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Primary Atopic Disorders

Joshua D. Milner

Department of Pediatrics, Columbia University Irving Medical Center, New York, NY 10032, USA; email: jdm2249@cumc.columbia.edu

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Abstract

Primary atopic disorders describes a series of monogenic diseases that have allergy- or atopic effector–related symptoms as a substantial feature. The underlying pathogenic genetic lesions help illustrate fundamental pathways in atopy, opening up diagnostic and therapeutic options for further study in those patients, but ultimately for common allergic diseases as well. Key pathways affected in these disorders include T cell receptor and B cell receptor signaling, cytokine signaling, skin barrier function, and mast cell function, as well as pathways that have not yet been elucidated. While comorbidities such as classically syndromic presentation or immune deficiency are often present, in some cases allergy alone is the presenting symptom, suggesting that commonly encountered allergic diseases exist on a spectrum of monogenic and complex genetic etiologies that are impacted by environmental risk factors.

INTRODUCTION

TCR: T cell receptor

Much of the research on the genetics of atopic disease has focused on the hypothesis that allergy is a complex disease with common genetic underpinnings and specific environmental exposures. The pathways illuminated by this line of study have provided insight into the role of many of the genes anticipated by animal models of allergic effector biology (1). Another, nonexclusive, avenue that has begun to emerge more recently thanks to advances in genomic sequencing technology is the study of monogenic allergic diseases (2). These diseases can produce phenotypes much more striking in both severity and comorbidity than typical allergic disease, though the allergy can by and large be considered a severe form of typical allergic symptoms. The diseases also are remarkable for a lack of complete penetrance, providing potential opportunities to better study specific gene-environment interactions that could lead to allergic disease (3). While the number of patients with such disorders is not yet large enough to study on a population basis, it is an important open question whether the allergic phenotypes seen in monogenic diseases mirror common allergy in that the phenotypes have increased in recent generations as the result of Westernization.

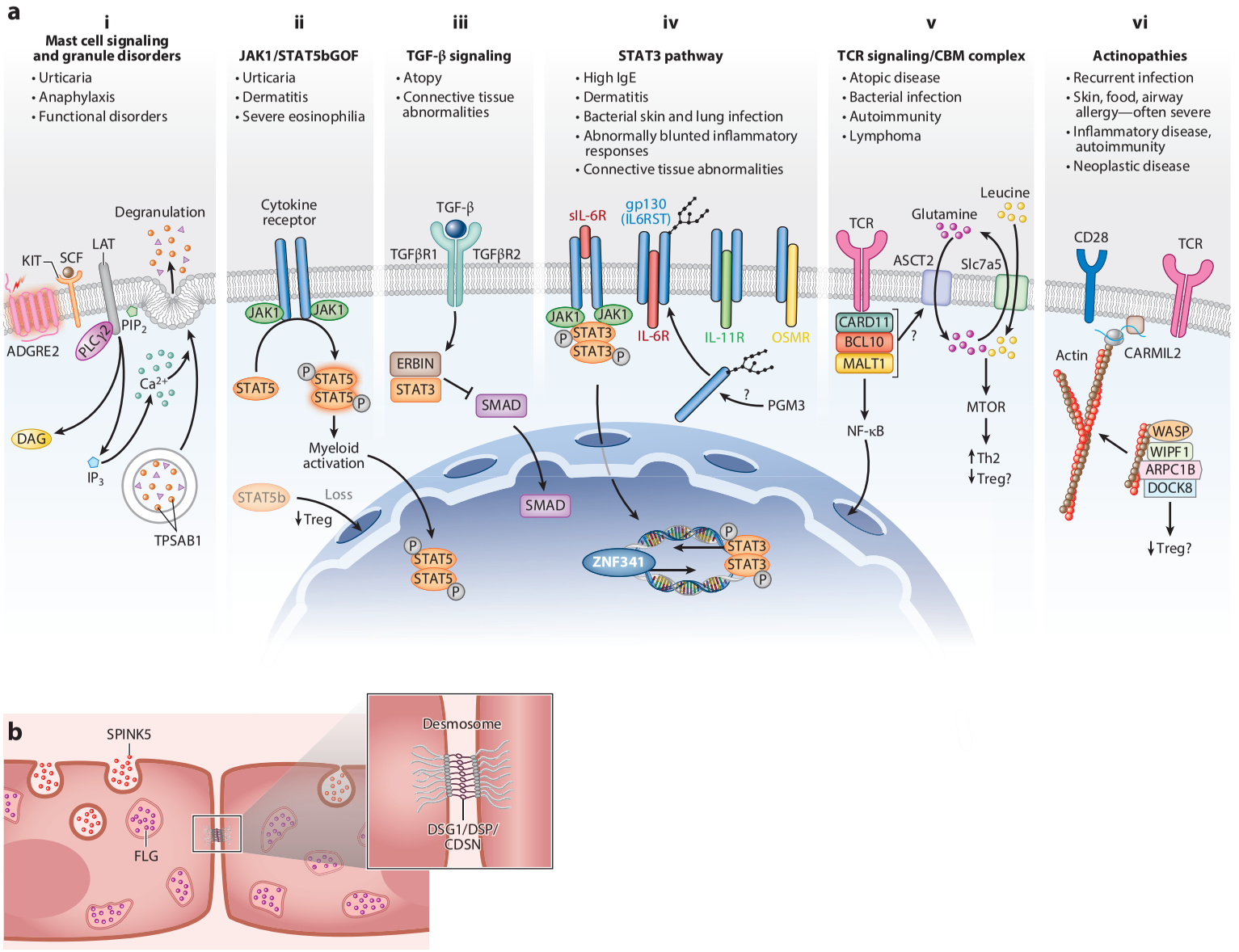
As these diseases have accumulated, a series of illuminating pathogenic pathways have coalesced—involving cytokine signaling, T cell receptor (TCR) signaling and actin dynamics, tolerance failure, intrinsic mast cell functions (**Figure 1*a***), and physical barrier function (**Figure 1*b***). In order to help distinguish allergic disease in the context of those with monogenic lesions from those that have other causes, the term primary atopic disorder (PAD) can be used to describe the condition of these patients (2). Patients with PADs may well have a primary immune deficiency as well, or a primary immune dysregulatory phenotype; however, to focus on allergic disease in these diseases of inborn errors of multiple pathways is critical both for patient care and understanding, as well as for research approaches.

In PAD cases where comorbid immune deficiency exists, the degree of impact of monogenic lesions on effector cell function can dictate the chances as to whether atopy will be present. As such, there are numerous examples of immune deficiencies so severe that hematopoietic stem cell transplantation is needed within the first year of life for survival, and in many cases, T cells may be lacking altogether, making it extremely difficult to mount an allergic response. However there are other examples of disease where mutations, often hypomorphic, allow for sufficient development of allergic effector cells but fail to fully prevent infection or pathogenic mechanisms that lead to allergic disease. Those disorders associated with substantial infection due to T cell defects, among others, are generally considered to be combined immune deficiencies (CID), to contrast with severe combined immune deficiencies (SCID), which result in the absence or near absence of T cell function. A subset of CID patients will develop atopic disease when the particular pathways that are partially ablated are normally responsible for preventing atopic disease (2).

In considering monogenic allergic disease, it is also important to separate the types of allergy one might observe, as they help define the clinical consequences of the underlying lesions and perhaps point to specific patterns of disease that can help identify the pathway or pathways involved. So for instance, marked IgE elevation might be associated with allergen-specific reactivity and defects of specific T and B cell tolerance pathways, chronic mucosal allergic inflammation such as eczema or eosinophilic gut disease might implicate barrier function defects, and urticaria or anaphylaxis in the absence of inflammation or antibody-mediated sensitization might point to aberrant intrinsic mast cell effector functions. The disorders described below are summarized in **Table 1**.

IMPAIRED TCR SIGNALING AND CYTOSKELETAL REMODELING

The association between allergic disease and immune deficiency is both across the board and focally enhanced in a number of disorders (4). One key determinant for whether allergic disease



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Schematic representation of pathways involved in primary atopic disorders. (*a*, *i*) In mast cells, mechanical stress can more easily activate ADGRE2, leading to degranulation, while PLAID mutant PLCγ2 can be activated by cold to lead to spontaneous calcium flux and degranulation. Increased alpha tryptase encoded by TPSAB1 leads to hereditary alpha tryptasemia. (*ii*) Activating mutations in JAK1 or STAT5b lead to myeloid-driven eosinophilia, dermatitis, and urticaria, while loss of STAT5b function leads to Treg defects and tolerance failure, which can include atopy. (*iii*) TGFβR1 or TGFβR2 activates SMADs, but ERBIN/STAT3 complexes normally prevent SMAD entry to the nucleus. Mutations of any of these genes are associated with connective tissue abnormalities and atopy. (*iv*) gp130 pairs with a variety of cytokine receptors to activate STAT3, which can upregulate ZNF341—which in turn upregulates STAT3. Loss of function along the entire pathway leads to distinct features of high IgE, atopy, and poor inflammatory responses. (*v*) The CBM complex is activated by antigen receptor and can control mTORC1 activation via control of glutamine transport. Hypomorphic mutations in this pathway can lead to viral skin infection, bacterial infection, and substantial atopic disease. (*vi*) Actin assembly downstream of TCR activation is critical for host defense and for adequate Treg function. Lesions in CARMIL2, WASP, WIPF1, DOCK8, and ARPC1B, all of which contribute to normal actin dynamics in one way or another, lead to recurrent infection in the pattern of combined immune deficiency, as well as substantial tolerance failures and atopic disease. (*b*) Structural proteins in keratinocytes such as filaggrin, or protease inhibitors such as SPINK5, as well as intercellular adhesion molecules such as CDSN, DSG1, or DSP all maintain barrier integrity in the outer layer of skin. Complete loss of function in any of them leads to ichthyosis or severe eczema, while milder mutations in FLG are risk factors for commonly encountered eczema. Abbreviations: CBM, CARD11/BCL10/MALT1; PLAID, PLCγ2-associated antibody deficiency and immune dysregulation; TCR, T cell receptor; Treg, regulatory T cell; WASP, Wiskott-Aldrich syndrome protein.

Th2: type 2 T helper

Treg: regulatory T cell

will be present in an immune deficiency is, as might be imagined, the presence of sufficient effector mechanisms to launch an atopic response. As such, patients lacking T cells who have SCID, for instance, will not be capable of developing allergic disease, lacking IgE or type 2 T helper (Th2) cells. Remaining allergic effectors such as eosinophils or type 2 innate lymphoid cells (ILC2s) do not appear to be sufficient to cause allergic pathology. However, when there is even a small leaky T cell population in patients with SCID, substantial homeostatic, oligoclonal expansion can occur, and the clinical presentation is termed Omenn syndrome (OS). These patients develop marked lymphoproliferation and organomegaly, elevated IgE despite the marked reduction in B cells, and severe inflammatory, erythrodermic skin disease with T cell infiltration that resembles the most severe cases of atopic dermatitis (5–8).

The allergic effector component of the OS phenotype has a number of potential explanations that may also apply to other disorders of limited TCR repertoire not as severe as OS. These include clonotypic gaps in regulatory T cell (Treg) specificity that cannot limit effector T cell responses (9–11); a lack of central tolerance due to poor upregulation of AIRE in the abnormal SCID thymus (12); and clonotypic gaps in high-affinity antigen-specific effector T cells, which

Table 1 Genetic mutations in primary atopic disorders

Altered process	Genes
Impaired TCR signaling and cytoskeletal remodeling	*CARD11*, *MALT1*, *WAS*, *WIPF1*, *ARPC1B*, *DOCK8*, *CARMIL2*
Altered cytokine signaling	*STAT3*^{DN}, *STAT1*^{GOF}, *STAT5B*^{LOF}, *STAT5B*^{GOF}, *JAK1*^{GOF}, *IL4RA*^{GOF}, *IL6ST*, *IL6R*, *TGFBR1*, *TGFBR2*, *ERBB2IP*, *ZNF341*
T cell repertoire restriction	*RAG1*, *RAG2*, *DCLRE1C*, *ADA*, *IL2RA*, *IL7RA*, *CHD7*, *LIG4*, *ZAP70*, 22q11del
Tolerance failure	*FOXP3*, *IL2RA*, *STAT5B*^{LOF}, *TGFBR1*, *TGFBR2*, *WAS*, *ARPC1B*, *MALT1*, *CARD11*, *STAT1*^{GOF}
Glycosylation	*PGM3*
Skin barrier disruption	*FLG*, *CDSN*, *DSG1*, *DSP*, *SPINK5*
Mast cell deregulation	*PLCG2*, *ADGRE2*, *TPSAB1*

Abbreviation: TCR, T cell receptor.

lead to weaker stimulation of a given antigen-specific naive T cell during priming, resulting in Th2 skewing (13), to be discussed further below.

In many ways, the repertoire disturbances of OS are a special case of syndromic atopy in the sense that the allergic disease is not allergen specific due to the marked repertoire restriction. However one potential mechanistic overlap may exist between OS and other PADs with intrinsic defects, specifically in the realm of TCR signaling.

The initial strength of TCR-peptide-MHC (pMHC) interaction can strongly contribute to the ultimate T helper fate of the naive T cell, in addition to, if not superseding, other costimulatory and cytokine cues more typically associated with T helper differentiation (14–20). Indeed hypomorphic germ line mutations of TCR signaling molecules, in contrast to knockout mouse models, in ζ chain of TCR-associated protein kinase 70 (*Zap70*); linker for activation of T cells (*Lat*); caspase recruitment domain family, member 11 (*Card11*); and others can lead to profound spontaneous atopic phenotypes (21–24).

CARD11 is a member of the CARD11-BCL10 (B cell chronic lymphocytic leukemia/lymphoma 10)-MALT1 (mucosa-associated lymphoid tissue lymphoma translocation gene 1) (CBM) complex, which links certain lymphocyte receptor engagement with downstream NF-κB and mTOR signaling (25, 26). Complete biallelic loss of CARD11 or BCL10 signaling leads to a combined immunodeficiency necessitating hematopoietic stem cell transplantation, while MALT1 loss of function (LOF) results in CID with variable expressivity of severe atopic dermatitis and other elements of tolerance loss such as inflammatory gut disease (27–32). Similar to that seen in the mouse, hypomorphic, dominant negative mutations in *CARD11* can result in substantial atopic dermatitis, elevated serum IgE, and other allergic phenotypes. Not all patients develop allergy, and in some cases, carriers have only allergic disease, which they eventually grow out of. There is also variably observed bacterial respiratory infection, viral skin infection, and autoimmunity, showing the pleiotropy of these types of mutations (33, 34).

The pathogenesis of allergic disease in MALT1 or CARD11 mutant patients may be multifactorial. Studies of hypomorphic CARD11 mouse models have suggested a numerical defect in Tregs due to poor TCR activation (24, 35). Further evidence for CBM complex–dependent MALT1 paracaspase activity in Tregs might also suggest a mechanism for loss of tolerance (36–43).

Patients with hypomorphic CARD11 mutations, however, do not have differences in Treg number ex vivo or suppressive capacity in vitro, though a focal Th2 regulatory defect cannot be ruled out.

An effector cell–intrinsic mechanism may also be at play. CARD11LOF T cells fail to activate ASCT2 for normal glutamine uptake after activation. In turn, the low intracellular glutamine pools fail to adequately activate mTORC1, a key metabolic regulator of T helper differentiation (44). Loss of mTORC1 component Rheb leads to poor Th1 and enhanced Th2 differentiation (45), and a similar phenotype can be found in ASCT2 mutant mice. MALT1 and CARD11 mutant patients both have impaired mTORC1 activation in addition to their NF-κB defect. Human naive T cells differentiated in the absence of glutamine have a profound shift away from Th1 cytokine expression even under Th1-skewing conditions. GATA3 expression is enhanced as well in low-glutamine conditions (46). Poor ex vivo expression of IFN-γ and in vitro Th1 differentiation were also clearly observed in patients with mutations in CARD11. The extent to which the patients' Th2 phenotype emerges because of a further intrinsic Th2 bias of differentiating T cells, or simply the lack of counterregulating Th1 cytokines, requires further study.

The CBM complex activates NF-κB, and another open question surrounds the role of impaired NF-κB signaling in human atopic disease. The numerous monogenic disorders affecting NF-κB components are not associated with atopic disease despite adequate effector function, suggesting that lesions upstream lead to allergy independently of NF-κB. That said, a number of mouse

CBM complex: CARD11-BCL10-MALT1 complex

mTORC1: mammalian target of rapamycin complex 1

Th1: type 1 T helper

models at least suggest that NF-κB pathway mutants could lead to allergic disease especially in the context of viral infection (47), and patients with mutations in EDAR1 and 2, which primarily signal through NF-κB, can develop significant atopic dermatitis and other allergic phenotypes (48, 49).

The case of EDAR mutations is instructive since the defect is thought to be largely restricted to keratinocytes. While skin barrier defects are covered in a subsequent section, it is relevant to note here that mutations in another keratinocyte-restricted gene, *CARD14*, can lead to atopy as well. CARD14 is structurally and functionally analogous to CARD11, forming the keratinocyte CBM complex. Dominant negative mutations in CARD14 have been found in multiple patients with severe atopic dermatitis and skin infections. CARD14 gain-of-function (GOF) mutations are known to lead to skin inflammatory diseases that resemble psoriasis, enhanced NF-κB expression, antimicrobial peptide (AMP) expression, and autoexpression of CARD14 protein. In contrast, CARD14LOF keratinocytes fail to normally activate NF-κB, or upregulate CARD14 and AMP expression (50). The loss versus gain of AMP expression mimics a key difference between more typical, common psoriasis and atopic dermatitis whereby AMP expression is excessive in psoriasis and impaired in atopic dermatitis. It is thought that in common atopic dermatitis, impaired endogenous AMP production is secondary to local Th2 cytokines downregulating expression, explaining the superinfections seen in atopic dermatitis skin, in contrast to inflamed psoriatic skin (51). Whether the primary AMP production defect in CARD14 could directly lead to atopic dermatitis—perhaps via introduction of Th2 driving bacterial products—remains to be determined.

Intriguingly, the dermatitis and other mucosal inflammatory and infectious phenotypes seen in some MALT1LOF patients is fully cured with bone marrow transplantation (30, 52, 53). As such, while MALT1 is expressed in skin keratinocytes, and CARD14 is thought to signal through MALT1 to upregulate NF-κB and AMPs, the hematopoietic compartment alone appears to account for the atopic dermatitis and elevated IgE seen in MALT1LOF. It is also possible that the conditioning regimen for transplantation and reconstitution processes has some effect on risk for atopic dermatitis even in the context of a genetic lesion (54).

Another pathway that can affect TCR signaling and leads to substantial atopy when mutated relates to actin polymerization and cytoskeletal rearrangement. After TCR stimulation, Wiskott-Aldrich syndrome protein (WASP) is released by its inhibitor and stabilizer WASP-interacting protein (WIP) so that it is free to associate with the actin-related protein (ARP) 2/3 complex, leading to actin polymerization and subsequent structural changes associated with migration and proliferation (55).

LOF in X-linked *WASP* leads to Wiskott-Aldrich syndrome (WAS), classically characterized by severe atopic dermatitis, thrombocytopenia, combined immunodeficiency, and neoplastic disease (56). In addition to eczematous dermatitis, these patients also have a substantial predisposition toward food allergen sensitization and clinical food allergy (57). Other mutations in WASP lead to X-linked thrombocytopenia (XLT) and neutropenia. XLT can lead to a more limited atopic phenotype as well (57). Biallelic LOF in related actin polymerization genes (*WIPF1*) encoding WIP (58) and actin-related protein 2/3 complex subunit 1B (*ARPC1B*) (33, 59, 60) lead to very similar phenotypes to WAS, including the substantial atopic diathesis.

Another stabilizing target of WIP is dedicator of cytokinesis 8 (DOCK8)—a guanine nucleotide exchange factor whose activity is essential to normal WASP function (61). It is therefore not surprising that LOF mutations in *DOCK8* lead to a combined immunodeficiency remarkable for severe viral skin infection—which can lead to neoplastic disease—in addition to bacterial respiratory infection. Allergic disease in DOCK8 deficiency is quite prevalent and severe (62), perhaps more so than WAS since loss of DOCK8 activity may be compensated in mast cells (57, 63, 64).

Treg failure appears to be a key mechanism for atopic disease in these actinopathies, as Treg function has been shown to be impaired in patient cells (57, 65–68) and deletion of *WASP* specifically in Tregs alone leads to substantial allergic sensitization and even more allergen reactivity than in germ line *WASP* mutants. The decreased severity in germ line mice is likely due to the importance of WASP in normal mast cell function (64).

DOCK8 deficiency may also lead to an intrinsic predisposition toward Th2 differentiation and away from Th1 (69), while WAS T cells appear to have an intrinsic bias away from Th1 cells as well (70, 71), again raising the question as to whether loss of IFN-γ alone can be a key mechanism for atopic diathesis. *WASP* mutations even appear to hinder certain Th2 phenotypes as well (72), providing another potential explanation for the severity of Treg-restricted *WASP* deletion in the mouse model.

Another scaffold protein potentially linked directly to actin dynamics is capping protein regulator and myosin 1 linker 2 (*CARMIL2*), encoding RGD, leucine-rich repeat, tropomodulin and proline-rich-containing protein (RLTPR). RLTPR appears to be critical for CD28 signaling in human T cells by linking CD28 signaling to CARD11 (73), and LOF mutations in *CARMIL2* lead to a combined immunodeficiency that can be associated with substantial comorbid atopy including severe atopic dermatitis, elevated IgE, allergic asthma, food allergy, and cold urticaria. Furthermore, the affected patients also had reduced numbers of Tregs (74–76). Further investigation will hopefully clarify the relative roles of impaired CARD11 activation, tolerance failure, or other intrinsically disordered actin dynamics in the pathogenesis of the atopic phenotypes in these patients.

ALTERED CYTOKINE SIGNALING

While TCR signaling appears to confer intrinsic defects in differentiation and in tolerance leading to atopic disease in the context of bacterial respiratory infection and viral skin infection, the actions of cytokines upon recent stimulation of naive T cells of course have a major impact upon differentiation as well, in addition to the many other ways in which cytokines may impact effector cells of all sorts.

A Number of PADs with Altered Cytokine Signaling Have Emerged

Altered cytokine signaling pathways appear to be a rather fundamental cause of PADs. One of the most obvious lesions in which allergic disease would be expected is loss of IL-12 or IFN-γ signaling; these key Th1-related cytokines are well known to counterregulate Th2 and atopic responses in mouse models and in in vitro differentiation. In humans, such disorders are associated with increased Th2 cytokine production (77). However, while allergic disease can be present, it is not particularly enriched in those affected patients reported (78) either because of a lack of substantial Th1 counterregulation of Th2 effector functions in vivo in humans, or because of the tremendous burden of opportunistic infections that may inhibit Th2 effector function in vivo in ways independent of Th1-related cytokines.

STAT3 Pathway Disorders

One major pathway that appears to substantially contribute to monogenic allergic disease is the STAT3 signaling pathway. Mutations of STAT3, as well as in upstream and downstream members of the pathway, lead to overlapping clinical entities. The most immunologically characteristic elements include bacterial infection of the mucosa, poor inflammatory responses, dermatitis, and

marked IgE elevation. Chronic mucocutaneous candidiasis is variably associated, while viral or mycobacterial infection is not particularly characteristic.

***STAT3*^{DN}:** dominant negative *STAT3* mutations

Dominant negative mutations in *STAT3* (*STAT3*^{DN}) lead to a disorder initially described as Job syndrome, then autosomal dominant hyper-IgE syndrome (AD-HIES) (79, 80). Patients can develop recurrent bacterial sinopulmonary infections leading to abnormal lung cysts, chronic mucocutaneous candidiasis, a newborn rash, chronic eczematoid dermatitis, and recurrent staphylococcal skin abscesses deemed cold due to the lack of the cardinal signs of inflammation—calor (warmth), rubor (redness), dolor (pain), and tumor (swelling) (81–83). In addition patients have substantial connective tissue abnormalities involving head and facial dysmorphism, easily broken bones, hypermobile joints, and arterial tortuosity and aneurysm formation. The marked IgE elevation, however, is what gave the disorder one of its names.

While patients tend not to have primary viral illnesses, herpesvirus reactivation such as varicella zoster virus recurrence and Epstein-Barr virus viremia does occur. Lymphomas, both Hodgkin and non-Hodgkin, are also enriched (84–86). The impaired chronic viral and tumor surveillance may at least in part be due to decreased circulating memory T cell formation, which is intrinsic to STAT3DN (87, 88).

In addition to high IgE, *STAT3*^{DN} patients have peripheral eosinophilia and tissue infiltration of eosinophils, in particular in the gastrointestinal tract (89). Nonetheless, despite the elevated IgE and eosinophilia, patients with *STAT3*^{DN} are relatively protected from IgE-mediated food allergy and anaphylaxis (87, 90). This protection mirrors the global defect in inflammation seen in these patients, suggesting a common mechanism. However, a number of reasons have been posited for the poor allergic responses, including failure to make adequate antigen-specific IgE, a role for STAT3 in normal mast cell degranulation, and a role for STAT3 in normal vascular endothelial responses to histamine (87, 91, 92). The elevation in IgE itself is also not well understood. Th2 cytokines are enriched among the reduced number of memory T cells, but interestingly mouse models strongly suggest that the predisposition to IgE production is B cell intrinsic (93, 94). Notably, there is a developmental defect in B cell maturation in a number of PADs, and transitional B cells in particular have an intrinsic predisposition to IgE class-switching (94, 95). Furthermore, impaired TLR9 signaling in B cells, which appears to be dependent on both DOCK8 and STAT3, may contribute to intrinsic IgE class-switch predilection as well (96).

The IL-10 receptor utilizes STAT3 for signaling transduction and tends to protect against many types of inflation inflammation, and its absence leads to severe early-onset colitis. However, such disease is not present in *STAT3*^{DN} despite poor IL-10R signaling, potentially reflecting other defects in inflammatory cells and mediator responses. Certain types of autoimmunity have been reported, including systemic lupus erythematosus (97–99), autoimmune vasculitis, dermatomyositis, and membranoproliferative glomerulonephritis. Whether these diseases are truly enriched in the *STAT3*^{DN} cohort remains to be determined.

The connective tissue defects in *STAT3*^{DN} are important since they overlap with a number of other monogenic disorders to be discussed later in this review, some of which lead to allergic disease as well. These include retained primary teeth, easily fractured bones, joint hypermobility, craniosynostosis, characteristic facies, and scoliosis (82, 100, 101). Vascular abnormalities are seen in *STAT3*^{DN} as well, such as arterial tortuosity, dilation, and aneurysm formation (102–107).

STAT3 activation leads to expression of a series of target genes, which leads to a complex array of biological responses. Part of the responses are autoregulatory. SOCS3 upregulation, for instance, leads to inhibition of STAT3 and other JAK-STAT signaling pathways. Interestingly, study of patients with ZNF341 mutation has shown that a positive feed-forward loop exists as well, whereby cytokine-induced STAT3 activation leads to upregulation of STAT3 expression itself via

the transcription factor ZNF341. Recessive ZNF341 LOF mutations lead to a phenotype quite similar to *STAT3*^{DN} including marked serum IgE elevation, bacterial skin and respiratory tract infections, fungal infections, and atypical inflammatory responses such as cold abscesses, as well as connective tissue abnormalities that were perhaps not as significant as those seen in *STAT3*^{DN} (108, 109).

Th17: type 17 T helper

Upstream of STAT3, a key cytokine coreceptor critical for signaling for a variety of cytokines including IL-6, IL-11, IL-27, OSMR, LIF, and others is gp130, encoded by *IL6ST*. gp130 can also signal via other STATs, and as such despite the very small sample size of recessive *IL6ST* LOF demonstrates phenotypic overlap with but also distinction from *STAT3*^{DN}. Bacterial infection, connective tissue abnormalities and high IgE were all noted in GP130 deficiency, as was diarrhea, keratitis, and neurodevelopmental delay in one of the patients. Again while the small sample size precludes judgment regarding the severity or type of allergic disease, the phenotype largely appears similar to *STAT3*^{DN}. Notable laboratory findings include poor upregulation of the inflammatory marker, CRP, in the context of infection, and quite similar to the case of *STAT3*^{DN}, low frequencies of memory T and B cells, mucosal-associated invariant T (MAIT) cells, and Th1 and Th17 cells (110, 111).

Given the overlap between gp130 deficiency and *STAT3*^{DN}, it stands to reason that loss of gp130-associated cytokine receptors would also contribute to disease. One might have imagined that poor responses to STAT3-dependent, gp130-independent cytokine IL-21 or IL-10 could explain the high IgE for a number of reasons; however, it is not clear that would be the case in humans. IL-21 deficiency in mice can lead to elevated baseline IgE (112), though not in all models, and in fact IL-21 may have an obligatory role in certain Th2 responses (113). IL6$^{-/-}$ mice can develop elevated IgE despite a Th2 cytokine production defect, and it is postulated that this elevation is indirect, due to a secondary IL-21 production defect (114). Il-21 signaling may suppress IgE class-switching (115), possibly via ID2 induction, and prevent anaphylaxis (116). However in humans IL-21 signaling, likely through STAT3, appears critical at least for in vitro IgE class-switching (117), and patients who lack IL-21 or IL-21R may have had some mild elevation in IgE but nothing approaching the levels seen in HIES, and without a rash or other atopic phenotypes (118, 119). Similarly, IL-10 is thought to be critical in establishing tolerance to allergens (120); however, IL-10R deficiency leads to early-onset inflammatory bowel disease, but as mentioned above not IgE elevation or atopy (121).

Two unrelated patients with LOF mutations in the *IL6R* gene, encoding the IL-6 receptor, have been identified. The IL-6 receptor is the gp130 binding partner for IL-6-mediated signaling. The patients had atopic dermatitis, elevated IgE bacterial sinopulmonary infection, and substantial skin and soft tissue infections—often due to staphylococcus. As with gp130/STAT3/ZNF341 LOF, they had abnormal inflammatory responses, including the absence of elevations in CRP (122).

The findings in IL6R LOF may well clarify which gp130/STAT3-dependent cytokine is critical for suppressing IgE/atopy during development. Furthermore, these patients provide context to data showing that a common coding variant in IL6R that leads to diminution of function can predispose to asthma (123), elevated IgE levels in asthma (124), and persistent atopic dermatitis (125). The same variant actually protects from other types of inflammatory disease such as rheumatoid arthritis and type 1 diabetes. This is especially of interest since IL-6 receptor blockade is utilized in a number of such inflammatory diseases but does not lead to allergic disease, nor does the presence of naturally arising IL-6 autoantibodies, which are associated with staphylococcal cellulitis and skin abscesses (126), arguing that there is an early-life window when IL-6-mediated signaling is critical to prevent allergy.

JAK1/STAT5b Pathway

STAT5B^{GOF}: gain-of-function *STAT5B* mutations

JAK1^{GOF}: gain-of-function *JAK1* mutations

EGID: eosinophilic gastrointestinal disease

The role for STAT5 signaling in atopic disease is complex. Somatic heterozygous GOF mutations in STAT5b within the hematopoietic compartment can lead to massive neonatal eosinophilia, urticaria, diarrhea, and granulomatous disease (127). The patients' phenotype was predicted in part by a series of experiments in mice lacking PLCB3, which appears to be a negative regulator of STAT5b. The increased STAT5 signaling in PLCB3 leads to a myeloproliferative atopic phenotype (128, 129). The exact STAT5b mutation in *STAT5B*^{GOF} has previously been reported in association with leukemia and lymphomas (130–132), some of which are associated with eosinophilia (133). It is therefore interesting that the neonatal-onset somatic mutation does not lead to overt neoplasm over the years, but rather what looks to be an inborn error leading to a PAD (127).

Further evidence for the contribution of GOF in this pathway is found in a report of a family with a GOF heterozygous mutation in JAK1 (*JAK1*^{GOF}) that can lead to STAT5B phosphorylation (134). Unlike the STAT5bGOF patients, carriers had severe atopic dermatitis; however, quite similar to STAT5bGOF patients, they had marked peripheral and tissue eosinophilia and allergic asthma. Treatment with ruxolitinib, a JAK inhibitor, led to marked clinical improvement and resolution of eosinophilia, highlighting the power of precision medicine whereby the pathogenic lesion could be identified and directly treated to resolve allergic disease.

It is relevant here to note that mutations in *TYK2*, which bridges cytokine receptor signaling to STATs similarly to JAKs, were described in a single patient with markedly elevated IgE and mycobacterial infection, and as such were posited to be a cause of hyper-IgE (135). The initial patient had a defect in IL-6 signaling, which would be consistent with the observation that IL-6 receptor LOF leads to IgE elevation. However subsequently, numerous patients were identified with *TYK2* deficiency and none had atopy or high IgE, nor was there an IL-6 receptor signaling defect based on ex vivo and transfection experiments, suggesting that the IL-6 defect was not intrinsic to TYK2 in the initially reported patient (136).

TGF-β Pathway Mutations

In addition to substantial mouse data, abnormal TGF-β signaling has been implicated in a series of human allergic diseases including severe asthma and eosinophilic gastrointestinal disease (EGID) (137, 138). How exactly the normal signaling prevents allergic disease is not entirely clear. Clear LOF in *TGFB1* appears to lead to tolerance failure, though not in the form of allergic disease (139), while *TGFB1* GOF mutations, which lead to a number of developmental defects and connective tissue abnormalities, are not associated with allergic disease (140). In addition, increased TGF-β signaling as measured by SMADs has been observed in association with abnormal connective tissue phenotypes in certain atopic patients (141, 142). Perhaps most strikingly, heterozygous mutations in transforming growth factor beta receptor 1 and 2 (*TGFBR1* and *TGFBR2*) found in Loeys-Dietz syndrome lead to vascular and connective tissue abnormalities that strongly overlap with those seen in STAT3 pathway disorders (143) and are associated with substantial IgE-mediated food allergy, EGID, allergic asthma, and atopic dermatitis. These patients and mouse models of the disease are noted to have enhanced SMAD2/3 phosphorylation in primary cells ex vivo, though contributing further to the lack of clarity in how TGF-β might lead to allergic disease, the receptor mutation itself is thought to be LOF (144). Abnormal Th2 cytokine production by Foxp3^{+} T cells points toward a potential mechanism (145). Allergic disease has not yet been carefully measured in other mutations associated with altered TGF-β signaling or availability such as those with mutations in FBN, TNXB, SMAD3, TGFB2, TGFB3, and SKI (146–148).

While it is still unresolved how TGF-β signaling leads to allergic disease in the disorders above, one possible link between STAT3 pathway mutations and the TGF-β pathway may be found in

a family with a heterozygous LOF mutation in erbb2-interacting protein (*ERBB2IP*), encoding ERBIN. The patients presented with significant EGID, allergen-specific reactivity, and connective tissue abnormalities (149). When STAT3 induces and then forms a complex with ERBIN, SMAD2/3 nuclear localization is limited. However in lymphocytes from ERBIN or STAT3LOF patients, TGF-β pathway activation was enhanced, leading to increased IL4Rα expression, a TGF-β target in certain cell types (150). IL4Rα activation by TGF-β is a rather important potential mechanism for atopic phenotypes, since it is of course well known to lead to Th2 differentiation and IgE production, a common GOF *IL4RA* variant increases the risk for a number of allergic diseases (151), and IL4Rα may have a direct role in mediating pruritus in neurons (152).

Impaired function of Tregs—alluded to above in relation to actinopathies, CBM complex formation, and others—is a fundamental mechanism that can lead to allergic diseases. X-linked loss of forkhead box P3 (*Foxp3*) function in male mice (153) describes the scurfy phenotype and in humans the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome (154–156). While patients are best known for early-onset, severe autoimmunity, which can be fatal, they also can develop severe atopic dermatitis, allergen reactivity, high IgE, and eosinophilia (157). Treg function is dependent on IL-2 receptor signaling via STAT5b, and as such LOF in IL-2 coreceptor CD25 (158), encoded by *IL2RA*, and the LOF mutations in *STAT5B* can lead to phenotypes, including atopy, similar to IPEX. STAT5bLOF patients also have susceptibility to viral infection—likely due to poor IL-2-mediated effector functions—and short stature, likely due to roles for STAT5b in growth factor signaling as well (159, 160).

Why there is selectivity for Th2 dysregulation and not other forms of inflammation and autoimmunity in some PADs where Tregs are implicated is not well understood. There is in vivo precedence for the direct and specific role for FOXP3 in Th2 disease, however. Mice with specific deletion in the conserved noncoding sequence 1 (CNS1)—which has been shown to be critical for peripheral Treg identity in controlling FOXP3 expression—develop spontaneous allergic inflammation of the mucosal surfaces (161). Tregs from patients with a specific mutation in the domain swap interface of FOXP3 have a selective inability to control their own Th2 cytokine production, leading to a highly Th2-skewed phenotype in the patient; the same is true in a mouse model (162).

SKIN BARRIER DISRUPTION

Another fundamental pathway required to prevent allergic disease is skin barrier function. Multiple disorders have been described that affect the physical skin barrier and lead to severe atopic disease. Filaggrin, encoded by *FLG*, serves as a physical barrier protein in a number of ways, including being processed into natural moisturizing factor (NMF) (163). Biallelic LOF mutations in *FLG* cause a severe form of eczematous dermatitis, ichthyosis vulgaris (164). These extreme cases show the spectrum of consequences from altered filaggrin expression. LOF heterozygous *FLG* variants are highly associated with common atopic dermatitis and other allergic disease (165, 166). Filaggrin expression is actually lowered by Th2 cytokines, illustrating a vicious cycle in allergic disease (167, 168).

Another key structure in skin barrier function is the desmosome, a junctional protein complex that helps seal the keratinocyte barrier and resists mechanical stress (169, 170). Mutations in multiple subunits of the desmosome lead to structural abnormalities that cause barrier defects, and to severe atopic dermatitis and/or ichthyosis vulgaris including corneodesmosin (*CDSN*), desmoplakin (*DSP*), and desmoglein-1 (*DSG1*) (171–173). Biallelic LOF mutations in *CDSN* result in peeling skin syndrome, type B, which is characterized by diffuse ichthyosis and erythroderma of the skin, severe itching, marked IgE elevation and other symptomatic allergic disease (171). Perhaps even more severe are dominant mutations in *DSP* (172) and recessive LOF mutations in

DSG1 (173), which result in severe dermatitis, multiple allergies, and marked metabolic wasting, or SAM syndrome.

Desmosome turnover is a highly ordered process involving protease activity for degradation and protease inhibitors to regulate its rate. Lymphoepithelial Kazal-type-related inhibitor (LEKTI), encoded by serine protease inhibitor Kazal-type 5 (*SPINK5*), serves as a key protease inhibitor in desmosomes (174), and autosomal recessive LOF mutations in *SPINK5* lead to Comel-Netherton syndrome, characterized by destabilized desmosomes, excessive desquamation, severe ichthyosis and erythroderma, trichorrhexis invaginatum (bamboo hair), elevated IgE, and atopy, as well as recurrent infections, all of which may be responsive to intravenous immune globulin therapy (175).

How does defective barrier function lead specifically to allergic phenotypes? Proposed reasons include inappropriate allergen penetration of mucosal immune cells that are normally shielded from external antigens/allergens, leading to antigen presentation and reactivity; growth and penetration of microbiota and their toxins, such as *Staphylococcus aureus*, which has an adjuvant effect on allergic inflammation; and the simple water loss that leads to a milieu more conducive to pruritus and more inflamed, with scratching (176–178). Emollient therapy alone, in restoring barrier function without immunomodulation per se, might even prevent atopic dermatitis in infants (179).

MAST CELL DEREGULATION

Mast cell effector functions underlie many of the most commonly encountered allergic phenotypes. As such, monogenic disorders affecting mast cell function comprise a distinct subset of PADs, one of which tends to differ from many other types that are more commonly associated with comorbid immune deficiency or chronic inflammation such as atopic dermatitis, or even IgE elevation.

One such group is physical urticarias. Physical urticarias are quite striking, in that stimuli such as heat, cold, vibration, and even certain light wavelengths can trigger mast cell degranulation, most easily observed clinically in the form of wheals and flares. The overwhelming majority of patients with physical urticarias do not have them from birth, nor are they lifelong. Their cause remains largely elusive, though in the case of cold urticaria there is some evidence that autoimmunity could have a role (180). However in some cases a PAD has been identified that leads to a physical urticaria. One such example is PLCγ2-associated antibody deficiency and immune dysregulation (PLAID) (181–183). Patients with PLAID develop pruritus and erythema with evaporative cooling—which is distinct from the typical cold urticaria, which is triggered by contact with cold objects such as ice. PLAID patients' urticarial symptoms are present from birth and are lifelong. Deletions of the autoinhibitory cSH2 domain underlie known cases of PLAID. These deletions appear to lead to cellular anergy at physiologic temperatures in cells that express substantial PLCγ2—which is nearly all hematopoietic cells, with the notable exception of T cells. This anergic phenotype likely explains the poor B cell class-switching observed and comorbid humoral immune deficiency seen in a subset of PLAID patients (181–183). The slightest of subphysiologic temperatures leads to marked spontaneous PLCγ2 activity (184)—leading to calcium flux and ERK activation—which in mast cells leads to degranulation without the presence of a ligand. Such activity occurs in other myeloid cells, which may explain the skin granulomas that can form in a subset of patients, likely due to the slight decrease in temperature at the body surfaces (183). The mechanism by which PLCγ2 deletions lead to the complex signaling abnormalities likely affects its role as a scaffold protein in addition to the lack of autoinhibitory activity (185). The cold urticaria in PLAID is entirely distinct from the inflammatory rash that was confused for cold urticaria seen in familial cold-induced autoinflammatory disorders caused by

NLR family pyrin domain containing 3 (*NLRP3*) inflammasome mutations. The inflammasome rashes did appear urticarial, but they were neutrophilic, not mast cell related (186).

Vibratory stimuli can also physically trigger mast cell degranulation and urticaria. In one case, a founder population from Lebanon carried a mutation in *ADGRE2*, encoding EGF-like module-containing mucin-like hormone receptor–like 2 (EMR2), leading to lifelong vibratory urticaria with systemic symptoms when significant (187). EMR2 is a G protein–coupled receptor that binds to glycosaminoglycans such as dermatan sulfate. When physical shearing forces are applied—such as in vibration—a noncovalently bound subunit of the receptor dissociates, leading to cellular activation and mast cell degranulation, even in normal individuals, for reasons that are not well understood (188). The particular *ADGRE2* mutation in the Lebanese-descent cohort lowers the threshold for this physical dissociation and subsequent mast cell degranulation (187).

Finally, mast cell mediators themselves have genetically determined pathogenic roles leading to PADs. One such example is the case of familial alpha tryptasemia syndrome (189, 190). Tryptases are well known serine proteases found in mast cell granules. Their activation of PAR2 and other receptors has been posited to lead to a number of atopic and nonatopic phenotypes such as pruritus and tissue remodeling (191, 192), and elevations of basal serum tryptase are associated with a wide variety of symptoms, some typically associated with acute (such as flushing, itching, and anaphylaxis) and chronic (such as dysautonomia and fatigue) mast cell degranulation (193–197). There are two major secreted tryptase isoforms: alpha and beta tryptase. Secreted tryptases found in granules are typically packaged with heparin in a mature form as tetramers. Interestingly, alpha tryptase is catalytically inactive yet present in over two-thirds of the general population. Alpha/beta heterotetramers can form naturally, and have distinct properties and targets of action, including EMR2. Alpha/beta heterotetramers substantially increase the capacity for vibratory stimuli to dissociate EMR2, and patients with increased copy number of the alpha isoform of tryptase at TPSAB1 are substantially more likely to experience urticaria with vibratory stimuli (198). Four to six percent of Caucasians carry these copy number increases, accounting for the vast majority of elevations in basal serum tryptase. These patients actually have increased basal levels of tryptase, most of which is alpha tryptase secreted in monomer form. Carriers of the increased alpha tryptase copy number have hereditary alpha tryptasemia (HAT), and those who are symptomatic with the above-described phenotypes have hereditary alpha tryptasemia syndrome (HATS). Whether these monomers also have a pathogenic role in some of the chronic symptoms seen in HATS remains to be seen.

ADDITIONAL PADs

A number of additional PADs not clearly linked to a specific pathogenic mechanism nonetheless provide opportunities for study of allergy pathogenesis. Autosomal recessive hypomorphic mutations in phosphoglucomutase 3 (*PGM3*) can lead to a multisystem disorder of infection, immune dysregulation, connective tissue abnormalities, and neurodevelopmental deficits. One element of the immune dysregulation is profound allergic disease including severe atopic dermatitis, food allergy, immediate and delayed hypersensitivity to medications, EGID, asthma, seasonal allergy, allergic bronchopulmonary aspergillosis, allergic fungal mastoiditis, and food-protein-induced enteropathy syndrome (199–203). *PGM3* is a critical enzyme in the hexosamine pathway required for normal production of uridine diphosphate *N*-acetylglucosamine (UDP-GlcNAc) (202, 204), which is essential for normal glycosylation. Complete absence of PGM3 is not consistent with life, and as such these are hypomorphic mutations that lead to poor cytosolic UDP-GlcNAc production, which in turn leads to measurably lower glycosylation in certain tissues, in particular naive T cells (202, 204). How this leads to allergic disease is not understood. IgE glycosylation

itself appears to be normal (205). One potential mechanism suggests that adequate *N*-glycosylation of gp130 is required for normal surface expression, resulting in impaired signaling by gp130-dependent cytokines, which could explain some overlap of PGM3 deficiency with *IL6ST* LOF patients. The finding is complicated by the fact that PGM3-deficient patients have mostly effector memory T cells in the periphery, which normally have low gp130 expression. However it is an example of what may be a multifactorial pathogenesis, raising the question as to which proteins must be normally glycosylated to prevent atopic disease.

Another disease that is related to marked IgE elevation and some other atopic features is prolidase deficiency. Autosomal recessive LOF mutations in *PEPD* (206) lead to dermatitis and skin ulcerations, recurrent respiratory infections and mucosal inflammation, hepatosplenomegaly, elevated IgE, facial dysmorphism, and developmental delay (207–209). Prolidase is a dipeptidase involved in collagen breakdown whose absence leads to the accumulation of dipeptides (210). While poor type I interferon signaling, which can theoretically oppose atopy, has been noted (211), other patients with type I interferon defects have not been noted to have allergic disease.

CONCLUSION

The increasing number of PADs now recognized have either affirmed or revealed the relevance of multiple biological pathways in the pathogenesis of allergy. In some cases more than one pathway may be affected, which could well reflect that multiple pathways that lead to (or should prevent) atopic phenotypes could stem from nodal genetic programs. It is critical to note that the PADs described are ones that have been identified. There are likely many more monogenic allergic disorders that have not been identified that likely involve both known and novel pathogenic mechanisms. Furthermore, as the case of CARD11 deficiency and others can illustrate, commonly appearing allergic disease may well be monogenic in some cases. The lesions and pathways identified can impact allergic disease in the general population in a variety of ways, providing evidence that common allergic disease can also benefit from precision medicine, which incorporates genetic findings and identifies affected pathways to design rational individualized therapies.

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