Invited Review

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Primary Atopic Disorders: Expanding Field of Inborn Errors of Immunity

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Abstract

Inborn errors of immunity cover a broad spectrum of diseases from immune deficiency syndromes to hyperinflammatory conditions. Primary atopic disorders are a recent member of this spectrum as a group that embracing monogenic immune deregulatory diseases causing allergic and atopic phenotypes. Liable genetic alterations lead to signaling pathways and cellular functioning changes, which skew to type-2 immune responses. Elucidation of these pathways and identifying these disorders have the utmost importance, since early identification of some of these disorders significantly changes the prognosis and targeted treatments offer improved outcomes. In this review, these broad-spectrum of diseases including recent findings were categorized and affected pathways and clinical phenotypes were explained.

Keywords: Primary atopic disorders, field of inborn, immunity

Introduction

Inborn errors of immunity (IEI) are genetic diseases comprised of a wide range of immune-mediated phenotypes including infections, autoimmunity, autoinflammation, susceptibility to malignancy and atopy. Those IEI associated with significant atopy- whether the other immune comorbidities are noted or not, are proposed to be termed as primary atopic disorders (PADs) (1).

The primary causes of allergic disease coalesce around immune cell-intrinsic and skin barrier abnormalities. PADs caused by mutations in genes impacting the skin barrier and regulation of the type II, or allergic, immune response have been well described. Immune-mediated mechanisms can include abnormal T-cell receptor (TCR) or cytokine signaling, immune tolerance breakdown, and irregularities in mast cell function (Figure 1). Our knowledge of the full spectrum of PADs is limited by the referral biases leading to reports of cohorts. However, more severe, early-onset allergic disease, autoimmune or infectious comorbidities, non-immune syndromic comorbidities, and atypical clinical courses are all red flags of PADs (1). It is vital for healthcare providers to be skilled in identifying PADs and to offer effective, and sometimes precision treatment choices (2). Although most severe cases are usually associated with monogenic causes, many patients with PADs demonstrate more benign phenotypes as well. Even amongst carriers of the same mutation, some people do not show any symptoms associated with the disease; others demonstrate benign symptoms that can be managed with conventional therapy, and yet others can have severe, difficult-to-treat symptoms for whom which targeted treatments might lead to better outcomes. This incomplete penetrance and variability in the expression of the disorders is the rule, not the exception, for many PADs (3). Many PADs can also be managed similarly to common allergic disorders. However, precision treatments such as monoclonal antibodies or Janus Kinase (JAK) inhibitors can be helpful in resistant cases, which will be described in more detail in the later sections.

In this review, we provide an update regarding novel PADs or insight into previously known PADs in subtopics based on their molecular and cellular mechanisms and aim to encourage clinicians to be vigilant in identifying these rare conditions.

The Omenn Syndrome (OS) Phenotype

Unlike most other PADs, the phenotype of erythroderma, atopic dermatitis (AD)-like rash, lymphoproliferation, eosinophilia and high immunoglobulin E (IgE) is seen in OS, is the result of "leaky" severe combined immune deficiency (SCID), whereby a few T-cell clones emerge in the context of what otherwise appears like SCID, and oligoclonally expand (4-7). OS, while very rare, tends to present after about 2-3 months, but before 1 year of age, and is not tied to allergen-driven atopic disease.

The CBM Complex in Rare and Common Atopic Disease

Activation and differentiation of T-cells occur after stimulation of T-cell receptors. When there is a disruption in this signaling pathway, abnormal activation results in immune regulation failure and differentiation skewing. One example is CADINS [CARD11-associated atopy with dominant interference of nuclear factor kappa B (NF-kB) signaling]. CARD11 protein is a member of the CBM (CARD11-BCL10-MALT1) signalosome complex. Complete loss of function mutations in the CBM complex result in severe immune deficiency (4,5). Complete loss of function of a gene occurs when the protein is not expressed at all, or the expressed protein does not have any function- this is often associated with such severely impaired cellular function that atopic disease cannot occur. *MALT1* loss-of-function (LOF) mutations leads to severe immune deficiency, atopy, failure to thrive and mucosal inflammation (6,7). On the other hand, hypomorphic mutations cause partial loss of a gene function. Heterozygous, hypomorphic, and dominant negative mutations in *CARD11* lead to AD, asthma, food allergy, eosinophilic esophagitis (EoE) and allergic rhinitis (8). The mechanism behind this phenomenon is not likely related to NF-kB activation as none of the patients with mutations in downstream NF-kB pathway genes show atopic features (9-12). Of note, common MALT1 variants are associated with risk for allergies (13,14).

Several reports have suggested that dupilumab, a monoclonal antibody against IL-4 and IL-13, is effective in CADINS patients and other primary and common atopic disorders (15-18). CARD14 is a member of the Caspase recruitment domain-containing (CARD) protein family and complexes with BCL10 and MALT1 in keratinocytes and epithelial and mucosal tissues (19). While gain of function mutations in CARD14 lead to psoriatic autoinflammatory skin disease and NF-kB activation (5,20,21); hypomorphic, dominant negative (DN) *CARD14* mutations disrupt barrier function and impair NF-kB activation and antimicrobial peptide production, leading to severe eczema and other atopic features, along with recurrent bacterial and viral skin infections (19). Common CARD14 variation also regulates epidermal filaggrin levels - a key skin barrier protein whose loss contributes perhaps more substantially to the risk for atopic dermatitis than any other genetic factor (22).

CARD9 complexes with BCL10 and MALT1 in dendritic cells, macrophages, and neutrophils (21). It facilitates response to pattern recognition receptors and further activates the NF-kB pathway. Patients deficient in CARD9 are susceptible to mucocutaneous and systemic fungal infections and exhibit eosinophilia and elevated serum IgE (19). Common heterozygous variants in *CARD9* are associated with an increased risk of allergic bronchopulmonary aspergillosis (ABPA) (23,24).

Antigen Receptor Signaling and Actin Reorganization Defects Associated with Atopy

TRAF3 is an adaptor protein that plays multiple roles in various intracellular signaling cascades and acts as a negative regulator of cytokine and B-cell receptor signaling NF-kB2 pathway in B cells, and a positive regulator of TCR and certain TLR signaling. Interestingly, haploinsufficiency of TRAF3 has recently been described to lead to variably penetrant B-cell-mediated autoimmunity, lymphoproliferation, humoral immune deficiency with bronchiectasis, atopic and autoinflammatory diseases (25). A variant in TRAF3 in a patient with herpes simplex encephalitis (26) has been shown to be a relatively common variant not associated with viral infection per se, but it does appear to be a risk allele for a number of immune-mediated phenotypes.

Another PAD caused by disruption of TCR signaling is CARMIL2 (RLTPR) deficiency. CARMIL2 is an actin-uncapping protein specific to lymphoid lineage and essential for stimulation through CD28 and Treg development (27). It also plays roles in actin polymerization and cell polarity (28); therefore, it can be included in the subsequent section. Although it has a role in CD28 signaling, CARMIL2 deficiency differs from CD28 deficiency and regulates NF-KB signaling through PKC-θ (29). Autosomal recessive CD28-deficient patients have a high susceptibility to cutaneous HPV infections (30), whereas CARMIL2 deficiency will result in immunodeficiency with broad susceptibility to various pathogens, including HPV, and accompanied by eczematous dermatitis, food allergy, asthma, EoE, allergic rhinitis, EBV positive smooth muscle tumors, and inflammatory bowel disease (28,29,31-33).

Immune Disorders Caused by Cytoskeletal Dysfunction

After TCR stimulation, cell activation via the immunologic synapse and proliferation relies on actin polymerization and cytoskeletal rearrangement. Defects in one of the proteins involved in this step result in immune deficiency and immune dysregulation syndrome, which commonly come along with allergy, eczema associated

with petechia, autoimmunity, neoplastic manifestations and bleeding problems (4,34). One of the most well-known diseases in this group is Wiskott-Aldrich syndrome, caused by X-linked mutations in the Wiskott-Aldrich syndrome protein (WASP). Upon activation, WASP is released from WIP (WASP Interacting Protein) which causes substantial changes in the migration and proliferation of the cells (35). Biallelic loss of function mutations in *WIPF1*, *ARPC1B* and *ARPC5* cause a similar phenotype to WAS which presents with combined immunodeficiency, recurrent infections, autoimmunity, allergies, bleeding problems, eczema and high IgE (36-39). DOCK8 is another protein that is essential for WASP function by stabilizing WIP. DOCK8 deficiency manifests as susceptibility to viral infections, eczema, high IgE, autoimmunity, and neoplastic transformation (40). Serine/threonine kinase 4 (STK4) has regulatory roles in apoptosis and cytoskeletal rearrangement and its deficiency results in severe combined immunodeficiency phenotype like DOCK8 deficiency; however, although eczematous lesions and high IgE levels can be seen, the severity of atopic symptoms would be less in STK4 deficiency than DOCK8 deficiency (41,42). CDC42, on the other hand, is a GTPase regulating cell motility, migration, and polarization by organizing actin cytoskeleton. Germline mutations in this gene cause neonatal onset of pancytopenia, autoinflammation, rash and hemophagocytic lymphohistiocytosis (NOCARH syndrome) and have been reported to demonstrate atopic features like high IgE levels, rash and eczematous lesions and food allergies (43). ERM protein family (ezrin-radixin-moesin) crosslinks plasma membrane proteins to actin cytoskeleton (44). Moesin deficiency causes impaired chemotaxis and immunological synapse formation, resulting in X-linked immunodeficiency syndrome with atopic features manifesting with eczema, bacterial and viral infections, especially VZV and lymphopenia. Thrombotic thrombocytopenia was also reported (45). LOF mutations in the *NCKAP1L* gene cause the missing HEM1 protein, which has roles in mTORC2 activation and actin regulation by activating the Arp2/3 complex. Loss of this protein causes immunodeficiency syndrome with immune hyperactivation features. These patients were reported to have susceptibility to infections,

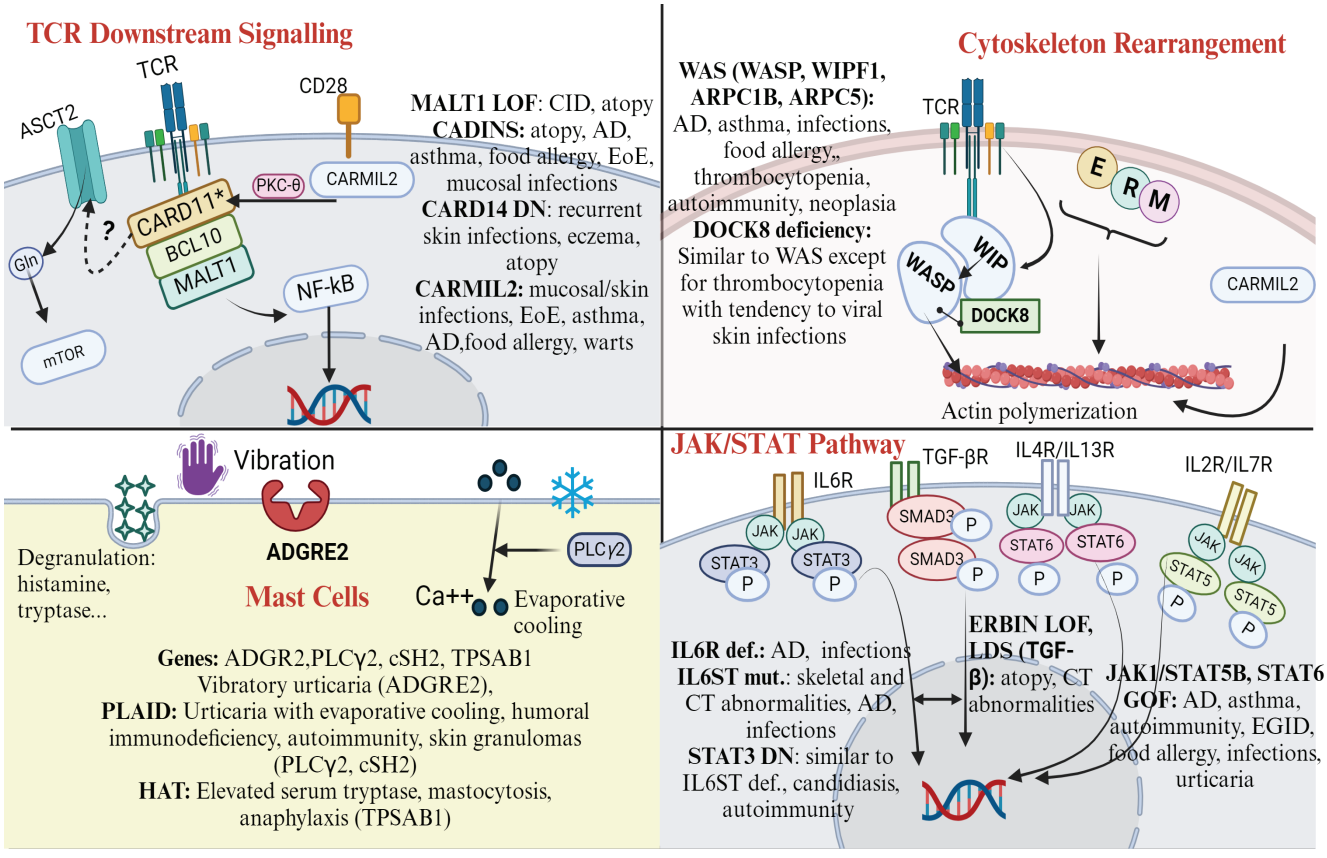

Figure 1. Overview of primary atopic disorders
AD: Atopic dermatitis, EoE: Eosinophilic esophagitis, DN: Dominant negative, Gln: glutamine, HLH: Hemophagocytic lymphohistiocytosis, EGID: Eosinophilic gastrointestinal disease, ERM: Ezrin-radixin-moesin, WAS: Wiskott-Aldrich syndrome, CT: Connective tissue, LOF: Loss-of-function, LDS: Loetz Dietz syndrome, GOF: Gain-of-function
*: CARD14 is found in keratinocytes, located in downstream of keratinocytes receptors; such as Dectin-1
This figure is created with BioRender.com

autoimmune diseases, and atopic diseases such as asthma and elevated IgE levels (46).

Theories for why atopic disease develops in these diseases include abnormal Treg function (47)- perhaps due to insufficient TCR stimulation-and intrinsic Th2 skewing similar to that seen in CBM complex mutation or others. Interestingly, DOCK8-deficient patients' lymphocytes undergo cytothripsis when migrating through tissue. The broken-up cells appear to serve as an adjuvant for tissue Th2 inflammation, suggesting another possible mechanism for allergy in patients with cytoskeletal defects (48,49).

Hematopoietic stem cell transplantation (HSCT) remains the standard of care for most actinopathy patients (50). Resolution of recurrent infections and eczema appear as a response to treatment. However, food allergy, autoimmunity and cancer development may persist (1). The persistence of autoimmunity and malignancy development might be associated with mixed or split chimerism status after transplantation and previous exposure to oncogenic viruses (51). In contrast, persistent allergies might be associated with long-lived recipient derived plasma cells (52). One critical point to consider is to transplant these patients at an early age, before end-organ damage or malignancy occurs, since the disease progresses more severely in late childhood and adolescence. Therefore, identifying these patients during infancy or toddler period has the utmost importance. Early in life they can only present with milder symptoms such as atopic dermatitis and recurrent mucosal infections. On the other hand, gene therapy offers promising results for treating WAS, as it has previously shown improvement in immune cell function and clinical symptoms (53).

Disturbances in JAK/STAT Signaling Pathway-Gain and Loss

JAK - signal transducers and activators of transcription (STAT) family includes seven transcription factors (STAT1, STAT2, STAT3, STAT4, STAT5A/B, and STAT6) and four receptor-associated kinases (JAK1, JAK2, JAK3, TYK2), which regulate various cellular functions, including immunity, growth, differentiation, and survival (54). Abnormalities in the JAK-STAT pathway have been implicated in the pathology of several immune-mediated inflammatory diseases, including atopic diseases (55).

One of the major pathways that is important among monogenic allergic diseases is the interleukin (IL)-6/STAT3 signaling pathway. Disruption of the IL-6-mediated immune response clinically associates with an attenuated acute phase inflammatory response and subsequent susceptibility to serious bacterial infections (56-59). Even neutralizing anti-IL-6 autoantibodies can lead to this phenotype (59-61). The association of allergy with IL-6 signaling-either in PADs or common association- is significant. Numerous common *IL6R* variants are associated with multiple atopic and asthmatic phenotypes (62). IL-6 receptor deficiency leads to atopic manifestations such as eczema, elevated IgE and eosinophilia, reduced inflammatory responses (including absent CRP), and recurrent skin and lung infections (63). While IL6R deficiency is limited to immune-mediated phenotypes, loss of gp130, encoded by *IL6ST*, has additional skeletal phenotypes due to the non-redundant role for other cytokines that signal through gp130. Recessive IL6ST deficiency leads to variable presentation of autosomal recessive hyper-IgE syndrome. In contrast, milder, DN *IL6ST* mutations lead to severe, destructive lung disease with pneumatoceles and bronchiectasis, frequently associated with Aspergillus infection or ABPA, staphylococcal lung infection, elevated IgE and eosinophilia.

Downstream of IL-6 receptor/gp130 are JAK1 and STAT3, while ZNF341 is a transcription factor that regulates *STAT3* expression (64,65). The overwhelming majority of heterozygous *STAT3* LOF mutations act in a DN fashion (66), a raft of immune and non-immune mediated multisystem disorders, including symptoms seen in IL6R and/or gp130 deficiency-eczema, eosinophilia, elevated IgE levels, mucocutaneous candidiasis, respiratory infections, lupus-like autoimmunity, structural lung disease and connective tissue abnormalities (66-68). Haploinsufficiency of *STAT3* may lead to a distinct disorder, including fatal invasive aspergillosis, allergic rhinitis, eosinophilic esophagitis and elevated IgE. However, it is of interest that conditional heterozygous $Stat^{+/-}$ mice have few immune-mediated phenotypes (69,70).

Phosphoglucomutase 3 (PGM3) deficiency due to biallelic hypomorphic mutations in *PGM3* can lead to profound allergic disease with severe AD, food allergy, asthma, EGIDs, allergic rhinitis, ABPA, and food-protein induced enteropathy syndrome accompanied by infectious, inflammatory, musculoskeletal and neurodevelopmental comorbidities. Some phenotypic similarities with IL6ST/STAT3/ZN341 deficiency may be explained by decreased N-glycosylation of gp130, leading to diminished surface gp130 expression (71-75).

One of the findings in STAT3 DN patients is evidence of abnormal TGF-β activity (76,77). This may help explain the phenotypic overlap of multisystem atopy and connective tissue abnormalities seen in ERBIN LOF and Loeys-Dietz syndrome (LDS), both impacting TGF-β signaling. The infectious phenotype seen in those two disorders is quite limited compared to STAT3 DN, leading to a rather unique "atopy + connective tissue abnormalities alone" phenotype (78,79).

The management of patients with JAK/STAT loss of function typically involves antimicrobial prophylaxis and immunoglobulin replacement to prevent infections, and

HSCT has also emerged as a potential treatment (58,80). Enhanced IL-4 receptor expression has been noted in STAT3 DN, ERBIN and LDS patients, explaining the excellent response to dupilumab in otherwise refractory atopic settings (81-84).

In contrast to the loss of function in the IL6/STAT3 pathway, patients with *STAT3* gain-of-function (GOF) develop marked classical autoimmune and lymphoproliferative phenotypes, with few connective tissue abnormalities, and little allergic disease except for eczematous dermatitis in a subset (85).

However, gain of function mutations in JAK1, and the downstream STAT5 and STAT6, lead to striking atopic phenotypes, depending on the specificity of the signals propagated by JAK1 or the given activated STAT (2,86,87). *JAK1* GOF mutations primarily manifest with marked eosinophilia and eosinophilic tissue inflammation, atopic dermatitis, autoimmunity and failure to thrive; phenotypes associated with *STAT6* GOF mutations encompass treatment-resistant atopic dermatitis, hypereosinophilia, eosinophilic gastrointestinal disease, asthma, elevated serum IgE levels, IgE-mediated food allergies, anaphylaxis, infections, growth impairment, and vascular brain malformations (88-91). This condition results from heterozygous missense mutations occurring in multiple protein domains of STAT6, primarily near the TF-DNA interface, which, by increasing electro-positivity, enhances STAT6's DNA binding and contributes to its gain of function pathology. STAT6 plays a crucial role in allergic inflammation processes. *STAT5* GOF mutations may result in immunodeficiency, hematologic abnormalities, and infection predisposition (2,86,87). Individuals carrying *JAK1* GOF mutations, leading to STAT5B phosphorylation, exhibit features such as allergic asthma, and peripheral and tissue eosinophilia resembling STAT5B GOF patients, yet distinguishably, they also manifest severe atopic dermatitis (2,92,93). STAT5 signaling role in atopic diseases is rather complicated. Somatic heterozygous GOF mutations in *STAT5B* occurring within the hematopoietic compartment have been shown to result in severe neonatal eosinophilia, urticaria, diarrhea, and granulomatous disease (87). Interestingly, the same *STAT5B* GOF mutation has been linked to leukemia and lymphomas, some involving eosinophilia. This finding suggests different outcomes for *STAT5B* GOF mutations; neonatal-onset somatic mutations do not seem to result in overt neoplasms over time, but instead appear to be associated with an inborn error leading to a PAD. Precision treatments using JAK inhibitors have proven highly effective in ameliorating clinical symptoms and immune biomarkers in individuals with *STAT5B* GOF, *STAT6* GOF and *JAK1* GOF mutations (2,88,89,94). Monoclonal antibodies like omalizumab (targeting IgE), dupilumab (targeting IL-4 and IL-13), reslizumab, benralizumab, and mepolizumab (targeting IL-5) have proven to be effective in treating eczema and other allergic symptoms; in some cases, HSCT can help restoring immune function and alleviating infection rates and dermatological issues, particularly when performed at a young age (95-98).

Monogenic Disorders Impacting Mast Cells

Mast cells are critical for the development of allergic reactions (84). Monogenic disorders affecting mast cell function form a distinct subset of PADs -especially when comorbid immune deficiency or dysregulation is lacking (4). Several disorders have been described to be associated with physical urticaria-though again differing from typical physical urticaria in that the phenotype is present from birth and lifelong. These include autosomal dominant familial vibratory urticaria -mast cell degranulation due to mechanical stress caused by a specific missense substitution in *ADGRE2* (encoding EMR2) identified in a Lebanese founder population (100). The disruption of EMR2 by mechanical stress is a normal process in mast cells but amplified in the affected patients. Interestingly, EMR2 can be cleaved by heterotetramers of alpha and beta tryptase (101), and individuals with increased copies of alpha tryptase are more prone to vibratory urticaria. Excess copies of alpha tryptase, caused by duplications of the alpha allele at *TPSAB1*, lead to Hereditary alpha-tryptasemia (HAT). HAT is relatively common (~5% of Caucasians) and this is explaining elevated basal serum tryptase in the overwhelming majority of individuals and also potentially increasing the risk for developing mastocytosis, anaphylaxis or both (102-104). Recent genome-wide association studies have shown that a locus linked to HAT is also associated with urticaria risk (105,106).

The historical term "familial cold urticaria" is used to refer to what is now called Familial Cold Autoinflammatory syndrome (FCAS) resulting from *NLRP3* mutations, which typically result in excessive IL-1 production (107). The cold-induced "urticaria" observed in these patients is only due to systemic, not local cooling, and leads to a neutrophilic urticaria-like rash distinct from typical mast cell degranulation. Different autoinflammatory disorders like FCAS can be associated with different risks -increased or decreased- for clinical and laboratory atopic phenotypes (108,109). True mast-cell mediated familial urticaria is the predominant phenotype in PLAID (PLCG2 associated antibody deficiency and immune dysregulation). Patients with PLAID experience pruritus and erythema upon exposure to evaporative cooling. Unlike typical cold urticaria, PLAID-related urticaria is presents from birth, persists throughout life, and is not triggered by the ice cube test. Deletions in the autoinhibitory cSH2 domain are associated with PLAID. These deletions paradoxically

lead to cellular anergy at normal body temperatures in cells expressing PLCγ2, resulting in poor B-cell class-switching and concurrent humoral immune deficiency, as well as autoimmunity due to loss of B-cell tolerance, which are variably observed in PLAID patients (110-112). Minor drops in temperature below physiological levels lead to spontaneous PLCγ2 activity, resulting in mast cell degranulation without receptor-ligand interaction. Similar activity in other myeloid cells may explain the formation of skin granulomas with body temperature drop in some patients (110,113).

Immune Dysregulatory Disorders - Tregopathies

Immune dysregulatory disorders associated with atopy and allergy are IPEX (Immune dysregulation-Polyendocrinopathy-Enteropathy-X-linked) and IPEX-like disorders. IPEX is caused by mutations in *FOXP3* gene, which is the main transcription factor for Tregs (114,115). Tregs are the main lymphocyte subset responsible for immune tolerance and control immune responses in the body (116). Impairment of Tregs leads to various autoimmune manifestations along with severe eczema, associated with Th2 reprogramming in this cell population (117). Patients also develop other allergic manifestations such as food allergies (118-120). Type of mutation in *FOXP3* causes different phenotypes of the IPEX disease. DNA-binding domain mutations lead to spontaneous multiorgan autoimmunity, whereas organ-specific autoimmunity originates from non-DNA binding domains and depends on environmental and other genetic factors as well (119-121).

CD25 is the receptor for IL-2 and marker for Tregs, also has a role in Treg maintenance (122,123). Loss of function mutations of *CD25* result in IPEX-like syndromes (124). IL-2 receptor transmits its signals via STAT5B, therefore, STAT5B deficiency also leads to IPEX-like syndromes (125). Unlike *STAT5B* GOF mutations, atopy in STAT5B deficiency is due to defective Treg function rather than hyperactivation of Th2 responses. These patients also have growth hormone insensitive dwarfism (126).

Epithelial Barrier Defects

Disruption of the epithelial barrier leads to atopy development possibly due to increased antigen exposure (4). Monogenic causes of epithelial barrier disruption are also included in PADs. Filaggrin is a barrier protein and loss of this protein by *FLG* mutations causes ichthyosis vulgaris, severe atopic dermatitis and food allergy (127-129). Desmosomes are part of the keratinocyte barrier and mutations in desmosomal genes (*CDSN*, *DSP*, *DSG1*) lead to allergic phenotype (130-132). The severity of the allergic and atopic phenotype again depends on the type of mutation in these genes. It can range from ichthyosis vulgaris to SAM (severe dermatitis - multiple allergies - metabolic wasting) (130,131). *SPINK5* encodes protease inhibitor for desmosomes and LOF mutations in *SPINK5* gene cause Comel-Netherton syndrome, manifests as desquamation, severe ichthyosis, bamboo hair, and recurrent infections in addition to atopy (133). Dupilumab and immunoglobulin replacement therapy are effective in the management of these manifestations (134-137).

Disruption of Th1/Th2 Counter-Regulation

IKAROS is a pleiotropic transcriptional repressor with a substantial role in lymphocyte differentiation. Gain-of-function mutations in *IKZF1* lead to Th2 skewing, and patients can develop allergic disease, asthma, eosinophilia, lymphoproliferation, and immune dysregulation. Enhanced repression of IFN-γ and Treg abnormalities may explain the Th2 skewing and predisposition to allergic disease (138).

Conclusion

PADs arise from genetic alterations that might affect variety of cell types and functions. Some of these diseases originate from aberrations of immune cell, caused by the loss or gain of functions of the different signaling pathways. In contrast, others are caused by disruptions in cytoskeletal rearrangement inside the cell, which lead to migration and differentiation problems. The main goal of this review is to raise awareness in clinicians to be wary of these disorders when there are multiple red flags such as early-onset, resistant atopic disease, elevated levels of eosinophils and IgE, and concomitant immunological abnormalities like autoimmunity and recurrent infections. We also aim to encourage researchers to study more about these diseases in depth by emphasizing the importance of understanding the disease mechanisms to develop efficient and targeted treatments.

Authorship Contributions

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