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Insights into the pathogenesis of allergic disease from DOCK8 deficiency

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Abstract

Clinical observations and mechanistic studies in DOCK8-deficient patients and mice have revealed multiple mechanisms which could contribute to their unusually prevalent and severe allergic disease manifestations. Physical interactions of DOCK8 with STAT3 in B cells and T cells may contribute to increased IgE isotype switching or defective immune synapse formation that decreases TCR signal strength. A newly discovered $T_{FH}13$ cell type promotes the development of life-threatening allergy via production of IL-13 and is increased in DOCK8 deficiency. Cytoskeletal derangements and cytothripsis, which were previously shown to account for the increased susceptibility to viral skin infection in DOCK8 deficiency, can lead to interplay between myeloid cells and T cells to ultimately increase production of IL-4, IL-5, and IL-13. Finally, effects on ILC2 may also contribute to allergic disease.

Background

DOCK8 deficiency is a combined immunodeficiency (CID) that is caused by mutations in an atypical guanine-nucleotide exchange factor for activating CDC42 [1,2]. The disease is hallmarked by not only increased infection susceptibility but also allergic disease. The infections in these patients show a predilection for the skin, and they are typically caused by *Staphylococcus aureus* or various persistent viruses, with human papillomavirus (HPV) also predisposing to development of squamous cell cancers [3]. The skin infections usually occur superimposed upon and are aggravated by atopic dermatitis, which starts in infancy and can become severe or extensive enough to necessitate wet-wrap therapy or dupilumab (anti-IL-4Rα monoclonal antibody) [4]. It is important to emphasize that allergic disease is not limited to allergic inflammation occurring in some forms of eczema, but it encompasses other clinical manifestations of immediate hypersensitivity. Other manifestations of clinical allergy in DOCK8-deficient patients are allergic rhinitis, sometimes requiring allergen

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Declaration of Interest

none.

immunotherapy; mild-to-moderate persistent asthma; and food allergies that can present with life-threatening anaphylaxis or alternatively as eosinophilic esophagitis. Patients often have elevated serum IgE, leading to a diagnosis of hyper-IgE syndrome. Overall, allergic disease is more prominent in DOCK8 deficiency than in most other CIDs.

DOCK8 expression is largely restricted to the immune system, and hematopoietic stem cell transplantation (HSCT) cures the infection susceptibility that is otherwise the major cause of death in DOCK8-deficient patients. Without such treatment, the natural history is death in over half of patients by the end of their second decade and increased morbidity in those surviving [5]. HSCT also cures atopic dermatitis and normalizes total serum IgE, but whether HSCT cures all manifestations of allergic disease is unclear. Despite encouraging post-HSCT improvements in allergen-specific IgE reactivity including skin prick testing, clinical food allergies did not fully resolve in all patients in up to a 3- or even 8- year windows after HSCT [6-8]. It remains to be seen whether longer follow up post-HSCT will demonstrate eventual resolution of food allergies in these patients.

Interestingly, in a large proportion of patients, somatic repair of the DOCK8 genetic defect can spontaneously occur, leading to re-expression of DOCK8 protein and slowing the development of disease [9]. Somatic repair was associated with decreased total atopic burden, but no statistically significant differences were seen when this was broken down for different clinical allergic manifestations (Figure 1) [9]. In a few patients, somatic repair has even been reported to resolve overall clinical disease severity over time, with the caveat that the clinical scoring scale used disproportionately reflects infectious manifestations [10]. It was unreported whether clinical allergic disease manifestations, besides laboratory markers of allergy, resolved. The divergent outcomes probably depend upon extent of correction across different lymphocyte subsets, which can reflect whether correction occurred early during lymphocyte development. It should be noted that most regimens for HSCT involve reduced intensity conditioning, which are not fully myeloablative; similarly, somatic repair is only rarely observed in myeloid as compared with lymphoid cells. Thus, although a role for DOCK8-deficient myeloid cells cannot be completely excluded, the results generally suggest that the allergic disease primarily is driven by DOCK8-deficient lymphocytes.

Mechanisms of allergic disease in DOCK8 deficiency

Atopic disease in DOCK8 deficiency encompasses a spectrum of phenotypes. Immediate type I hypersensitivity reactions underlie classical IgE-mediated food allergen-induced anaphylaxis and environmental aeroallergen-triggered allergic rhinoconjunctivitis or allergic asthma. When combined with more delayed, non-IgE-mediated allergen-induced inflammation or other factors such as disrupted epithelial barriers and microbial colonization, the IgE-mediated mechanisms can evolve into other presentations such as eosinophilic esophagitis or chronic atopic dermatitis. Compared to Job syndrome – which is the prototypical hyper-IgE syndrome caused by *STAT3* dominant negative mutations and has a higher prevalence and severity of some forms of allergic disease compared to the general population – multiple allergic phenotypes and food allergies are more prevalent and more severe in DOCK8 deficiency [11]. The dichotomy between high serum IgE and lesser extent of clinical allergic disease in Job syndrome has been attributed to decreased vascular

permeability [12] and impaired FcεR1-mediated signaling and degranulation of mast cells [13], although low levels of specific IgE antibodies may also contribute to the decreased reactivity [11]. Although based upon limited numbers of patients, ZNF341 deficiency, which results in loss of downstream STAT3 transcriptional activity, also features non-eczematous allergic disease that seems less prevalent and less severe than that seen in DOCK8 deficiency, while other hyper-IgE syndromes that impair STAT3 signaling downstream of IL-6 receptor/OSM130 seem to have milder or absent allergic disease [14]. Together, clinical observations in the different hyper-IgE patient groups suggest that the more prominent allergic disease in DOCK8 deficiency likely results from non-STAT3-mediated mechanisms, in addition to STAT3-mediated mechanisms (Table 1, and elaborated further below).

STAT3 activation can be caused by stimulation of the B cell receptor, TLR9, and various cytokine receptors (such as for IL-21, IL-6, and IL-10). Several studies have previously reported mechanistic connections between DOCK8 and STAT3. In B cells from DOCK8-deficient patients, TLR9-induced (via the TLR9 agonist CpG) phosphorylation of STAT3 is impaired, but IL-21- (or IL-6-) induced phosphorylation of STAT3 proceeds normally [15]. Furthermore, isotype switching to IgE can be induced *in vitro* upon CD40 cross-linking in the presence of IL-4. In healthy donor B cells, this process can be suppressed by stimulating in the presence of either the TLR9 agonist CpG) or IL-21 [16]. However, in B cells from either DOCK8- or STAT3- deficient patients, CpG is unable to suppress CD40/IL-4 stimulated IgE isotype switching, although the effect on CD40/IL-21 stimulated IgE isotype switching was not similarly tested [17]. Thus, STAT3-relevant pathways required for IgE production include those stimulated by IL-21 and IL-6, but probably not TLR9. Overall, these results indicate that this selective defect in B cell signaling may contribute to but is unlikely to completely account for the increased IgE in DOCK8 deficiency.

Additionally, a mechanistic connection between DOCK8 and STAT3 has been reported in T cells. T cells from DOCK8-deficient patients have impaired phosphorylation of STAT3 at between 15 to ~60 minutes of stimulation with either IL-6 or IL-21 [18]. Furthermore, DOCK8 physically associates with STAT3 to promote STAT3 activity, suggesting a model whereby DOCK8 functions to amplify STAT3 responses [18]. This STAT3-related defect has been proposed to contribute to the defective T_H17 differentiation intrinsic to naïve patient T cells [18]. How such a defect might contribute to allergy-promoting increased production of certain cytokines (IL-4, IL-5, IL-13) observed in DOCK8-deficient T cells (but normal T_H2 differentiation *in vitro*) is unclear [1,18-20]. By contrast, STAT3-deficient patients have decreased numbers of memory $CD4^+$ $CD45RA^-$ T cells, which produce more IL-13 and IL-5, but not IL-4 [21], and their total $CD4^+$ T cells also produce normal amounts of IL-5 and IL-4 [11,22-24]. Thus, this dichotomy in the range of T_H2 type cytokines produced by DOCK8-deficient versus STAT3-deficient patients suggests that the loss of DOCK8 can promote production of allergic-type cytokines independently from its effects on STAT3.

An alternative explanation for how absence of DOCK8 might promote production of T_H2 type cytokines reflects DOCK8's role in regulating cytoskeletal rearrangements through its ability to activate CDC42. Normal immunological synapse formation requires cytoskeletal rearrangements during conjugate formation of T or B cells with antigen presenting cells. However, DOCK8-deficient T cells (or B cells) exhibit poor immunological synapse

formation, thereby compromising their ability to sustain signaling for optimal activation after antigen receptor stimulation [25,26]. Since decreased T cell receptor (TCR) signal strength favors T_H2 over T_H1 cell polarization through various mechanisms [27], the defective immunological synapses in DOCK8-deficient T cells could thereby lead to similar downstream effects on cytokine production. Disrupted immunological synapse formation in DOCK8-deficient T_{reg} cells might also compromise their ability to suppress effector T cells (including T_H2 cells), although different reports testing the suppressive activity of DOCK8-deficient T_{reg} cells have yielded conflicting results [28-32]. Since DOCK8-deficient patients rarely have overt autoimmune disease despite their having detectable autoantibodies, a defect affecting T_{reg} cells would be expected to be milder than what is seen for classical T_{reg}-opathies and would also have to account for a preferential impact on allergy-promoting T effector cells.

More recently, DOCK8-deficient patients and mice were discovered to have increased numbers of a new and rare T cell subtype distinct from T_H2 cells [28**]. These $T_{FH}13$ cells express high levels of IL-13, IL-4, and IL-5 but low levels of IL-21. Moreover, they express the *BCL6* and *GATA3* transcription factors characteristic of T_{FH} cells, unlike T_H2 cells which characteristically express *GATA3* but not *BCL6*. $T_{FH}13$ cells are also increased in DOCK8-sufficient peanut-allergic or aeroallergen-sensitized individuals or in Dock8-deficient mouse models of allergy. These conditions reflect high affinity allergen-specific IgE responsible for mast cell degranulation and anaphylactic reactions. By contrast, $T_{FH}13$ cells are not seen in helminthic infections that are associated with low affinity IgE and increased IL-4 but not IL-13 production. Since mice in which $T_{FH}13$ cells were selectively deleted lose high-affinity IgE while maintaining elevated total IgE, this dichotomy suggests that levels of $T_{FH}13$ cells are the more relevant biomarker for clinical allergy. How loss of DOCK8 results in the differentiation and/or expansion of $T_{FH}13$ cells and whether $T_{FH}13$ cells are abnormal in the other hyper-IgE syndromes that impact STAT3 signaling but show less severe clinical allergy are unknown. It should be noted that in contrast to results from a different immunization regimen [33], this study showed high levels of total IgE in mice in which Dock8 was selectively deleted in T cells but not in mice in which Dock8 was constitutively deleted, suggesting that the increased allergy was intrinsic to the $T_{FH}13$ cells. However, in another study mice completely lacking Dock8 developed elevated IL-4, IL-15, and IL-13 following infection with *Cryptococcus neoformans*, influenza virus, or immunization with OVA peptide in complete Freund's adjuvant, although not to helminth infection [34**]. As DOCK8-deficient humans encounter many microbes and infrequently exhibit somatic repair in their non-T cells, this suggests that their defects in non-T cells might nevertheless contribute to allergic-type responses.

With regard to this last point, how the DOCK8 defect affecting cytoskeletal rearrangements could regulate allergic-type cytokine production has recently been delineated in a complex series of steps (Figure 2). DOCK8 regulates lymphocyte shape integrity, which is important during migration in dense environments such as the skin [35]. Loss of DOCK8 results in cytothripsis ("cell shattering"), a form of cell death triggered by cell migration through these tissues, which compromises lymphocyte effector functions, resulting in poor control of virus skin infections. Dock8-deficient mononuclear phagocytes also undergo cytothripsis, but more readily in less dense tissue microenvironments than T cells [34**]. Their cell

death releases IL-1β, which promotes GM-CSF production by $CD4^+$ T cells and amplifies the downstream T cell cytokine response. Cytothripsis, IL-1β, and GM-CSF contribute to the increased IL-4, IL-5, and IL-13. Whether this regulatory axis specifically affects $T_{FH}13$ vs. T_H2 cells has yet to be clarified, as well as a potential role for STAT3 in any of these step(s). Furthermore, if this mechanism holds in humans, targeting IL-1 might ameliorate development of allergic disease in DOCK8-deficient individuals. Additionally, other conditions, such as autoinflammatory disorders with increased IL-1β production or pulmonary alveolar proteinosis with neutralizing anti-GM-CSF antibodies, might also affect development of allergic disease.

Finally, Dock8-deficient mice have recently been reported as having increased numbers of type 2 innate lymphoid cells (ILC2) producing IL-5 and IL-13, as well as increased numbers of T_H2 cells, eosinophils, and mast cells in the lamina propria of the small intestine [36*]. The ILC2 were approximately 5-fold more numerous than T_H2 cells, suggesting their increase locally in the gut might contribute to the heightened food allergies. Furthermore, their presence was found to depend upon DOCK8 expression in hematopoietic cells as well as DOCK8's ability to promote CDC42 activation. As DOCK8-deficient patients have decreased numbers of ILC2 in peripheral blood [37], the different numbers between mice and humans might reflect altered cell migration. Examining this cell type in other tissue compartments, as well as their sensitivity to conditioning regimens used in DOCK8 HSCT, would be highly informative.

Conclusions

DOCK8 deficiency is a monogenic infection susceptibility disorder that is less recognized as also a being *bona fide* monogenic allergic susceptibility disorder. Recent studies have provided new insights into the regulation of allergic responses and have raised interesting questions for future research. Foremost among these is the potential role of $T_{FH}13$ cells in allergic manifestations in other inborn errors of immunity such as actinopathies including the Wiskott-Aldrich syndrome, whether they are regulated by STAT3, and how maintenance of lymphocyte integrity in $T_{FH}13$ might also influence clinical allergy.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Zhang Q, Davis JC, Lamborn IT, et al. : Combined immunodeficiency associated with DOCK8 mutations. N Engl J Med 2009, 361:2046–2055. [PubMed: 19776401]

2. Engelhardt KR, McGhee S, Winkler S, et al. : Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. J Allergy Clin Immunol 2009, 124:1289–1302 e1284. [PubMed: 20004785]

3. Tirosh O, Conlan S, Deming C, et al. : Expanded skin virome in DOCK8-deficient patients. Nat Med 2018, 24:1815–1821. [PubMed: 30397357]

4. Ollech A, Mashiah J, Lev A, et al. : Treatment options for DOCK8 deficiency-related severe dermatitis. J Dermatol 2021, 48:1386–1393. [PubMed: 34043252]

5. Aydin SE, Kilic SS, Aytekin C, et al. : DOCK8 deficiency: clinical and immunological phenotype and treatment options — a review of 136 patients. J Clin Immunol 2015, 35:189–198. [PubMed: 25627830]

6. Happel CS, Stone KD, Freeman AF, et al. : Food allergies can persist after myeloablative hematopoietic stem cell transplantation in dedicator of cytokinesis 8-deficient patients. J Allergy Clin Immunol 2016, 137:1895–1898. [PubMed: 26827248]

7. Raedler J, Magg T, Rohlfs M, et al. : Lineage-specific chimerism and outcome after hematopoietic stem cell transplantation for DOCK8 deficiency. J Clin Immunol 2021, 41:1536–1548. [PubMed: 34080085]

8. Pillay BA, Avery DT, Smart JM, et al. : Hematopoietic stem cell transplant effectively rescues lymphocyte differentiation and function in DOCK8-deficient patients. JCI Insight 2019, 5:e127527, 10.1172/jci.insight.127527 [PubMed: 31021819]

9. Jing H, Zhang Q, Zhang Y, et al. : Somatic reversion in Dock8 immunodeficiency modulates disease phenotype. J Clin Immunol 2014, 34:361.

10. Pillay BA, Fusaro M, Gray PE, et al. : Somatic reversion of pathogenic DOCK8 variants alters lymphocyte differentiation and function to effectively cure DOCK8 deficiency. J Clin Investig 2021, 131:e142434, 10.1172/JCI142434 [PubMed: 33290277]

11. Boos AC, Hagl B, Schlesinger A, et al. : Atopic dermatitis, STAT3- and DOCK8-hyper-IgE syndromes differ in IgE-based sensitization pattern. Allergy 2014, 69:943–953. [PubMed: 24898675]

12. Hox V, O'Connell MP, Lyons JJ, et al. : Diminution of signal transducer and activator of transcription 3 signaling inhibits vascular permeability and anaphylaxis. J Allergy Clin Immunol 2016, 138:187–199. [PubMed: 26948077]

13. Siegel AM, Stone KD, Cruse G, et al. : Diminished allergic disease in patients with STAT3 mutations reveals a role for STAT3 signaling in mast cell degranulation. J Allergy Clin Immunol 2013, 132:1388–1396. [PubMed: 24184145]

14. Chen YH, Spencer S, Laurence A, et al. : Inborn errors of IL-6 family cytokine responses. Curr Opin Immunol 2021, 72:135–145. [PubMed: 34044328]

15. Jabara HH, McDonald DR, Janssen E, et al. : DOCK8 functions as an adaptor that links TLR-MyD88 signaling to B cell activation. Nat Immunol 2012, 13:612–620. [PubMed: 22581261]

16. Wade-Vallance AK, Allen CDC: Intrinsic and extrinsic regulation of IgE B cell responses. Curr Opin Immunol 2021, 72:221–229. [PubMed: 34216934]

17. Massaad MJ, Cangemi B, Al-Herz W, et al. : DOCK8 and STAT3 dependent inhibition of IgE isotype switching by TLR9 ligation in human B cells. Clin Immunol 2017, 183:263–265. [PubMed: 28882618]

18. Keles S, Charbonnier LM, Kabaleeswaran V, et al. : Dedicator of cytokinesis 8 regulates signal transducer and activator of transcription 3 activation and promotes TH17 cell differentiation. J Allergy Clin Immunol 2016, 138:1384–1394 e1382. [PubMed: 27350570]

19. Lambe T, Crawford G, Johnson AL, et al. : DOCK8 is essential for T-cell survival and the maintenance of CD8(+) T-cell memory. Eur J Immunol 2011, 41:3423–3435. [PubMed: 21969276]

20. Tangye SG, Pillay B, Randall KL, et al. : Dedicator of cytokinesis 8-deficient CD4(+) T cells are biased to a T(H)2 effector fate at the expense of T(H)1 and T(H)17 cells. J Allergy Clin Immunol 2017, 139:933–949. [PubMed: 27554822]

21. Ma CS, Wong N, Rao G, et al. : Monogenic mutations differentially affect the quantity and quality of T follicular helper cells in patients with human primary immunodeficiencies. J Allergy Clin Immunol 2015, 136:993–1006 e1001. [PubMed: 26162572]

22. Gudmundsson KO, Sigurjonsson OE, Gudmundsson S, et al. : Increased expression of interleukin-13 but not interleukin-4 in CD4+ cells from patients with the hyper-IgE syndrome. Clin Exp Immunol 2002, 128:532–537. [PubMed: 12067309]

23. Rodriguez MF, Patino PJ, Montoya F, et al. : Interleukin 4 and interferon-gamma secretion by antigen and mitogen-stimulated mononuclear cells in the hyper-IgE syndrome: no TH-2 cytokine pattern. Ann Allergy Asthma Immunol 1998, 81:443–447. [PubMed: 9860038]

24. Becker KL, Rosler B, Wang X, et al. : Th2 and Th9 responses in patients with chronic mucocutaneous candidiasis and hyper-IgE syndrome. Clin Exp Allergy 2016, 46:1564–1574. [PubMed: 27474157]

25. Randall KL, Chan SS, Ma CS, et al. : DOCK8 deficiency impairs CD8 T cell survival and function in humans and mice. J Exp Med 2011, 208:2305–2320. [PubMed: 22006977]

26. Randall K, Lambe T, Johnson A, et al. : Dock8 mutations cripple B cell immunological synapses, germinal centers and long-lived antibody production. Nat Immunol 2009, 10:1283–1291. [PubMed: 19898472]

27. Bhattacharyya ND, Feng CG: Regulation of T helper cell fate by TCR signal strength. Front Immunol 2020, 11:624. [PubMed: 32508803]

28 ••. Gowthaman U, Chen JS, Zhang B, et al. : Identification of a T follicular helper cell subset that drives anaphylactic IgE. Science 2019, 365:eaaw6433, 10.1126/science.aaw6433. [PubMed: 31371561] This is a paradigm-shifting study reporting the discovery of a new T follicular helper subset that makes IL-13, called $T_{FH}13$. While initially discovered in DOCK8 deficiency, the cell type functions in other allergic conditions.

29. Janssen E, Kumari S, Tohme M, et al. : DOCK8 enforces immunological tolerance by promoting IL-2 signaling and immune synapse formation in Tregs. JCI Insight 2017, 2:e94298, 10.1172/jci.insight.94298 [PubMed: 28978806]

30. Janssen E, Morbach H, Ullas S, et al. : DOCK8 deficient patients have a breakdown in peripheral B cell tolerance and defective regulatory T cells. J Clin Immunol 2014, 34:S213.

31. Singh AK, Eken A, Hagin D, et al. : DOCK8 regulates fitness and function of regulatory T cells through modulation of IL-2 signaling. JCI Insight 2017, 2:e94275, 10.1172/jci.insight.94275 [PubMed: 28978795]

32. Wilkie H, Janssen E, Leyva-Castillo JM, Geha RS: DOCK8 expression in regulatory T cells maintains their stability and limits contact hypersensitivity. J Investig Dermatol 2021, 141:1503–1511 e1503. [PubMed: 33171169]

33. Janssen E, Tohme M, Butts J, et al. : DOCK8 is essential for LFA-1-dependent positioning of T follicular helper cells in germinal centers. JCI Insight 2020, 5:e134508, 10.1172/jci.insight.134508 [PubMed: 32573493]

34 ••. Schneider C, Shen C, Gopal AA, et al. : Migration-induced cell shattering due to DOCK8 deficiency causes a type 2-biased helper T cell response. Nat Immunol 2020, 21:1528–1539. [PubMed: 33020661] This elegant study delineates a complex series of events linking DOCK8 deficiency, cytothripsis with IL-1β release from dying mononuclear phagocytes, and GM-CSF production from T cells, to cause the increased IL-4, IL-5, and IL-13 production for allergy.

35. Zhang Q, Dove CG, Hor JL, et al. : DOCK8 regulates lymphocyte shape integrity for skin antiviral immunity. J Exp Med 2014, 211:2549–2566. [PubMed: 25422492]

36 •. Matsubara K, Kunimura K, Yamane N, et al. : DOCK8 deficiency causes a skewing to type 2 immunity in the gut with expansion of group 2 innate lymphoid cells. Biochem Biophys Res Commun 2021, 559:135–140. [PubMed: 33940384] This intriguing although limited study uses CyTOF to enumerate IL-5- and IL-13- expressing T cells and iLC2 within the GI tract of Dock8-deficient mice, suggesting a role for ILC2.

37. Eken A, Cansever M, Okus FZ, et al. : ILC3 deficiency and generalized ILC abnormalities in DOCK8-deficient patients. Allergy 2020, 75:921–932. [PubMed: 31596517]

Highlights:

- DOCK8 deficiency features infection susceptibility and monogenic allergy.
- $T_{FH}13$ cell numbers are increased in DOCK8 deficiency and drive anaphylaxis.
- Cytothripsis, IL-1β, and GM-CSF increase IL-4, IL-5, and IL-13 production.
- ILC2 as well as T_H2 cells are increased in the gastrointestinal tract.
- How STAT3 drives clinical allergy needs additional investigations.

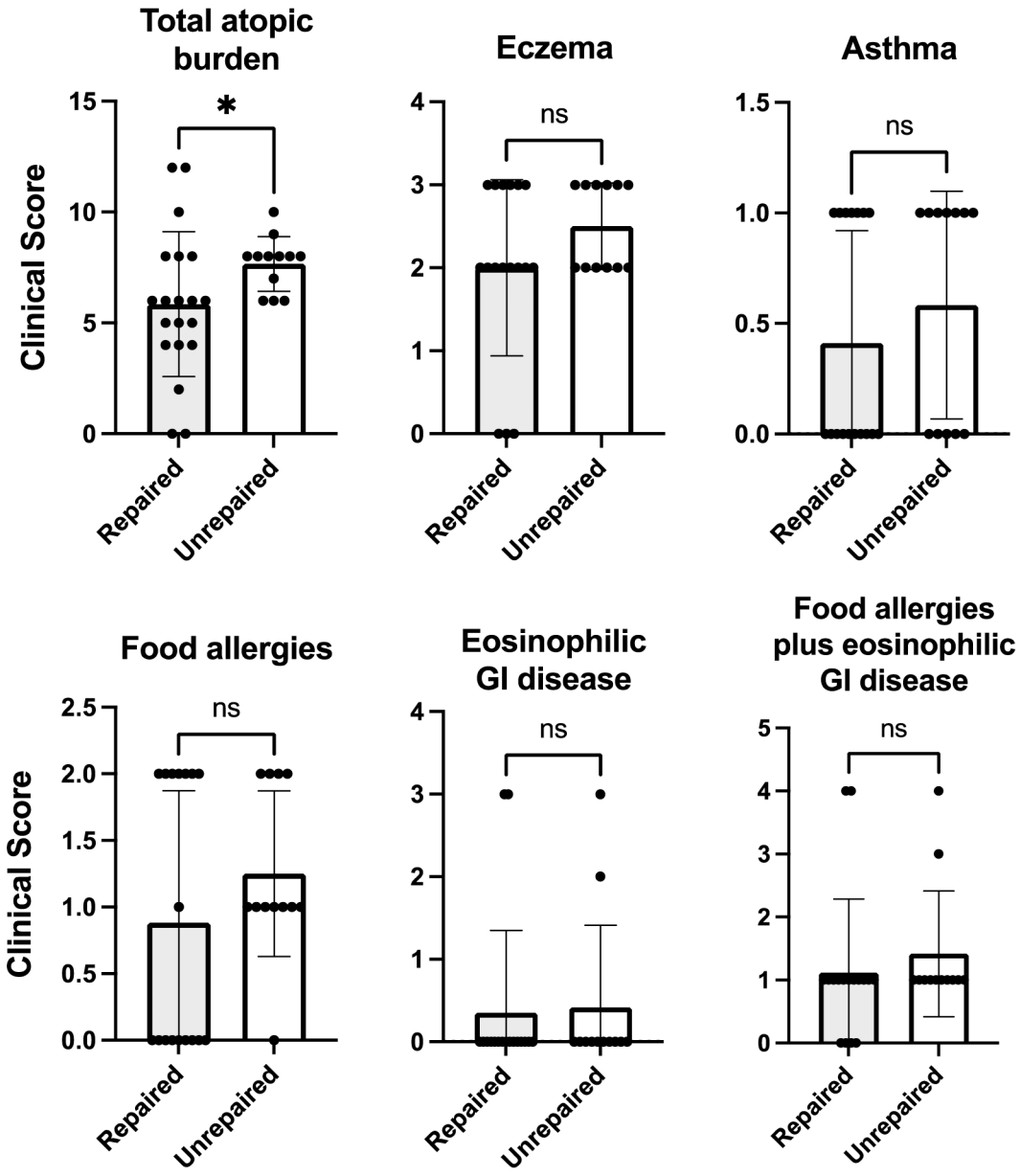

Figure 1.

Disease burden of allergic disease is decreased in DOCK8-deficient patients having somatic repair (n=17), as compared to unrepaired DOCK8-deficient patients (n=12). Data were from [6] (Table E1) showing scores for allergic disease at time of analysis. Eczema was scored at worse stage as 0=absent, 1=mild, 2=moderate, 3=persistent. Asthma was scored as 0=absent, 1=present. Food allergy was scored as 0=absent, 1=present, 2=present with anaphylaxis. Eosinophilic GI disease was scored as 0=absent, 1=esophagitis, 3=GI (gastrointestinal) tract beyond esophagus. Since allergic disease presents early in life in DOCK8-deficient patients, no score adjustment for young ages was performed. *p=0.0254 by Mann-Whitney U-test; ns, not significant.

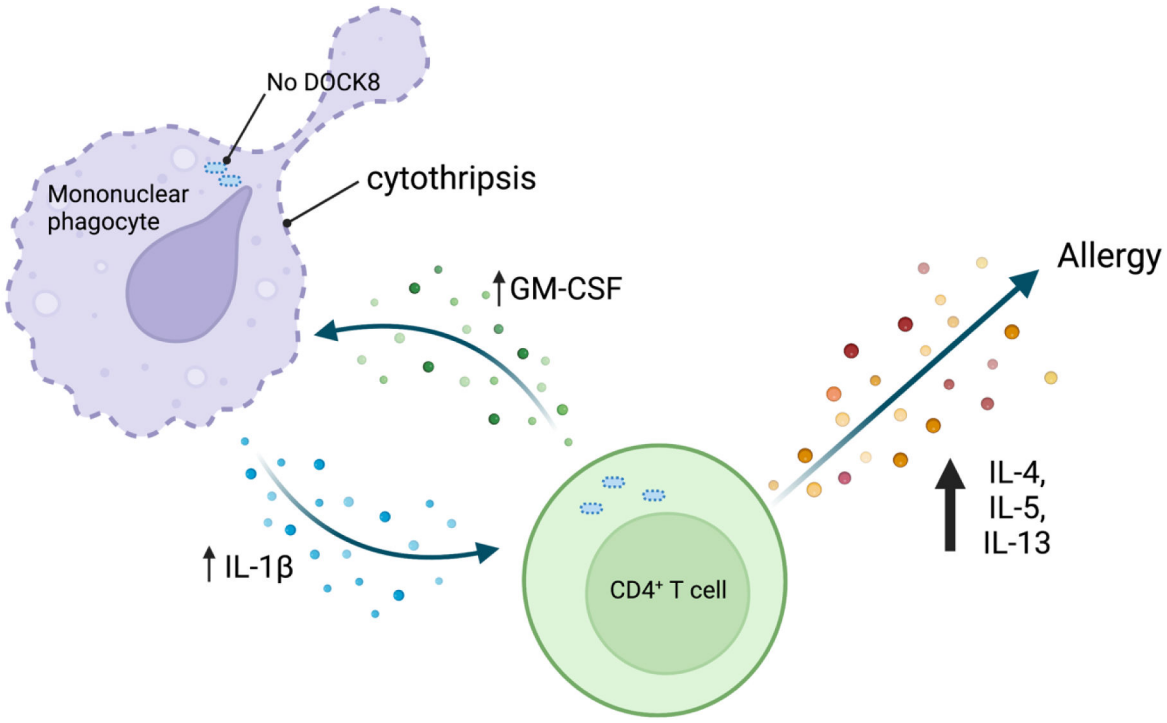

Figure 2.

Cytothripsis promotes allergic type cytokine production in DOCK8 deficiency. As shown in [34], loss of Dock8 in mice results in cytothripsis of mononuclear phagocytes as they travel through certain tissues. The cell death activates caspases, which process pro-IL-1β into its mature form that is released from the dying cell. IL-1β stimulates $CD4^+$ T cells to increase their production of GM-CSF, which in turn feeds back to increase pro-IL-1β expression for amplification of cytokine responses. Caspases, IL-1β, and GM-CSF are required for the resulting increased production of IL-4, IL-5, and IL-13 to predispose to allergy. Created with Biorender.com.

Table 1.

Mechanisms accounting for the increased prevalence and severity of allergy in DOCK8 deficiency

• Impaired ability to activate STAT3 during TLR9 stimulation for inhibition of IgE isotype switching
• Defective immune synapse formation decreasing TCR signal strength, thereby favoring T_H2 polarization
• Increased $T_{FH}13$ cells promoting high affinity allergen-specific IgE for mast cell degranulation
• Cytothripsis of migrating mononuclear phagocytes with IL-1β secretion causing GM-CSF production by T cells, which in turn amplifies overall T cell production of IL-4, IL-5, and IL-13
• Increased ILC2 cells in the gastrointestinal tract through DOCK8's ability to promote CDC42 activity.