss of DOCK8 also causes immune deficits through other mechanisms including a milder generalized cell survival defect and skewing of T helper cell subsets. Recent work has uncovered roles for DOCK8 in dendritic cell responses that can also help explain the virus susceptibility, as well as in regulatory T cells that might help explain autoimmunity in a minority of patients. Fortunately, hematopoietic stem cell transplantation cures the eczema and infection susceptibility of DIDS, but not necessarily the other disease manifestations including food allergies.

Keywords

DOCK8; combined immunodeficiency; hyper-immunoglobulinemia E syndrome; virus infections; food allergy; atopic dermatitis; cancer

Introduction

DOCK8 immunodeficiency syndrome (DIDS), sometimes termed DOCK8 deficiency, has been previously reviewed elsewhere (1–3). DIDS is a combined immunodeficiency that has several unusual clinical features (see pictorial summary in Figure 1A). Most but not all cases of DIDS are associated with elevated serum IgE. Because of this, the disease was initially referred to as an autosomal recessive hyper-immunoglobulinemia E syndrome (AR-HIES)

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due to its clinical resemblance to autosomal dominant (AD)-HIES (4). AD-HIES, also known as Job syndrome, is by dominant negative mutations in the *STAT3* transcription factor. Like Job syndrome, DIDS features prominent eczematous dermatitis, recurrent sinopulmonary infections, *Staphylococcus aureus* skin abscesses, elevations in serum IgE, and sometimes mucocutaneous candidiasis. However, DIDS lacks the distinctive facial appearance, as well as the connective tissue, skeletal, and dental abnormalities, that are characteristic of Job syndrome. Furthermore, DIDS features severe allergies that include life-threatening anaphylaxis triggered by foods, as well as chronic virus infections that prominently target the skin and which can be associated with the development of squamous cell cancers. These two features are not typical of Job syndrome or of most combined immunodeficiencies.

Other, rarer forms of AR-HIES exist that can be distinguished from DIDS. PGM3 deficiency is caused by hypomorphic mutations in the phosphoglucomutase 3 (*PGM3*) gene that catalyzes the generation of UDP-N-acetylglucosamine, a required building block for both N- and O- linked glycosylation (5–7). Compared to DIDS, autoimmunity, neurocognitive defects, neutropenia, and skeletal abnormalities are prominent or unique features to PGM3 deficiency. Recently, ZNF341 deficiency was reported to impair *STAT3* transcription and autoinduction through the lack of this transcription factor, which normally binds to the *STAT3* promoter (8, 9). As expected, this leads to an AD-HIES phenocopy, but not the severe life-threatening allergies or intractable virus infections of the skin that are characteristic of DIDS. Although TYK2 deficiency was initially reported as a form of AR-HIES, follow up studies in more patients revealed that susceptibility to mycobacteria and viruses were characteristic features but not elevated serum IgE or severe allergies (10). Other immunodeficiencies such as the Wiskott-Aldrich syndrome, Omenn syndrome, and IPEX syndrome can also present sporadically with features similar to DIDS including elevated serum IgE.

Patients found retrospectively to have DIDS have been followed longitudinally at the NIH Clinical Center since the 1980's. To date, a total of 53 patients spanning ages from 6 months to 43 years old, have been evaluated and followed here by us. These patients have been studied on research protocols that focus on the natural history of this disease, basic science investigations into pathogenic mechanisms, and optimizing treatment including hematopoietic stem cell transplantation.

Genetic basis of disease

The Human Genome Project, International HapMap Project, and 1000 Genomes Project led to the appreciation that considerable variation among individual human genomes derives from structural variations, rather than single nucleotide polymorphisms (11). Thus, we reasoned that structural variations might contribute to monogenic disorders of immunity, and that technological improvements in detecting structural variants could reveal new genetic causes of disease in some patients. To test this hypothesis, we performed comparative genomic hybridization arrays, which allows for the unbiased detection of large deletions and duplications, in patients with AR-HIES. This approach revealed large homozygous or compound heterozygous deletions in the *DOCK8* gene in affected patients but not their

unaffected family members (12). Around the same time, other groups used homozygosity mapping with sequencing of shared regions to identify autosomal recessive mutations in *DOCK8* in different cohorts of AR-HIES patients (13).

One interesting aspect of the molecular etiology of DIDS is that large deletions affecting the *DOCK8* gene are frequently observed. In our NIH cohort of DIDS patients, ~62% of unrelated patients had at least one large deletion on one or both alleles (Table 1). The deletions probably reflect the presence of many repetitive sequence elements in this locus which facilitate recombination. The remaining mutations found in the patients consist of typical splicing, frameshift, or nonsense mutations. With the exception of one reported DIDS patient who had a missense mutation in the conserved DHR2 domain that is required for DOCK8's guanine-nucleotide exchange activity (14), all other reported mutations caused loss of DOCK8 protein expression. This property makes it easy to screen for suspected patients, as absent or severely reduced levels of DOCK8 protein can be determined quickly by intracellular flow cytometric analysis (15, 16).

Although most mutations found in DIDS patients are loss-of-function mutations that are clearly predicted to abolish DOCK8 protein expression, some patients may actually express low but detectable levels of DOCK8 protein. This observation reflects the presence of DNA repair in somatic cells, which occurs at a high level at the *DOCK8* locus because of DNA recombination. Specifically, the same repetitive sequence elements in the *DOCK8* locus that facilitate the generation of large germline deletions, also contribute to the somatic repair of mutations. When 34 North American DIDS patients were studied at our center, somatic repair was found in half of this cohort (15). Detailed genetic investigations revealed gene conversion and intragenic crossover recombination events, as well as compensatory second-site point mutations and original-site point reversions. Interestingly, distinct repair events could be found in different lymphocyte subsets even within the same patient. Somatic repair occurred predominantly in antigen-experienced effector/memory phenotype T cells, and to a lesser extent in natural killer (NK) cells or B cells. Together, these observations support the idea that certain regions of the genome are in a dynamic state in mitotically active cells, to a degree greater than often appreciated, and that variants conferring a selective growth or survival advantage can render these genetic changes more readily detectable.

These genetic discoveries have important clinical corollaries. First, somatic reversions are a major determinant for genotype-phenotype relationships in DIDS. DIDS patients exhibit variable levels of somatic repair, which correlate with age but inversely with cumulative disease burden (15). Although somatic repair arising spontaneously in any single patient can ameliorate disease, it appears insufficient to cure DIDS. This can be explained because repair occurs predominantly within individual T cell clones, not within a hematopoietic stem cell or early T cell progenitor. Because the entire repertoire of T cells is not repaired, defective immune function remains.

Second, knowledge of the exact germline mutations in any given patient can help with predictions of disease course. For example, large homozygous deletions make somatic repair impossible. This is because no intact template corresponding to the deleted region on the other allele exists for recombination-mediated repair to occur. Certain regions of the world

such as the Middle East have high rates of consanguineous unions and hence higher likelihood of large homozygous deletions with no possibility of somatic repair. This explains why DIDS patients from those regions tend to have earlier disease onset with more severe disease course. In practical terms, this situation argues for early genetic diagnosis of DIDS to facilitate and expedite definitive treatment.

Virus infections of the skin

As mentioned above, DIDS is characterized by chronic virus infections that have a predilection for the skin (17). The viruses responsible are herpes simplex virus, varicella-zoster virus, human papillomavirus, and molluscum contagiosum virus. These DNA viruses are commonly encountered in the general population during childhood, when most of these viruses establish latent infections following initial infection. In DIDS, initial virus infections are not usually very severe. Rather, the viral rashes never clear or become persistent after reactivation from latency. Over time, but especially evident starting in early adolescence, the infections extend over larger areas of skin as the disease progresses.

In DIDS, the herpes simplex virus infections involve the skin or oral mucosal surfaces and can eventually cause keratitis or even contribute to periodontitis (18). These infections are often ulcerating and difficult to control, and their chronicity can lead to acyclovir resistance. Varicella-zoster virus infections can cause recurrent episodes of shingles, as well as central nervous system vasculitis and stroke (see below). Human papillomavirus infections cause enlarging warts that can become disfiguring, interfere with normal bodily functions, or develop into squamous cell carcinomas. Anogenital infections can also result in cervical dysplasia, cervical cancer, or penile cancer during adulthood (unpublished). In the case of human papillomavirus or molluscum contagiosum virus, various topical therapies that physically or chemically remove skin lesions, stimulate toll-like receptor (TLR) pathways, or contain antiviral medications (such as cidofovir) can cause transient improvement but relapse is frequent (17). Use of systemic cidofovir or interferons can also be helpful, but tolerance is often limited by side effects (17, 19–21).

Of historical note, unlike the other viruses, which normally establish latent infections in the healthy host, molluscum contagiosum virus causes an acute infection characterized by scattered skin lesions that typically resolve after a few months. For this reason and an inability to culture the virus, the molluscum contagiosum virus genome was only sequenced after isolation from a DIDS patient carrying a high burden of such skin lesions (Steve Holland, personal communication) (22). Because of the high burden of virus skin lesions, DIDS patients have also been useful in skin virome studies that have uncovered new strains of human papillomavirus (Kong and Segre, Nat Medicine, in press).

Our clinical observations of unusually severe virus infections of the skin in DIDS patients can be reproduced using models of experimental virus infections in mice. Although mice cannot be infected with human papillomavirus, molluscum contagiosum virus, or varicella-zoster virus, they are susceptible to herpes simplex virus. As predicted from our clinical observations of the patients, epicutaneous infections with herpes simplex lead to increased disease severity and lethality in mice genetically lacking Dock8 (23). Subsequent studies by

a different group similarly showed increased susceptibility of different Dock8-deficient mouse strains to herpes simplex virus infections (24).

We next asked what accounted for this localized infection susceptibility. At the time of our discovery of the genetic basis of this disease, little was known regarding the normal functions of DOCK8. DOCK8 is a member of the DOCK (Dedicator of Cytokinesis) family of atypical guanine-nucleotide exchange factors that promote activation of the small RHO family GTPase CDC42. Because CDC42 is important for biological processes that involve cytoskeletal rearrangement, we hypothesized that loss of DOCK8, by impairing activation of CDC42, could cause abnormal immune cell trafficking in the skin. To test this, we first examined the behavior of T cells and NK cells, which are important for killing virus-infected cells, in a skin-like microenvironment. DOCK8-deficient cells were allowed to enter into a skin sample or were placed inside a high-concentration collagen gel. Among tissues, skin has by far the highest collagen content; this component contributes structurally to a dense lattice made up by many highly confined spaces, which artificially mimics the skin's dermal collagen bundles and epidermal tight junctions. Microscopic imaging in such skin-like microenvironments revealed that the DOCK8-deficient lymphocytes adopt an abnormally elongated shape with deformed nucleus as they randomly move (23). These cells can migrate normally towards a chemokine gradient, but over a period of hours they eventually catastrophically break up into small pieces in an unusual form of cell death called cytothripsis (for "cell shattering") (Figure 1B).

Next, we established the functional consequences of this abnormal cellular behavior by utilizing a mouse model of experimental herpes simplex virus infection of the skin. In this model, resident memory CD8 T cells (T_{RM}) are crucial in protecting against virus emergence from a latent stage within the dorsal root ganglia, as evidenced by the development of a zosteriform rash (25). As would be predicted from our *in vitro* findings, adoptive transfer of T cells led to a preferential loss of Dock8-deficient virus-specific T_{RM} cells from the skin, leading to increased virus titers and worsened clinical disease (23). Two-photon live cell microscopic imaging also showed the abnormal morphology occurring in such T cells as they migrated within the infected skin. Additionally, the total numbers of CD4 T cells acutely infiltrating the skin are more markedly decreased in herpes simplex virus infected Dock8-deficient mice, suggesting that under certain circumstances cell migration may also be affected (24).

Biochemically, the process by which DOCK8 regulates lymphocyte shape integrity requires not only the activation of CDC42, but also downstream activation of p21-activated kinase (PAK1/2) (23). However, the abnormal morphology and cytothripsis are not phenocopied by cells lacking the Wiskott-Aldrich syndrome protein, which in cells from healthy donors is normally activated in parallel with PAK1/2 by CDC42. impaired actin polymerization occurs in lymphocytes from both DIDS and Wiskott-Aldrich syndrome patients, reflecting a shared complex between both proteins and WASP-interacting protein (WIP) (26). The shared defect in actin polymerization could contribute to the functional abnormalities in cell adhesion and transendothelial cell migration that are observed when DOCK8, Wiskott-Aldrich syndrome protein (WASp), or WIP are lacking (26). However, Wiskott-Aldrich syndrome patients generally have fewer types and less severe virus skin infections despite sharing other clinical

features (27). This dichotomy supports the concept that the defective lymphocyte shape integrity unique to DOCK8-deficient cells is especially important for the pathogenesis of the prominent skin virus infections. Further work is needed to identify other factors downstream of PAK1/2 that affect the cytoskeleton to specifically coordinate movement for prolonged durations through dense tissues.

Other virus infections

DIDS patients can have detectable Epstein-Barr virus (EBV) in the peripheral blood, with levels typically no more than several tens of thousands of genome copies/mL. In our cohort at the NIH, of 44 who had EBV PCR in blood tested, 16 were viremic (36%). No patients were known to be EBV-infected without detectable blood PCR. However, in patients who had no detectable EBV PCR, many were on immune globulin replacement so their EBV-naïve status could not be confirmed. DIDS patients infected with EBV do not experience fulminant infectious mononucleosis, but the increased virus burden probably contributes to the development of EBV-associated lymphomas and lymphoproliferative disease (28), which can be the first grossly obvious manifestation of DIDS. In contrast, systemic cytomegalovirus (CMV) infection, with detectable virus in the blood along with retinitis and meningitis, has been reported in only a few DIDS patients. Within the NIH cohort, we have seen CMV viremia but without signs of CMV disease. CMV disease seems to correlate with increased morbidity and mortality in DIDS patients (13). Similarly, a few DIDS patients have also developed progressive multifocal leukoencephalopathy with detectable JC virus, including one within the NIH cohort. Furthermore, it should be pointed out that although DIDS patients have difficulty with mucocutaneous herpes simplex virus infections, no patients have been reported to develop herpes simplex virus encephalitis. Overall, although very serious when they occur, disease from EBV, CMV, or JC virus is much less common than the profound problems DIDS patients experience with herpes simplex virus, varicella-zoster virus, human papillomavirus, and molluscum contagiosum virus infections of the skin.

The increased susceptibility to non-skin centered viruses may reflect the progressive lymphopenia that predominantly affects T cells, which are important for killing virus-infected cells elsewhere in the body besides the skin. Apart from the cytothripsis that predominantly affects resident memory $CD8^+$ T cells (which remain in the skin and do not recirculate through the body), there is a milder generalized T cell survival defect that can be observed in circulating naïve, central memory, and effector memory phenotype T cells when isolated from peripheral blood or when subsequently cultured (29, 30). A similar generalized survival defect is also seen affecting natural killer T cells (31). The decreased T cell numbers can also reflect decreased T helper type 1 (T_H1) cells, which produce IL-2 required for T cell growth and proliferation and IFN-γ required for immunomodulatory antiviral T cell immunity (Figure 1B).

NK cells also exert antiviral effects by killing virus-infected cells, especially herpesgroup viruses where viral products downregulate MHC class I expression and thereby evade cytotoxic T cells. Like T cells from DIDS patients, NK cells from DIDS patients can be reduced in number and appear to exhibit a mild generalized survival defect when isolated

from peripheral blood (12) (and unpublished). However, unlike *in vitro* expanded $CD8^+$ T cells, which on a per cell basis have normal cytotoxicity, DOCK8-deficient NK cells have defective cytotoxicity due to abnormal immune synapse formation with failure of localized F-actin accumulation (32, 33). Additionally, when stimulated by an NK cell activating receptor (NKp30), DOCK8-deficient NK cells show not only impaired cytotoxicity, but also impaired production of IFN-γ and other cytokines (34). Although stimulation with IL-2 for several hours was unable to improve NK cell cytotoxicity (32), in our experience longer-term *in vitro* expanded NK cells from DIDS patients exhibited normal cytotoxicity (unpublished), suggesting that under certain circumstances, this defect can be overcome.

Finally, the increased susceptibility to viruses in DIDS patients may reflect generalized defects in dendritic cell function. Plasmacytoid dendritic cells, which are early responders to virus infection, are decreased in peripheral blood of DIDS patients and consequently produce less antiviral type I interferons when stimulated (20). Additionally, Dock8-lacking dendritic cells show impaired interstitial migration within the dermis and through the subcapsular sinus floor of lymph nodes in mice; this, in turn, impairs priming of T cells in the lymph nodes (35, 36) (Figure 1B). More recently, the migration of $CD11b^+$ migratory type 2 conventional dendritic cells was shown to be selectively impaired, leading to failure to prime for follicular T helper cell (T_FH) differentiation, which in turn impaired production of high-affinity, class-switched antibodies in a mouse model of influenza virus infection (37). Thus, impaired dendritic cell functions could indirectly compromise T and B cell responses directed against virus pathogens in DIDS patients.

Other infections

DIDS patients typically present in infancy with eczema, which can be complicated by abscesses, cellulitis, or other soft tissue bacterial infections (17). These infections are usually caused by *Staphylococcus aureus*, which normally colonizes the skin but can invade when the epidermal barrier is disrupted. Some patients develop a mild mucocutaneous candidiasis, which has been attributed to the decreased T helper type 17 (T_H17)-type cells that are important for antifungal host defense through the subsequent elaboration of antimicrobial peptides and chemokines that draw in neutrophils to sites of infection (38) (Figure 1B). This process of T_H17 differentiation requires STAT3 activation, which is impaired in DIDS T cells upon IL-6 or IL-21 stimulation (14). It is unknown whether cytothripsis of DOCK8-deficient lymphocytes within the skin also contributes to the localized bacterial and fungal infections, particularly if the infections become chronic because of progressive immune deficits.

Most DIDS patients also develop recurrent sinopulmonary infections starting in childhood, as evidenced by sinus surgeries and/or placement of myringotomy tubes. The sinopulmonary infections are caused by the usual bacterial pathogens such as *Streptococcus pneumoniae*. Pneumonias occur frequently in approximately one third of patients, and frequently leads to development of bronchiectasis, which has been seen in 42% of our NIH cohort (39). Sepsis also occurs, often caused by *Staphylococcus aureus*, or more rarely *Enterococcus*, *Acinetobacter*, *Candida*, or others, presumably through a break in skin-barrier function such as with central venous access (12, 40). Interestingly, patients rarely have bacterial

gastrointestinal infections, except for occasional reports of *Salmonella* enteritis, in contrast to experimental infections in Dock8-deficient mice showing impaired host defense against *Citrobacter rodentium* (41).

Severe bacterial infections in the DIDS patients, such as recurrent pneumonias, can be decreased by immunoglobulin replacement when indicated. Many patients have defective antibody responses, especially to capsular polysaccharide antigens, due to impaired class switching and affinity maturation, as well as decreased numbers of memory B cells and marginal-zone like B cells (42, 43). These defects were shown to be caused by impaired responses of B cells specifically to the TLR9 ligand CpG, leading to impaired DOCK8-mediated adaptor function for SYK-STAT3 signaling (43). Various reports conflict regarding whether loss of DOCK8 impairs B cell antigen receptor-mediated signaling, although the relatively mild defects in humoral immunity in DIDS patients argue for an overall minor physiological role in pathogenesis that may be overcome by other factors such as strength of stimuli (42, 44).

DIDS patients can also be infected with opportunistic or unusual non-viral pathogens. These have been reported in more severely affected patients, as their lymphopenia progresses along with disease. *Pneumocystis jirovecii* is often found colonizing the airways and can lead to pneumonia, so patients are typically preemptively placed on antimicrobial prophylaxis (12, 45) (and unpublished). Some patients also have had elevated transaminases and biliary ductal dilation with occult *Cryptosporidium* infection, even before sclerosing cholangitis develops (46–48) (and unpublished). Biliary duct dilation is common when cryptosporidia are detected in the stool, and 15% of our NIH cohort had biliary-based liver disease, with detectable cryptosporidia found in 5/8 (some testing was performed prior to adopting more sensitive methods of cryptosporidia detection). Chronic giardiasis and amebiasis can occur (12, 40, 46, 49, 50). Whether susceptibility to these protozoal gastrointestinal pathogens occurs because of decreased generation and survival of ROR$\gamma\tau^+$ innate lymphoid cells (ILC), similar to what was previously demonstrated in *Citrobacter rodentium*-infected, Dock8-deficient mice, is unknown (41). Cryptococcal meningitis and abscess, *Aspergillus* sinopulmonary infection and brain abscess, *Histoplasma* pneumonia, and *Salmonella* enteritis have been rarely reported (12, 17, 40). In contrast, DIDS patients do not appear unusually susceptible to *Listeria*, *Toxoplasma*, or *Mycobacteria*.

Macrophages, when activated, contribute to innate immunity against these intracellular pathogens, suggesting that the overall consequences of Dock8 loss in macrophages, namely impaired migration, may be physiologically less important than the consequences of DOCK8 loss in lymphocytes or dendritic cells (51). Recently, loss of Dock8 in mouse bone marrow-derived macrophages was found to impair Il-10-induced Stat3 signaling and suppressive effects of anti-inflammatory M2-type differentiated macrophages (52). Additional studies are needed to determine whether loss of DOCK8 in macrophages also affects other processes such as phagocytosis. However, together the current literature suggest complex effects on macrophages, which might explain the lack of a net susceptibility to macrophage-sensitive pathogens.

Vasculopathy

Vasculopathy or vasculitis affects middle- and large- sized blood vessels in a subset of DIDS patients. In our cohort at the NIH, ~10% had aortic or cerebral vascular changes. Aortic aneurysms with extensive calcifications are seen, as well as dilatations of the large vessels coming off the heart (53, 54) (and unpublished). While these findings are not rare in the general population, they are usually only seen in older adults, unlike in DIDS where they occur in children and adolescents. Often abnormal vessels are detected incidentally when imaging studies are performed, for instance during computed tomography scans of the chest to look for bronchiectasis.

Vasculopathy can occur at other sites, for example renal artery stenosis, which was discovered in one DIDS patient during workup for hypertension (55), or celiac artery aneurysm with stenosis and thrombosis in another DIDS patient (56). Vasculopathy can also occur in the central nervous system of DIDS patients (4, 39). This can present with stroke or other neurological signs and symptoms, sometimes associated with various infections (57, 58). In other cases, the vasculopathy can give rise to an otherwise asymptomatic Moyamoya-like picture, with the presence of collateral circulation suggesting a chronic response to vessel damage or occlusion (58, 59) (and unpublished). Vasculopathy has also been observed in other combined immunodeficiencies, such as the Wiskott-Aldrich syndrome (60). Interestingly, the presence of varicella-zoster virus in aneurysmal large vessel walls was detected in a patient with Wiskott-Aldrich syndrome in whom tissue was available (60).

The pathogenesis of the vasculopathy in DIDS is unclear. One possible explanation is that the vasculopathy is autoimmune in nature, although frank autoimmune disease occurs rarely in DIDS as compared to some other combined immunodeficiencies (see below). However, we favor an alternative explanation: that the vasculopathy in DIDS is often a sequela of chronic or protracted infection. This idea is supported by reports of a variety of microorganisms isolated from the cerebrospinal fluid of DIDS patients, including *Cryptococcus*, JC virus, and varicella-zoster virus (13). In particular, varicella-zoster virus is known to productively infect endothelial cells, where it can cause tissue damage, inflammation, and vascular remodeling (61). The presence of virus within vessels is associated with intracranial vasculopathy or extracranial vasculopathy including giant cell arteritis and granulomatous aortitis, even in patients who do not have any obvious underlying immunodeficiency (61). However, other factors besides presence of virus in the vessel likely contribute to the development of vasculopathy. That the central nervous system is often where vasculopathy is encountered might be because of immune privilege in this site which makes pathogen eradication or control more difficult than at other sites of the body.

T cells are normally important for controlling initial infection by varicella-zoster virus as well as limiting its reactivation and spread from latent neural tissue reservoirs including to the arteries (62). Similar to what occurs in the skin during virus infections (see above section), chronic or protracted virus infections in the vessel walls could result in cytothripsis of DOCK8-deficient T cells in those tissues. This idea is plausible because the vessel walls of large arteries have a collagen content that is intermediate between skin and other tissues of the body (*i.e.*, ~10% of wet weight, as compared to ~30% or <1%, respectively). Thus,

antiviral T cells interacting with infected endothelial cells would encounter a tissue microenvironment with an intermediate density of confined spaces (63). Given sufficient time within this microenvironment, cytothripsis of DOCK8-deficient lymphocytes could further compromise antiviral immunity, leading to protracted vessel injury and repair in response to local virus reactivation. Unfortunately, no mouse models of varicella-zoster virus infection exist to readily test this hypothesis, so future studies to shed light on this problem will depend upon obtaining relevant tissue specimens from DIDS patients.

Allergic disease

By definition, HIES patients have eczematous dermatitis and most have high levels of IgE in the serum. However, the presence of allergen-specific IgE does not necessarily mean that the patients have severe allergic disease. For example, AD-HIES patients have no or minimal allergic disease because they lack functional STAT3 in mast cells, which is required for degranulation and histamine release (64). In contrast, most DIDS patients have asthma and food allergies, with prevalences in our cohort of 53% and 55%, respectively; these are greater than the estimated prevalences of up to ~10% and ~5%, respectively, in the general population (65). The increased prevalence of asthma in DIDS patients can be recapitulated in a Dock8-deficient mouse model, which shows increased airway hyperreactivity following antigen-sensitization in the airway (66). While the atopic dermatitis in DIDS patients is variably severe, the allergic rhinitis and asthma are milder, and are adequately controlled by medication without need for allergen immunotherapy. In contrast, food allergies are especially severe in DIDS patients, who often are allergic to multiple foods and have had life-threatening anaphylaxis. Moreover, some DIDS patients also develop eosinophilic esophagitis, a type of chronic allergic inflammation (12). It is the severity of food allergies that is particularly distinctive of DIDS, in comparison to other genetically defined HIES or combined immunodeficiencies.

The severe allergic disease in DIDS results from a relative increase in T helper type 2 (T_H2)-type cells producing IL-4 and IL-5, with a concomitant decrease in T_H1-type and T_H17-type cells (38). The defect is intrinsic to the T cells themselves; it does not occur during T cell differentiation but rather appears to reflect subsequent decreased T cell survival. In the patients, increased IL-4 promotes IgE isotype class-switching in B cells, as shown *in vitro* by the inability of the TLR9 agonist CpG to suppress IL-4/CD40-mediated class switching to IgE (67). In the patients, the increased IL-5 also contributes to increased eosinophil numbers, which in turn amplifies allergic responses initiated by mast cells. DIDS patients not only exhibit sensitization to food and environmental allergens but also overt allergic disease. This observation indicates that loss of DOCK8 in mast cells does not appreciably impair their function which is required for the final mediator of clinical allergy, *i.e.*, histamine release. Thus, although loss of DOCK8 in lymphocytes results in the failure to activate STAT3 under specific conditions (14, 41, 43, 67), the increased allergic disease in DIDS, contrasted to the lack of allergic disease in AD-HIES, argues against DOCK8 also acting through STAT3 in mast cells. The reason for this cellular difference is presently unclear.

In addition, from what is known from the general population, the pathogenesis of atopic dermatitis is complicated by contributions from other cytokines (68). While T_H2 cytokines are associated with the acute phase of allergic inflammation in the skin and contribute to barrier dysfunction, dysregulation of other cytokines including T_H1 cytokines paradoxically contributes to chronic allergic inflammation in the skin. Thus, the unbalanced T_H2/T_H1 profiles in DIDS could explain the initiation of allergic inflammation, but it is unclear exactly how the chronic allergic inflammation is sustained in these patients (Figure 1B). One particular T_H2 cytokine, IL-31, is responsible for itching that exacerbates the atopic dermatitis. Increased serum IL-31 was indeed seen in both a DIDS patient and in Dock8-deficient mice, where it was crucial for development of skin disease (69). This effect does not reflect a requirement for the guanine-nucleotide exchange factor activity of DOCK8; instead, an adaptor function contained in the N-terminal region of DOCK8, together with MST1, normally inhibits EPAS1 nuclear translocation and EPAS-dependent IL-31 transcription. These observations raise the interesting possibility that missense variants in the N-terminal region that do not result in loss of protein expression or affect CDC42-dependent processes like cell migration might contribute to atopic dermatitis in the general population.

Autoimmunity

Generally speaking, immunodeficiencies with partial defects in T cell function can be associated with autoimmune disease. In a retrospective analysis of 136 DIDS patients, autoimmunity was reported in 13%, with nearly half attributed to vasculitis, a third due to autoimmune hemolytic anemia, and 6% to nephropathy (39). Some cases attributed to central nervous system vasculitis without obvious antecedent infection may be misattributed if based upon negative blood serologies, because pathogen testing can be negative in the blood while positive in the cerebrospinal fluid. One DIDS patient was reported as having systemic lupus erythematosus with nephropathy, which responded to immunosuppressive therapy (70). In some instances, clinical features of immunodysregulation can suggest other disorders, such as IPEX, but autoimmune gastrointestinal disease is not a feature of DIDS (39, 71). Most likely the rates of autoimmunity are over-estimated and indolent infections that are difficult to detect likely contribute to much of the inflammatory disease. For instance, some DIDS patients have been diagnosed with sclerosing cholangitis; however, with more sensitive PCR-based techniques to detect microorganisms, cryptosporidia are often detected in the stool when traditional staining methods were negative. Autoimmunity outside of the vasculitis was rare in our NIH cohort, with an incidence of less than 5%.

Although most DIDS patients lack overt autoimmune disease, many have autoantibodies against cytoplasmic antigens and have expansion of autoreactive $CD21^{-/low}$ $CD10^{-}$ $CD27^{-}$ phenotype B cells, indicating impaired peripheral B cell tolerance (72). Using culture systems of mouse cells, impaired differentiation of anti-inflammatory M2-type macrophages lacking Dock8, including their decreased ability to suppress T cell proliferation, was observed (52). However, whether this actually occurs in DIDS patients and contributes to their developing autoimmune disease is unknown. DIDS patients have decreased regulatory T cell (T_{reg}) numbers and suppressor function, but the relative clinical consequences of these abnormalities are uncertain given that the patients' effector/memory T cell (T_{EM}) numbers

and functions are also impaired. Any effect on T_{reg} cells can only partially explain a tendency towards autoimmunity, as the few DIDS patients with overt autoimmunity lack the classical clinical features of complete T_{reg} deficiency, *i.e.*, autoimmune enteropathy or endocrinopathies.

A recent clue that might place in context the role of T_{reg} in the pathogenesis of autoimmunity in DIDS is our observation that autoimmunity is less frequent and less severe in our outbred population of patients as compared to reports from Middle Eastern patient cohorts. As previously discussed above, large homozygous deletions in the *DOCK8* gene, which preclude recombination-mediated somatic repair, are less likely to be seen in our North American population. Thus, we speculate that the relative levels of somatic reversion in T_{reg} vs. T_{EM} cell subsets might dictate the likelihood of autoimmune disease. Consistent with this possibility, conditional knockout of *Dock8* in T_{reg} – but not ubiquitous knockout of *Dock8* – causes multiorgan autoimmune disease in mice by impairing IL-2 signaling in T_{reg} cells (73, 74). In our model, we propose that autoimmunity would be less likely in any given patient when somatic reversions occur to a greater level in T_{reg} as compared to T_{EM} cells. On the other hand, autoimmunity would be more likely in any given patient when somatic reversions occur to a lesser level in T_{reg} as compared to T_{EM}. Future studies in patients are needed to test these predictions.

Cancer

Like other combined immunodeficiencies, DIDS predisposes to cancer. In a retrospective survey of DIDS patients, 17% had either hematological or epithelial cell cancers in childhood which contributed to ~6% mortality (39). Sometimes the cancer is the first grossly obvious sign of disease. Inadequately controlled Epstein-Barr virus infections are associated with EBV-related lymphomas such as diffuse large B cell lymphoma, as well as the rare EBV-lymphoproliferative disorder lymphomatoid granulomatosis (12, 28, 46). Additionally, non-EBV lymphoid malignancies have been reported, namely EBV-negative Burkitt lymphoma, non-Hodgkin lymphoma, cutaneous T cell lymphoma-leukemia, T cell lymphoma, and acute myeloid leukemia (AML) (12, 50, 55, 75).

An unusual feature of the cancer susceptibility in DIDS is the high frequency of non-lymphoid malignancies. The diffuse human papillomavirus infections are associated with the development of squamous cell carcinomas of the skin, which are sometimes metastatic, and with cervical dysplasia, cervical cancer, and penile cancer (39) (and unpublished). More rarely, microcystic adnexal carcinomas and the EBV-associated smooth muscle tumors leiomyoma/leiomyosarcoma have been reported (12, 46, 76, 77). Several studies have shown gene rearrangements with loss of *DOCK8* in squamous cell carcinomas and neuroblastoma, suggesting a potential tumor suppressive effect (78–80). However, it is unclear whether this is a consequence of the recombinogenic properties of the *DOCK8* locus, yielding passenger rather than driver *DOCK8* mutations for oncogenesis. Since DOCK8 is not normally expressed in non-hematopoietic tissues, we favor the former explanation. Whether DIDS patients exhibit impaired tumor surveillance, particularly in the case of malignancies involving the skin, because of cytothripsis is unknown.

Transplantation

The natural history of DIDS is dismal, as emphasized by results from a large retrospective report of 136 DIDS patients (39). Even with aggressive treatment and prophylaxis with antimicrobials and immunoglobulin replacement, half of patients die by their second decade of life and virtually all patients die by their fourth decade of life. Most deaths are caused by infection but some are caused by stroke/vasculitis or malignancy. In those patients surviving past the third decade of life, almost all are sick. Given the high morbidity and mortality, developing and optimizing therapies for DIDS is a priority. Despite anecdotes that antivirals such as IFN-α can be helpful (20, 21), in our experience those agents are poorly tolerated and are inferior to hematopoietic stem cell transplantation, which is the only definitive cure available for DIDS. Our experience at the NIH Clinical Center, mirroring those of other centers, has established good outcomes for matched related, matched unrelated, and more recently haploidentical related donor transplantations using a myeloablative, reduced-intensity conditioning regimen (49, 55, 77, 81–86). Cord blood donor transplantation for DIDS has been unsuccessful (55, 82, 86), probably because of the longer time to immune cell reconstitution as well as increased virus reactivation and disease. Most hematopoietic stem cell transplantations for DIDS have been performed in children, but in our experience even older patients having minimal end-stage organ damage and without cancer, including an adult in her 30’s treated at the NIIH Clinical Center, can have good outcomes (unpublished).

Transplantation clearly cures the eczema and infection susceptibility, including the viral skin infections, of DIDS patients. Not enough time has elapsed to determine whether the malignancy risk, in large part attributed to the chronic virus infections, also decreases. Additionally, because autoimmunity is rare in DIDS patients, not enough of those patients have been transplanted to determine whether autoimmunity can also be cured. However, food allergies remain a significant problem for many patients (87), an observation that has been replicated in a larger retrospective review of transplanted DIDS patients (Michael Albert, unpublished). Because donor chimerism in the bone marrow, as compared to peripheral blood, can be incomplete (87), It is likely that the conditioning regimens used do not fully eliminate long-lived plasma cells that continue to produce food allergen-specific IgE after transplant. However, since total IgE gradually decreases after transplant (87), food allergen-specific IgE might also gradually decrease so that these food allergies could eventually resolve. Similarly, the continued presence of long-lived autoimmune plasma cells might mean that patients could continue to have autoimmune disease even after transplant. However, it is also possible that reconstitution of DOCK8-replete donor T_{reg} cells might suppress autoimmune plasma cells and improve if not cure autoimmune disease in DIDS. Long-term outcome studies in more DIDS patients will help to shed light on these questions.

Conclusions

Longitudinal clinical observations of DIDS patients, particularly at the NIH Clinical Center, have guided our studies into this fascinating disease. Because of these studies, we now better understand DIDS disease pathogenesis and the normal functions of DOCK8 in regulating the human immune system. Like other combined immunodeficiencies, the infection

susceptibility in DIDS broadly reflects defects in lymphocytes and dendritic cells. Disease results from defective CDC42 activation, which mediates cytoskeletal shape changes for diverse biological processes such as cell migration, survival, and effector functions. However, unlike related combined immunodeficiencies, DIDS patients have an unusual susceptibility to a broad number of viral skin infections; the chronicity of these infections, especially for human papillomavirus, predisposes to the development of squamous cell cancers. While many mechanisms can explain the immunodeficiency, most of them do not satisfactorily account for the prominent targeting of disease to the skin in DIDS patients. Our work has established that DOCK8 is crucial for regulating the shape and integrity of lymphocytes, particularly of antiviral resident memory CD8 T cells, as they maneuver through the skin. In DIDS patients, the localized lymphocyte survival defect might also contribute to other skin disease such as the atopic dermatitis, mucocutaneous candidiasis, and skin cancers, as well as the vasculopathy, which can be associated with varicella-zoster virus reactivation. Additional studies to delineate the biochemical pathway affected may generate useful knowledge for overcoming this defect.

Finally, besides being a combined immunodeficiency, which can sometimes be associated with increased IgE, DIDS can also be viewed as a hyper-IgE syndrome, due the markedly high levels of serum IgE and even greater frequency and severity of allergic disease than other hyper-IgE syndromes. This disease feature results from T_H2 skewing with eosinophilia, as well as abnormal regulation of isotype switching, although a possible connection to alterations in cytoskeleton and cell survival has not been investigated. Biochemical studies supporting a physical association of DOCK8 with STAT3 under certain circumstances for optimal signaling in some immune cell types are intriguing, as they suggest a possible mechanistic link to other forms of hyper-IgE syndrome. Future studies to decipher the molecular underpinnings of DIDS that point to the similarities and differences to these related diseases will be informative.

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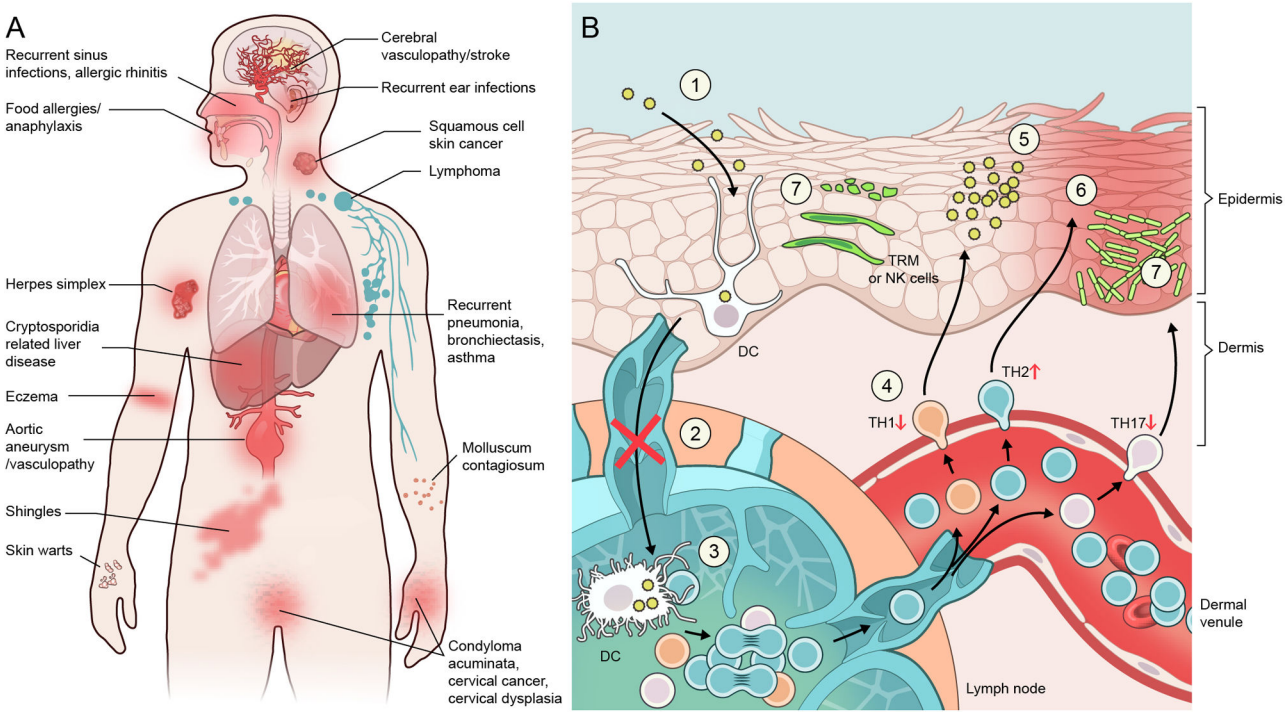

Figure 1.

A. Stylized illustration of a patient showing clinical features of DIDS.

B. Cellular pathogenesis of DIDS contributes to virus susceptibility and other skin manifestations of disease. Following virus infection of the skin (1), dendritic cells normally take up antigen and travel through the afferent lymphatics (2) to the lymph node where they prime T cells (3). Responding T cells differentiate and travel through efferent lymphatics to the blood, where they exit through venules into various tissues including the dermis of the skin. In DIDS, (2) and hence (3) are defective; additionally, T_H1-differentiated cells are decreased, T_H2-differentiated cells are increased, and T_H17-differentiated cells are decreased (4). Differentiated T cells extravasate into the skin where the cytokine imbalances contribute to increased virus replication (5), atopic dermatitis (6), and mucocutaneous candidiasis (7), respectively. In parallel, tissue resident memory T cells (T_{RM}) or NK cells normally kill virus-infected cells as they migrate continuously within the epidermis (7). In DIDS, these migrating cells undergo a form of cell death called cytothripsis, which compromises local antiviral immunity, also leading to increased virus replication (5).

Table 1.

Classification of germline mutations in *DOCK8* in the NIH cohort of DIDS patients

***DOCK8* mutations on both alleles**	**# families**	**% of families**
Large homozygous or compound heterozygous mutation	11	27.5
Compound heterozygous deletion (large deletion plus point mutation/small indel)	14	35
Point mutations/small indels	15	37.5
Total	40	100