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REVIEW

Atopic Dermatitis Immune Dysregulation as Dengue Predisposing Factor

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Introduction: The immune response is important in dengue's clinical manifestation, and the immune dysregulation in Atopic Dermatitis (AD) can permit immune evasion by viruses. There have been many studies describing the immune response in AD and the pathomechanism of dengue, but AD as a predisposing factor for dengue and its severity have not been much discussed. This review investigates how immune dysregulation in AD may be a predisposing factor for Dengue and its severe outcomes.
Methods: We conducted a comprehensive analysis of studies from the past decade, focusing on dendritic cells (DCs), macrophages, mast cells (MCs), Innate Lymphoid Cell 2 (ILC-2), Natural Killer (NK) cells, interferon (IFN), interleukin (IL) 4, IL-13, and T helper (Th) 2 in AD patients with healthy subject as a comparison, using databases PubMed, Science Direct, and Google Scholar.
Results: We got 44 articles that met inclusion criteria. From those articles, we resumed that moderate and severe AD patients' immune profiles showed increased DC, MCs, M2 macrophage, NK cells, and ILC2 in the lesional and non-lesional skin, decreased DC and NK cells in peripheral blood, alteration cytotoxicity of NK cells, Th2-skewed adaptive immune response in lesional and non-lesional skin, and peripheral blood. Increased DC, M2 macrophage, and MCs provide target cells for Dengue virus (DENV) replication. Alteration cytotoxicity of NK cells, ILC2, and Th2 skewed immune response facilitated immune evasion by DENV.
Conclusion: The innate and adaptive immune dysregulation in moderate and severe AD provides DENV target cells and facilitates virus immune evasion that can be a predisposing factor for dengue and severe dengue. Further research is recommended to clarify the association between AD and the incidence of dengue and severe dengue because this can be a consideration in determining the prognosis and management of Dengue.
Keywords: atopic dermatitis, adaptive immune response, dengue, innate immune response

Introduction

Dengue is a disease caused by the dengue virus, transmitted by the *Aedes aegypti* and *Aedes albopictus* mosquito, and has four serotypes namely DENV1 – DENV4.[1,2] Dengue is a world health problem since it is endemic in over 100 countries. The incidence rate and geographical spreading of dengue have increased in the last decades. According to WHO estimation, as many as 50 million people are infected with DENV and 25,000 people die because of dengue.[2,3] The clinical manifestations range of dengue is wide in humans, ranging from asymptomatic, fever, to plasma leakage and bleeding or severe dengue which can cause death.[4–6]

DENV infections are responded by the innate immune response and the Th1 adaptive immune response.[7,8] However, the type 2 immune response facilitated the DENV to continue replicating. Because of this, the type 2 immune response is one of the pathomechanisms of dengue.[9] Severe dengue is associated with innate immune response dysfunction,[10] excessive NK cell activity,[11] delayed Th1 response related to Th2 immune response,[10,12,13] and high levels of viremia.[11,14] Therefore, diseases with dysregulation of the immune response such as atopy, kidney disease, diabetes

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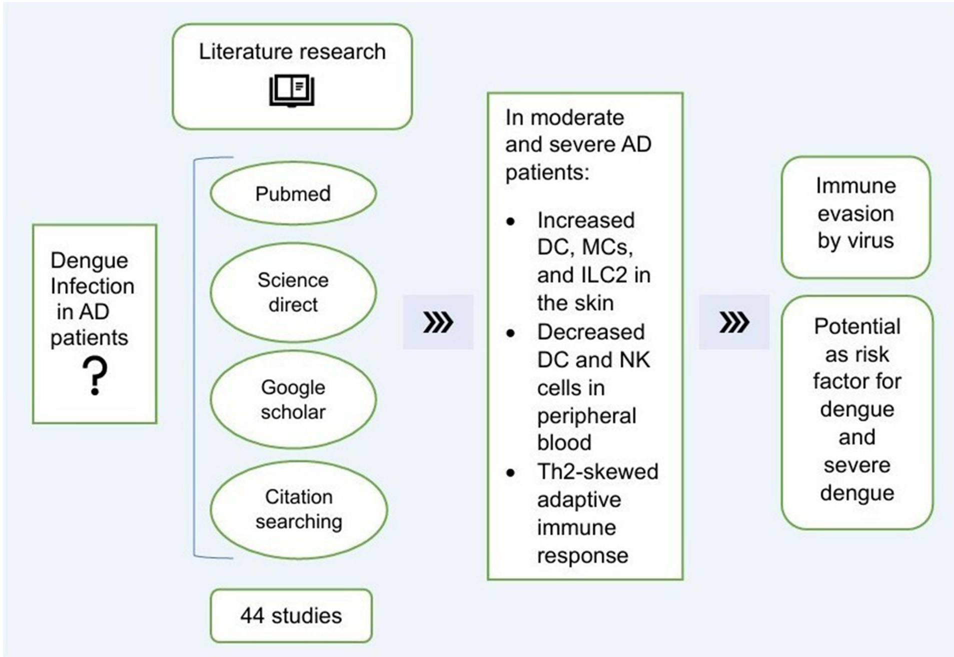
Graphical Abstract



mellitus, and obesity become risk factors for severe dengue.[15,16] Mosquito salivary proteins are also considered to have a part in dengue pathogenesis because they increase tissue cellularity at the site of the mosquito's bite which provides target cells for DENV replication and Th2 skewed immune response.[17–19]

In AD, which is one of atopic diseases, immune dysregulation is found to increase the risk of infection.[20] Type 2-skewed immune response is the hallmark of AD.[21] Allergic skin disease, which has the same basic disease mechanism as AD, is correlated with the severity of dengue. Pruritus, which is one of the symptoms of AD, is also associated with dengue.[22]

The immune dysregulation in AD potentially facilitates immune evasion by viruses that could increase dengue's incidence and severity. Studies regarding AD as a predisposing factor for dengue and its severity have not been widely described, however, there have been many studies explaining about immune profiles in AD and the pathomechanism of dengue. This article will discuss how the immune profile in AD could be a dengue predisposing factor and its severity. The understanding of the immune profile in AD, which is related to the immune response in dengue, can be used for further study to clarify the correlation between AD and dengue which is important in determining prognosis and management of dengue.

Materials and Methods

We reviewed the full text of the letters to the editor and original articles written in English about DC, macrophage, MC, ILC-2, NK cell, IFN, IL-4, IL-13, and Th2 profile of AD patients that could be an underlying factor for increasing dengue incidence and its severity, which are published within the last 10 years (January 1st 2014–July 31st 2024), with AD patients as the subject and healthy people as a comparison. We searched the literatures using PubMed database with keyword ((((atopic dermatitis[MeSH Terms]) OR (atopic eczema[MeSH Terms])) OR (atopic dermatitis[Title/Abstract])) OR (atopic eczema[Title/Abstract])) AND (((((((((((((((((((((((((((((((immune response, innate[MeSH Terms]) OR (adaptive immune response[MeSH Terms])) OR (cell, dendritic[MeSH Terms])) OR (cell, dermal dendritic[MeSH Terms])) OR (cell, epidermal dendritic[MeSH Terms])) OR (mast cells[MeSH Terms])) OR (cell, natural killer[MeSH

Terms])) OR (alpha interferon[MeSH Terms])) OR (interferon gamma[MeSH Terms])) OR (interleukin 4[MeSH Terms])) OR (interleukin 13[MeSH Terms])) OR (balance, th1 th2[MeSH Terms])) OR (cell, th1[MeSH Terms])) OR (cell, th2[MeSH Terms])) OR (innate immune response[Title/Abstract])) OR (adaptive immune response[Title/Abstract])) OR (dendritic cell[Title/Abstract])) OR (DC[Title/Abstract])) OR (DC-SIGN[Title/Abstract]))) OR (macrophage[Title/Abstract])) OR (mast cell[Title/Abstract])) OR (MC[Title/Abstract])) OR (innate lymphoid cell[Title/Abstract])) OR (ILC[Title/Abstract])) OR (natural killer cell[Title/Abstract])) OR (NK cell[Title/Abstract])) OR (interferon[Title/Abstract])) OR (IFN[Title/Abstract])) OR (interleukin 4[Title/Abstract])) OR (interleukin 13[Title/Abstract])) OR (th1[Title/Abstract])) OR (th2[Title/Abstract])) AND ((fft[Filter]) AND (humans[Filter]) AND (2014/1/1:2024/7/31[pdat]) AND (English[Filter])). We also searched literature from Google Scholar, citation searching, and the Science Direct database with keywords atopic dermatitis AND (dendritic cell OR macrophages OR mast cell OR natural killer cell OR innate lymphoid cell OR interferon OR interleukin OR T-helper) in addition to PubMed database.

Results

We reviewed 44 articles that describe immune profiles of AD patients that could be predisposing factors for dengue. The flow of our literature research is described in PRISMA flowchart (Figure 1). We resumed from those articles showing that there were innate immune dysregulations in lesional and non-lesional skin, and also in peripheral blood AD patients, especially in moderate and severe AD patients. There were M2-macrophages and DCs infiltration with increased DC-SIGN expression and an increased MCs number in lesional and non-lesional AD skin patients.[23–30] In contrast, the number of DCs in peripheral blood severe AD patients decreased[31] (Tables 1 and 2).

The ILC2 as one of some innate immune systems were increased in AD skin lesions.[32,33] In peripheral blood AD patients, their number decreased but was still higher in ILC proportion.[31,34] There were also decreased levels and alterations in type-1 interferon which is produced by innate immune cells[35,36] (Table 3). Other innate immune dysregulations were in the number and function of NK cells. There was an increase in NK cell numbers in skin AD patients. In contrast, there was a decrease in NK cell number expression in peripheral blood with a high expression of skin-targeted NK cells. There was also a reduction of NK cytotoxic functions and an enhancement of resting-NK cell subpopulation[37–44] (Table 4).

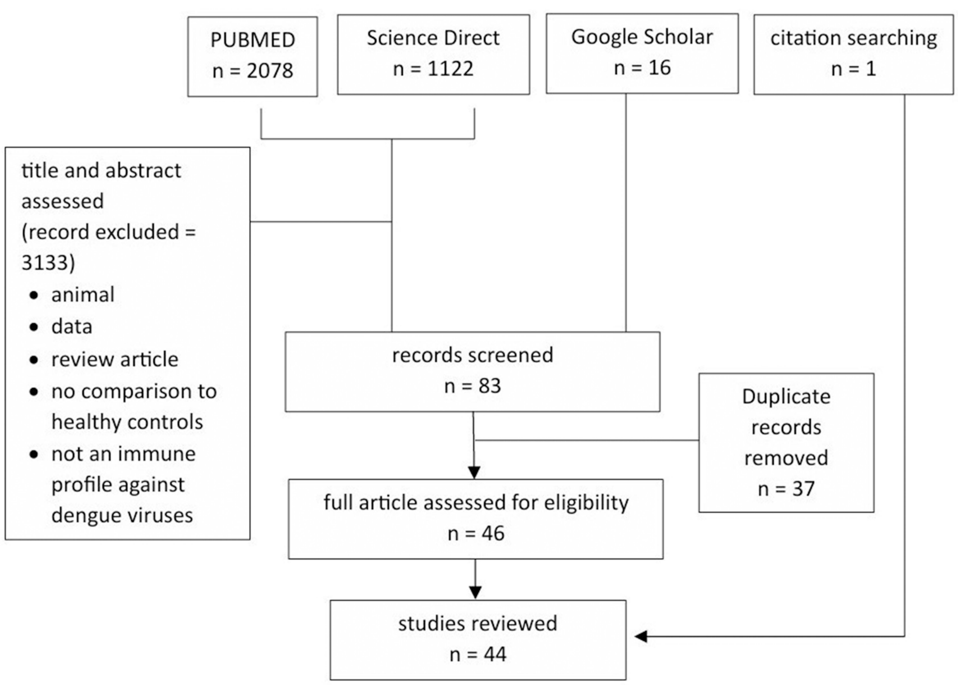


Figure 1 PRISMA flowchart.

Table 1 Summary of DCs and M2-Macrophages Profile in AD

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Zhang et al (2016)[23]	DC-SIGN expression on DCs from lesional skin biopsies by confocal microscope and flow cytometry; mild(5) and severe(5) adult AD patients; age and sex-matched healthy control subjects.	DC-SIGN increase in AD skin lesions especially in severe AD.
Guttman-Yassky et al (2019)[24]	Immunohistochemistry and RT-PCR of genes and protein expression on tape stripe of lesional and non-lesional skin; Moderate severe AD toddler patients (n=21); healthy (n=30).	Dendritic cell (FCεRI and OXO ligand receptors) and Th2 genes (IL13 and IL4) increased in lesional and non-lesional skin AD.
He et al (2020)[25]	Single-cell Ribonucleic acid (RNA) sequencing of lesional and non-lesional skin biopsies; Moderate to severe AD patients (n=5); healthy control subjects (n=7).	Inflammatory DCs proliferation ($CD1A^+FCER1A^+$) and T Cells that expressed type 2 cytokine ($IL13^+$) were found in the AD skin lesion.
He et al (2021)[26]	qRT-PCR, and RNA-sequencing of lesional and non-lesional tape stripe; Moderate-severe adult AD patients (n=20); Psoriasis (n=20); healthy volunteers (n=20).	Increased dendritic cell level (CD11b, DC-SIGN, IL3RA) and Th2 skewed (IL-13, IL-10, IL-31, CCL13, CCL17/TARC, CCL22, CCL24/ eotaxin-2, CCR4, and TNFRSF4/OX40) in lesion and non-lesional AD skin
He et al (2021)[27]	Immunohistochemistry and Real Time-PCR (RT-PCR) of lesional and non-lesional skin biopsies and blood; European American adult patients with AD (n=61) (mild:20; moderate: 17; severe 24), healthy control subjects (n=20).	Increased $DC\text{-}LAMP^+$ infiltrate AD skin lesions, and increased level of Th2 cytokines genes expression in both lesion and non-lesional in all severity AD, but mild AD primarily showed at the skin lesion.
Mitamura et al (2023)[28]	RNA-sequencing and visium array on lesional and non-lesional skin tissues; adult moderate to severe AD patients (n=7); healthy control (n=6).	High expression of CCL13 and CCL18 on M2 macrophage (CD163 and MRC1) and CCR7- DCs in the lesion skin from AD patients.

Table 2 Summary of MCs Profile in AD

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Luo et al (2022)[29]	H&E and TB staining; Pediatric AD patients (n=15); healthy control (n=15); normal skin tissues from plastic surgery.	Increased MCs in AD skin lesion.
Moon et al (2024)[30]	Immunohistochemistry skin biopsy after cowhide and histamine provocations; adult moderate-severe AD patients (n=10); psoriasis (n=10); Chronic Spontaneous Urticaria (n=11); Healthy control (n=12)	The number of MCs in non-lesional AD skin is twice as much as in healthy skin and induces prolonged itch in cowhide provocation

Table 3 Summary of ILCs and Type-1 Interferon Profile in AD

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Jin et al (2024)[31]	RNA sequencing on peripheral blood; severe AD patients (n=12); healthy controls (n=6).	Increased proportion of ILC-2 and Th2 cells, but decreased NK cell count with compromised cytotoxicity and decreased DC counts with Th2-DC profile in peripheral blood severe AD patient.
Bruggen et al (2016)[32]	Immunofluorescence ILC in situ staining of lesional skin biopsies; adult AD patients (n=13); psoriasis (n=13); healthy control (n=10).	Increased number of ILC-2 in AD skin lesions.
Alkon et al (2022)[33]	Flow cytometry, immune-histochemistry, and single-cell RNA sequencing on skin biopsies; adult AD patients or healthy individuals	Increased ILC in AD skin lesion that produced type 2 cytokine in the epidermis and upper dermis.

(*Continued*)

Table 3 (Continued).

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Čelakovská et al (2024)[34]	Flow cytometry on peripheral blood; Adult moderate-severe AD patients: (n=77); healthy control (n=40).	ILC-2 decreased in peripheral blood AD patients.
Ospelnikova et al (2017)[35]	Enzyme-linked immunosorbent assay (ELISA); acute moderate-severe AD patients (n=15); healthy people: (n=14)	Decrease in levels of type I IFN and IFNγ in stimulated blood of AD patients.
Karmon et al (2023)[36]	RNA-sequencing of AD lesional tissue (n=27); AD non-lesional (n=27); psoriatic lesions (n=28); psoriatic non-lesional (n=28); healthy control sample (n=38)	Altered RNA editing prevents IFN activation in AD skin lesions.

Table 4 Summary of NK Cells Profile in AD

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Mack et al (2020)[37]	In vitro stimulation assay and flow cytometry of peripheral blood and RNA-sequencing of lesional biopsies; moderate-to-severe AD and healthy volunteers as a control	Increased NK in skin lesions, but decreased NK cell count in peripheral blood AD patients. There is a change in the NK subpopulation, it lacks natural cytotoxicity receptors
Mobus et al (2021)[38]	Immunofluorescence staining and Digital cytometry of lesional and non-lesional skin biopsies; moderate to severe AD patients (n=57); healthy controls (n=31).	Increased NK cells in AD skin lesion, but a decrease in activated and an increase in resting NK cells in both lesional and non-lesional skin.
Wang et al (2023)[39]	RNA-sequencing of PBMCs; moderate-severe adult AD patients (n=56); healthy individuals (n=30)	Increased expression of the Th2/Th22 in peripheral blood moderate-severe AD patients, but TGF-β signaling and NK-cell signaling were decreased.
Worm et al (2023)[40]	Mass cytometry peripheral leucocytes; adults moderate AD patients (n=20); severe AD (n=20); healthy control (n=20).	Peripheral blood NK cells decreased in AD.
Bai et al (2024)[41]	Single-cell RNA sequencing analysis; adult psoriasis patients (n=28); contact dermatitis (n=18); mild-severe AD (n=24); healthy individuals (n=5)	Increased numbers of activated natural killer cells and CD4+ T memory cells in AD skin lesions.
Luo et al (2024)[42]	Immunofluorescence, RT-PCR, flow cytometry on skin and PBMCs samples; moderate to severe AD patients: children, adults, and elders; and age-matched healthy controls	In AD patients, there was an increased NK cell-related gene in skin lesions, but decreased in peripheral blood, expanded CLA+ Th2 T cells in blood, and increased macrophage-related genes in blood and skin lesions.
de Lima et al (2024)[43]	Flow cytometry on peripheral blood and immunohistochemistry of skin samples; Adult mild-severe AD patients (n=44); healthy non-AD volunteers (n=27)	High expression of CD56bright (CD56+CD16–) and CD56dim (CD56+CD16+) NK cells in peripheral blood severe AD, suggesting high skin targeting NK cells.
Ochayon et al (2024)[44]	Flow cytometry of peripheral blood; mild-severe AD children, adult peripheral blood mononuclear cells (PBMCs) as control	Peripheral blood NK of children with severe AD shows decreased cytolytic function and increased production of inflammatory cytokines.

There were also dysregulations in adaptive immune response in AD. There were gene up regulations and increased levels of IL4 and IL13 cytokines as the main cytokines in AD pathogenesis[45–53] (Table 5). Other cytokines and chemokines increased that reflect the Th2 skewed adaptive immune response also occurred in AD patients[54–67] (Table 6).

Discussion

Innate Immune Dysregulation

Dendritic Cells and Macrophage M2 Infiltration in the AD Skin

The DENV enters the human body through the skin by mosquito bites. DCs, Langerhans Cells (LC), and macrophages, which are innate immune cells, are some of the target cells for Dengue virus in the skin. Dengue virus replicates in those

Table 5 Summary of IL4 and IL13 Levels as Main Cytokines of Th2-Adaptive Immune Response in AD

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Totsuka et al (2017)[45]	Bio-Plex Protm Human Chemokine Panel 40-Plex; AD patients (n=9); healthy control (n=9)	Increased IL-4 serum level in AD patients.
Tsoi et al (2019)[46]	RNA-sequencing of lesional and non-lesional skin biopsies; AD patients, psoriasis patients, and healthy controls (n=147)	The IL-13 gene was a marker in AD skin patients.
Wang et al (2020)[47]	Multiplex immunoassay; AD patients (n=1312): childhood (n=400); young adulthood (n = 411); late adulthood (n=192); elderly (n=309); healthy control (n=60)	High IL4 serum levels of IL-4 in AD patients of all ages.
Rojahn et al (2020)[48]	RNA-sequencing and proteomic levels analysis; skin suction blistering: AD patients (n=4); healthy controls (n=5); full thickness skin biopsies: AD patients (n=4); healthy control (n=2)	Upregulation IL13 in AD skin patient.
Acevedo et al (2020)[49]	Flow cytometry and DNA methylation analysis of PBMC; Adult AD patients (n=10); healthy control (n=10)	Increased IL13 mRNA expression in CD4+ CLA+ T cells from AD patients.
Miranda et al (2021)[50]	Immunohistochemistry, moderate-severe adult AD patients (n=20)	Increased IL13 expression on moderate-severe AD skin lesion
Alkon et al (2023)[51]	Single-cell RNA sequencing of skin biopsies; Adult CNPG patient (n=7); AD (n=5); healthy control (n=4).	Strong IL-13 gene expression in AD skin lesions.
Wiegmann et al (2024)[53]	qPCR of skin biopsies; adult AD patient (n=17), Chronic nodular prurigo (CNPG) (n=14); healthy controls (n=10)	IL-4, IL-13 and IL-RA1 upregulation in AD skin lesion biopsy.
Xuan et al (2024)[52]	Mendelian randomization analysis, Quantitative-PCR (qPCR) of PBMCs; AD patients and healthy volunteers (n=4)	IL-13 gen was upregulated in both lesional skin biopsies and peripheral blood AD patients.

Table 6 Summary of Other Th2-Skewed Adaptive Immune Response in AD

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Czarnowicki et al (2015)[54]	Flow cytometric of peripheral blood; adult severe AD patients (n=42); healthy subjects (n=25)	Increased skin homing Th2/TC2 subsets frequencies and decreased Th1/TC1 in severe AD peripheral blood.
Noda et al (2015)[55]	RT-PCR and immunohistochemistry of lesional and non-lesional skin biopsies; adult European-American AD patients (n=25); Asian AD patients (n=27), European-American psoriasis patients (n=10); healthy subjects (n=27)	Profile genotype Asian and European-American patients with AD is Th2-skewed.
Brunner et al (2017)[60]	Proteomic assay of peripheral blood; Moderate-severe AD patients (n=59); psoriasis (n=22); healthy controls (n=18).	Increased Th1 and Th2 marker protein in AD serum patients.
Sanyal et al (2018)[61]	RNA-sequencing of lesional and non-lesional skin biopsies: adult African-American chronic AD patients (n=15); European-American chronic AD patients (n=15); healthy controls (n=16)	Increased Th2 gene expression in lesional and non-lesional skin biopsy European-American and African American AD patients.
Brunner et al (2018)[62]	Microarray, RT-PCR, and fluorescence microscopy of lesional and non-lesional skin biopsies; infants and young children (n=19); age-matched control subjects (n=18); adults (n=20); control skin (n=11)	Increased expression of Th2 markers and chemokines in skin lesion biopsy children and adult AD patients and decreased expression of Th1 children AD patients.
Pavel et al (2020)[63]	Skin and blood proteomics analysis; RNA sequencing of lesional and non-lesional skin; Moderate-severe adult AD patients (n=20); healthy individuals (n=28)	Increased Th2, Th1, Th17, and Th22 in lesional and non-lesional skin moderate-severe AD.
Tsoi et al (2020)[64]	RNA-sequencing, in vivo, and histological assays of non-lesional, acute and chronic AD skin lesions; AD patients (n=11); healthy controls (n=38)	Increased expression of the Th1, Th2, Th17 genes appears in non-lesioned which increases in acute and chronic lesions AD skin biopsy.

(*Continued*)

Table 6 (Continued).

Ref. (Year)	Methods /Samples/Subjects	Immune Profile
Czarnowicki et al (2020)[65]	Stimulation of blood cell populations and flow cytometry; Moderate-severe AD patients: infants and toddlers (n=39); children (n=26); adolescents (n=21), adults (n=43) healthy age-matched control (n=24-30 in each group)	Decreased Th1/Th2 ratio in peripheral blood in all ages AD patients.
Renert-Yuval et al (2021)[66]	RNA-sequencing, RT-PCR, immunohistochemistry of lesional and non-lesional skin biopsies; Moderate-severe AD patients: Infant (n=17), children (n=10), adolescent (n=14), adult (n=13), healthy control (n=46)	Th2/Th22 -skewed gene profile in the skin of all AD patients.
Pavel et al (2021)[67]	RNA-sequencing of lesional and non-lesional tape stripe; moderate-severe infants/toddlers AD patients (n=19); healthy controls (n=17)	Th2 dysregulation in AD lesion and lesional skin and lack Th1 skewing in infant/toddlers AD patients.
Mobus et al (2021)[56]	mRNA sequencing of skin biopsy; moderate-severe AD patients (n=59); healthy controls (n=31)	Type 2 cytokines gene dominated lesional and non-lesional skin AD.
Wu et al (2023)[57]	Magnetic Luminex assay; Adult moderate-severe AD patients (n=125); normal controls (n=60)	Th2 serum biomarkers increased in Chinese moderate-severe AD.
Del Duca et al (2023)[58]	RT-PCR of serum; Moderate-to-severe AD patients: infants (n=20); children (n=39); adolescents (n=21); adults (n=20); age-appropriate controls (n=83).	Increased Th2-related protein in all moderate-severe AD patients, but Th1-related protein serum increased only in children and adults.
Facheris et al (2023)[59]	RNA sequencing, RT-PCR, and immunohistochemistry of skin biopsies and blood; Adult Onset AD (n=15); Pediatric Onset AD (n=15); healthy controls (n=15)	Adult onset AD and Pediatric onset AD skin biopsy showed Th2/Th22 hyperactivation, but Th1 upregulations were seen only in Adult-onset AD.

cells and continues its life cycle.[68–70] The virus will attach its glycoprotein E to specific receptors on LC, macrophages, and DCs in the dermis and epidermis which initiate endocytosis.[7,71] The DENV receptors on target cells are Dendritic Cell-Specific Intercellular adhesion molecule-3 Grabbing Non-integrin (DC-SIGN), mannose receptor (MR), and C-type lectin domain family 5 member A (CLEC5A).[69,70,72]

After the DENV enters DCs, macrophages, and LCs, the viral antigen is recognized by pathogen-recognized receptors on the host cell and initiates the formation of type 1 IFN. Type 1 IFN initiates a signal to induce Interferon-stimulated genes (ISGs) which will create an antiviral state in the cell and surrounding cells, both infected and uninfected. ISG genes influence RNA production, protein turnover, and apoptosis, disrupting the life cycle and viral replication.[7,71] Type 1 IFN also induces Th1 activation which will strengthen the fight against the virus.[73] The infected cell host is also destroyed by NK cells to eliminate the virus.[74] But viruses do some immune evasion, and there is some immune dysregulation that permits virus to stay alive and do replication.[10,75]

On the lesional and non-lesional skin of AD patients, DC proliferation was found,[24,25,27] and expression of DC-SIGN increased.[23] Activated M2 macrophage was also increased in lesional and non-lesional skin from AD patients.[28] The increased levels of the cytokines IL4 and IL13 that occur in AD activate DC-SIGN and MR on DCs and macrophages.[76] The increased IL4 levels can cause macrophages and DCs to become permissive to dengue infection.[77]

Skin barrier disorder, which happens in AD, contributes to the type 2 immune response polarization. The skin barrier disorder in AD is due to a congenital deficiency of filaggrin protein[78,79] and environmental exposure.[80] Skin barrier disorder causes allergens and pathogens to enter the skin and stimulates DCs to produce thymic stromal lymphopoietin (TSLP), IL33, and IL25.[81] TSLP activates DCs and increases the number of DCs in the skin. Allergens that enter the skin due to barrier epithelial disruption also stimulate DCs activation. Those DCs direct differentiation of Th cell to Th2 cell by producing IL4 in lymph nodes. The activated Th2 cells produce more type 2 cytokines, IL4, IL5, and IL13.[82]

Even though there was an increased expression of DC-SIGN in the skin and decreased DC count in peripheral blood in AD patients,[23,31] AD has not been said to increase or decrease the incidence of dengue.[83] In contrast to AD, the decrease in the expression of DC-SIGN in peripheral blood DC in asthma and AR can reduce the risk of dengue infection. In a cohort study, it was found that the Hazard Ratio for asthma patients to get Dengue was 0.166 when compared to non-asthma.[84] In a cross-sectional study, the Odds Ratio for getting dengue in asthma and AR patients was 0.45 and 0.48. Internalization of DC-SIGN, which binds to House Dust Mites as the main allergen of asthma patients, causes a decrease in the number of DC-SIGN on the surface of DCs in asthma patients.[84,85]

Infiltration of Mast Cells

MCs are also related to dengue.[86] MCs are also some of the first innate immune cells that recognize the entry of the DENV into the skin. MCs can be infected by the DENV,[87] but virus replication does not occur in MCs.[88] The Dengue virus is found in the granules that are secreted by infected dengue MCs. These granules can enter the lymph vessels, suggesting that MCs may play a role in the systemic spread of the Dengue virus.[87]

MCs respond to the entry of the Dengue virus into the skin by secreting type I cytokines,[88] and chemokines CCL3, CCL4, and CCL5 which attract monocytes, T cells, and NK blood cells. MCs also secrete histamine and Vascular Growth Endothelial Factor (VEGF), which increase vascular permeability allowing for the entry of monocytes, T cells, and NK cells into the skin from blood vessels to help kill viruses.[77] In severe dengue, when the viral load increases due to failure of the immune response,[10] the number of MCs increases, along with elevated level of chimase which is only secreted by MCs.[10,86] Additionally, levels of VGEF and histamine rise, leading to increased blood vessel permeability.[86]

The increase in active MCs was found in AD lesional and non-lesional skin lesions,[29,30] which play two important pathogenesis roles: protective effect and promoting inflammation.[89] MCs maintain epithelial integrity and control Th2 inflammation.[90] The MCs are activated by allergen binding to the IgE in Fcε RI on MCs.[91] This binding stimulates MCs to produce IL4 and IL13 which direct Th2 activation. MCs also secrete histamine which causes vasodilation and increases blood vessel permeability as well as stimulate nerve endings which cause erythema, edema, and itching.[89]

The increase of MCs in AD may build protection against DENV infection.[88,92] However, DENV can infect MCs,[87] and there are other innate immune system defects in AD,[20,35,36,93] which results in ineffective elimination of the Dengue virus. A high viral load and an increase in the number of MCs potentially develop severe dengue in AD. In addition to MCs as the target cell of Dengue virus, mast cell degranulation in response to mosquito saliva can cause wheal. Wheals caused by the response to mosquito's saliva bring about flavivirus retention in the skin and increases replication.[94] The wheal diameter is also in line with the number of DCs and M2-macrophages at the bite site that could be dengue target cells.[17] M2-macrophages are not macrophages that have antiviral capabilities. M2-macrophages are different from classic macrophages (M1-macrophages) which have antiviral activity. M1-macrophages are activated by bacterial cell walls, lipoproteins, and IFN which phagocytose and produce Nitric Oxide to eliminate pathogens. M2-macrophages express arginase-1 and cytokine for tissue repair and are permissive to viruses.[68,95]

AD patients' skin is not healthy, both lesional and non-lesional. The non-lesional skin also showed prolonged itch responses and increased receptors for proteases and histamine expression on cowhide provocation.[30] Many people with AD also react to mosquito saliva as a type of allergen.[96] Allergic reactions to mosquito saliva positively correlate with the severity of AD,[97] leading to larger inflammatory wheals at mosquito bite sites and promoting DENV replication.[17,98]

Increment ILC-2

Other innate immune cells that are no less important are ILC1 which produces IFN-γ that induces ISG together with type I IFN to form an antiviral environment to eliminate viruses and direct the activation of Th1 adaptive immune cells. Activation of ILC2 helps Dengue virus to replicate, reach the bloodstream, and enhances viral infection in monocytes.[9]

In AD skin lesions, there is an increased number of ILC2.[32,33], which is also observed increased proportion of ILC2 in the peripheral blood of severe AD patients.[31] The increase in the number of ILC2s in AD is induced by Thymic stromal lymphopoietin production due to exposure to allergens or scratches on the lesion.[99] In addition, ILC2 is an innate immune cell that produces type 2 cytokines (namely IL4, IL5, and IL13) and directs the activation of Th2 cells which are not effective in virus elimination.[78] An increase in the number of ILC2s in AD can enhance the risk of dengue.

In contrast to the increase in type 2 cytokine in AD, the levels of type I IFN and IFN-γ were falling.[35] DC in AD also demonstrated a decrease in type I IFN production.[20,100] Although type I IFN gene expression increased in the lesional skin of AD, there are editing changes in the IFN RNA resulting in impairment of the innate immune system.[36] A decrease in type I IFN levels in AD potentially increases the risk of dengue and severe dengue.

NK Cells Alteration

The number of NK cells in lesional and non-lesional skin AD patients increased,[37,38,41,42] but NK-cell natural cytotoxicity and population were affected in severe AD.[43,44,101] Peripheral blood NK cells are deficient,[37,40,42] caused by migration to the skin[43] and increased NK cell death.[37] NK cells are cytotoxic ILCs that produce IFN-γ and other antiviral agents.[74] NK cells can even inhibit viral replication enhancement due to the Antibody-dependent enhancement (ADE) mechanism.[102] The decrease in the number of NK cells,[103,104] and impaired NK cell response in early infection of Dengue virus can increase the risk of severe dengue.[105,106]

Th2-Skewed Adaptive Immune Response

Viral-infected DCs and LC in the skin will go to the lymph nodes in the directions of CCR7 and CCL21 chemokines and initiate an adaptive immune response. DCs present viral antigens to CD4 cells via major histocompatibility complex (MHC) class I and II in lymph nodes. CD4 cells that bind to MHC class II of viral-infected DCs will be activated into Th1 cells according to the induction of type 1 IFN cytokines which are released by DCs. Th1 cells produce IFN-γ and TNF which activate macrophage phagosomes and strengthen cytotoxic CD8 cells. Th1 cells will also move to the medulla and induce B cells to produce anti-dengue IgM and IgG to neutralize viruses and strengthen complement and CD8 cells to destroy viruses.[8] CD8 cells that are formed and activated in the lymph nodes can also return to the skin at the initial infection site to clear the virus with the expression of CXCR3, CCR5, and the skin-homing marker cutaneous lymphocyte-associated antigen (CLA).[68]

If the immune response cannot control the virus, the virus will continue to replicate in the lymph nodes. As virus replication continues in the lymph nodes, the number of viruses increases and enters the blood circulation (viremia). In blood circulation, the virus infects blood vessel endothelial cells, monocytes, as well as macrophages, and DCs in other lymphoid organs such as the liver.[8,107] The virus can escape the immune system by inhibiting the induction of ISGs, so the virus can continue to replicate by infecting macrophages and DCs in the skin and lymph nodes.[75] Virus replication can even increase in secondary infections through the ADE mechanism.[8,71]

The viremia causes cell lysis and the production of inflammatory cytokines through complement activation and other immune responses which causes fever,[12] vascular permeability that can lead to shock,[11,108] and severe thrombocytopenia that can cause bleeding.[13,14] Bleeding in dengue infection is also caused by a decrease in coagulation factors due to liver damage.[14,73] Dengue, which is accompanied by bleeding and plasma leaking, is called severe dengue.[8]

The activation of the Th1 immune response can be inhibited by the IL4 as Th2 cytokine by increasing the GATA3 transcription factor which will suppress IFN-γ production and TBx21(T-bet) gene expression. On the other hand, IL12 as the Th1 cytokine can also reduce the Th2 immune responses by increasing the transcription factors T-bet and IFN-γ which reduce GATA3 expression and result in a decrease in IL4 cytokine production which inhibits Th2 cell activation.[109]

Polarization of the Th2 immune response is a hallmark in atopy patients. Allergens that enter the skin activate DCs and ILCs2 and direct the differentiation of Th cells into Th2 cells which produce IL4, IL5, IL13, and IL33 cytokines.[110–113] The increased expression of Th2 genes or Th2 cytokines level not only occurs in AD skin lesions[25,26,48,51–53,56,59,62,63] but also in non-lesional skin,[26,52,56,67] and peripheral blood AD patients,[33,39,45,47,49,52,54,55,57,58] especially moderate and severe AD patients.[27,50,56–58,60,63,65–67] Th1 adaptive immune response inhibition by Th2 polarization occurs in AD. There was a decrease in IFN-γ.[35] However, the disruption of the Th1 immune profile was variated. In pediatric AD patients, there was a decrease in Th1 expression.[60,67] In contrast, Th1 levels were found to increase in adult AD patients,[57,58,60,63,64] but the Th1/Th2 ratio remains decreased.[65]

The Th2 immune response to DENV is related to the dengue.[12,114] Severe dengue correlates with the impairment of the Th1 immune response which is related to a Th2 polarization immune response. The severity of dengue infection is associated with a decrease in T-bet levels. T-bet is a transcription factor for the formation of the cytokine IFN-γ.[115] The Th1 adaptive immune response impairment can be followed by an uncontrolled innate immune response by ILC and excessive NK cell activity.[103] Excessive NK cell activity is also associated with severe dengue.[11] The Th2 immune response polarization in AD may play a role in dengue and severe dengue pathogenesis.

Conclusion

Moderate-severe AD patients showed increased DCs, M2-macrophage, and MCs in the skin as they ported the entry of DENV. It may provide target cells for Dengue virus replication. Alteration in ILC2 and NK cells number and function, and also Th2 skewed immune response, which also occurs in moderate-severe AD patients facilitated immune evasion by Dengue virus. The innate and adaptive immune dysregulation in moderate and severe AD provides DENV target cells and facilitates virus immune evasion, which can be a predisposing factor for dengue and severe dengue. Further research needs to be carried out to clarify the correlation between AD and the incidence of dengue and severe dengue. AD on dengue needs to be considered in determining the prognosis and management of dengue infection.

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Disclosure

The authors declare that they have no financial interest or other conflicts of interest for this work.

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