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ERBIN and phosphoglucomutase 3 deficiency

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Abstract

ERBIN and phosphoglucomutase 3 (PGM3) mutations both lead to rare primary atopic disorders characterized by allergic disease and connective tissue abnormalities, though each disorder has its own rather unique pattern of multisystem presentations. Pathway studies show how ERBIN mutations allow for enhanced TGFb signaling, and prevent STAT3 from negative-regulating TGFb signaling. This likely explains many elements of clinical overlap between disorders of STAT3 and TGFb signaling. The excessive TGFb signaling leading to increased IL-4 receptor expression also provides the rationale for precision-based therapy blocking the IL-4 receptor to treat the atopic disease. The mechanism by which PGM3 deficiency leads to atopic phenotypes is not well understood, nor is the broad variability in disease penetrance and expressivity, though preliminary studies suggest an overlap with IL-6 receptor signaling defects.

Introduction

Primary atopic disorders — monogenic causes of symptoms associated with the effector mechanisms of type-II immunity and allergy [1,2] — provide examples of how complex pathways normally prevent the development of allergic disease, and how disruption can cause it. Two examples, autosomal-dominant deficiency of ERBIN (Erbb2 interacting protein) and autosomal-recessive phosphoglucomutase 3 (PGM3) deficiency, lead to complex phenotypes, reflecting the known and unknown complex roles these genes, and the pathways they impact, serve. They also serve as excellent examples of the value in studying primary atopic disorders. By drawing our attention to the clinical overlap with other primary atopic disorders, detailed study of the overlap in cellular and biochemical immunopathogenic pathways helps clarify how each contributes to atopic disease and other clinical phenotypes.

ERBIN mutation

Normal Transforming Growth Factor Beta (TGF-β) signaling appears critical to control human allergic diseases such as eosinophilic esophagitis and asthma, as well as mouse models of atopy [3–7]. Increased TGFβ signaling is seen in certain atopic patients with connective tissue abnormalities [8,9]. Biallelic loss-of-function (LOF) mutations in TGFB1 lead to loss of immune tolerance in the form of inflammatory bowel disease — in

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addition to immune deficiency and CNS abnormalities [10], while gain-of-function (GOF) mutations lead to developmental defects and connective tissue abnormalities [11]. Neither is associated with a type 2 T helper (Th2) diathesis or atopic disease among the small number of affected patients. In contrast, substantial allergic disease has been observed in Loeys–Dietz syndrome (LDS) [12,13] — which is associated with multiple connective tissue phenotypes observed in patients with loss of Signal transducer and activator of transcription 3 (STAT3) function [14–24]. LDS is caused by TGF beta receptor 1 (TGFBR1) and TGFBR2 missense mutations, and while enhanced Small Mothers Against Decapentaplegic (SMAD) 2/3 phosphorylation can be seen in patient tissue, models of acute proximal mutant receptor-mediated signaling lead to loss of function [25]. In a mouse model of LDS, loss of TGFβ signaling in esophageal epithelial cells leads to a tissue-intrinsic predisposition to developing eosinophilic esophagitis [26], while TGFβ signaling LDS lymphocytes has not yet been carefully measured, LDS patient-derived naive T cells skew toward a Th2 bias in the presence of TGFβ in a cell-intrinsic fashion [12]. A well-characterized polymorphism that increases TGFb1 transcription leads to a direct effect on epithelial cells, which increases mucosal permeability that is associated with allergic inflammation [7]. The conflicting observations regarding mutant TGFBR1 signaling in LDS mirror conflicting observations regarding the link between TGFβ and allergy risk derived from tissue studies and patients with monogenic disease.

Of note, patients with loss of function of the IL-11 receptor and gp130 (a co-receptor for IL-11R, among others) — both of which signal through STAT3 — develop skeletal and dental abnormalities that overlap significantly with that seen in patients with dominant negative STAT3 mutations (STAT3DN) mutations. Patients with certain recessive or dominant IL6ST loss-of-function mutations have significant allergic inflammation and elevated immunoglobulin E (IgE) as well [27–30]. The IL-11R/gp130/STAT3 signaling pathway — and how it might interface with TGFβ signaling — is therefore of great interest to study in understanding the overlap between congenital connective tissue abnormalities and allergic disease.

The commonality between patients with TGFB mutations and STAT3 loss of function may in part be explained by insight found in a family with a unique missense mutation in erbb2- interacting protein, encoding ERBIN. The patients presented with connective tissue abnormalities, including joint hypermobility and aneurysm formation, bacterial infections, significant eosinophilic gastrointestinal disease (EGID), IgE elevation, and allergen-specific reactivity [31]. Common genomic variation in ERBIN is also associated with scoliosis [32], a major connective tissue abnormality seen in LDS and STAT3DN patients.

ERBIN appears to be a key mediator of the cross-talk between STAT3 and TGFβ signaling, in that it is induced by STAT3 and complexes with it to impair SMAD2/3 nuclear localization and propagation of the TGFBR signal. While this pathway may have important consequences within connective tissue, which could explain the overlap of connective tissue symptoms in STAT3DN, TGFBR mutations, and ERBIN LOF mutation, another key outcome of the excess signaling appears to be increased interleukin-4 (IL-4) receptor alpha (IL4Rα) expression [33]. The excessive IL4Rα activation can promote allergic inflammation, switching to IgE and pruritus [34,35], and may explain the allergic

inflammation and IgE elevation seen in TGFB/STAT3DN/ERBIN patients [36–38]. Notably — treatment of STAT3DN and ERBIN LOF patients with IL4Rα blockade (dupilumab) led to marked success in treating the otherwise refractory skin and gut inflammation seen in these patients [39–45].

ERBIN mutations may also contribute to the atopic diathesis in an epithelium-specific fashion. Patients with loss of function in the epithelial barrier protein desmoglein (DSG1) develop severe atopic dermatitis, allergic inflammation and hypersensitivity and metabolic wasting (SAM) syndrome, another primary atopic disorder characterized by severe atopic dermatitis, allergic inflammation and hypersensitivity, and metabolic wasting. Mechanistic study suggests that DSG1 appears to drive normal ERBIN localization in epithelial cells, and as such, ERBIN dysfunction may contribute to the atopic phenotypes in SAM syndrome and related entities [46].

Phosphoglucomutase 3 deficiency

Autosomal-recessive hypomorphic mutations in *PGM3* can lead to a glycosylation disorder with a variety of clinical outcomes with variable penetrance and expressivity. Immune dysregulation, connective tissue abnormalities, and neurodevelopmental deficits have been described. In those with sufficient effector immune function (unlike those PGM3-deficient patients with severe combined immunodeficiency), the immune dys-regulation includes substantial allergic disease ranging from severe atopic dermatitis, to food allergy, immediate and delayed hypersensitivity to medications, EGID, asthma, seasonal allergy, allergic bronchopulmonary aspergillosis, allergic fungal mastoiditis, and non-IgE-mediated, specific food-induced enteropathy [47–51]. *PGM3* is required for the pathway that produces uridine diphosphate N-acetylglucosamine (UDP-GlcNAc) [50,52], which is essential for both N- and O-linked glycosylation, and complete absence of PGM3 is embryonically lethal. Hypomorphic PGM3 function leads to reduced cytosolic UDP-GlcNAc that then variably impacts critical proteins throughout the body. Naive T cells appear more sensitive to reduced UDP-GlcNAc compared with memory T cells, presumably due to the lack of compensatory metabolic states [50,52].

Notably, patients can present with immune deficiency or atopic disease alone, without infection or developmental abnormalities, and hematopoietic stem cell transplant can fully restore normal immune function [53,54]. While these rather critical observations highlight the tissue-specific variability in penetrance and expressivity of disease, they also suggest that PGM3 variation could contribute to common allergic disease. A small screen of L-PHA (phytohemagglutinin) binding in naive T cells derived from nonsyndromic patients with atopic dermatitis showed no difference from healthy controls, nor was there overlap with the lower range seen in PGM3 deficiency [48]. However, further studies of larger populations could help determine if lower L-PHA binding in naive cells correlates with atopic disease risk.

The relevance of the PGM3 pathway in atopy and immune disorders may be all the more relevant given that exogenous GlcNAc treatment of PGM3mut cells can improve the lower cytosolic UDP-GlcNAc levels observed in PGM3 mutant cells — suggesting a potential

precision therapeutic for PGM3mut patients, and in theory, those with impairments of the pathway, which lead to clinically relevant disease of any sort [50].

How any of the focal glycosylation defects in different immune cells lead to allergic disease is not understood. Measured glycosylation moieties on patient-derived IgE are normal [55], arguing against major B-cell-intrinsic glycosylation roles. One theory put forth suggests that adequate N-glycosylation of gp130 is required for its surface expression [56]. Reduction in N-glycosylation in relevant cells could therefore impair gp130-dependent cytokine signaling, leading to the overlap seen between PGM3 mutation and gp130/IL6ST LOF, including bacterial infection, connective tissue abnormalities, high IgE and allergic hypersensitivity, and inflammation, keratitis, neurodevelopmental delay, and other phenotypes [27–30]. While complicated by the fact that recently activated and/or effector T cells — that are enriched in PGM3-deficient patients — have lower gp130 surface expression in general, it nonetheless highlights the need to identify the focal pathways impacted, as they will likely unlock fundamental understanding of allergic disease pathogenesis.

Conclusion

ERBIN mutation and PGM3 deficiency are examples of very rare diseases that are nonetheless highly instructive to the biology behind multisystem syndromes impacting the immune system and allergy. Both point to potential precision diagnostics and therapies for the specific disorders, as well as the potential for relevance of those with common immunologic disease whose pathophysiology might overlap with these rare disorders. In addition, preliminary studies are suggestive of interactions with the IL-6/STAT3 signaling pathway in both disorders (Figure 1), potentially explaining the overlap of atopic and connective tissue abnormalities seen in patients with pathogenic mutations in ERBIN, PGM3, and the IL-6/STAT3 pathway. Further study of these patients, and expansion of the cohorts of those with pathogenic mutants in either gene, will help better define the mechanisms and impact of these mutations in allergic and immune disorders.

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Data Availability

No data were used for the research described in the article.

Abbreviations

PIDD	primary immunodeficiency disease
TCR	T cell receptor
pMHC	peptide-major histocompatibility complex
Th1	type 1 T helper

Th17	type 17 T helper
Th2	type 2 T helper
SCID	severe combined immunodeficiency
mTORC1	mammalian target of rapamycin complex 1
Treg	regulatory T cell deaminase
STAT3^{DN}	dominant negative STAT3 mutations
STAT5B^{GOF}	gain-of-function
LDS	Loeys-Dietz syndrome
EGID	eosinophilic gastrointestinal disease
JAK1^{GOF}	gain-of-function JAK1 mutations
UDP-GlcNAc	uridine diphosphate N-acetylglucosamine
ABPA	allergic bronchopulmonary aspergillosis
FPIES	food-protein induced enteropathy syndrome
SAM	severe atopic dermatitis, allergic inflammation and hypersensitivity and metabolic wasting

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• of special interest

•• of outstanding interest

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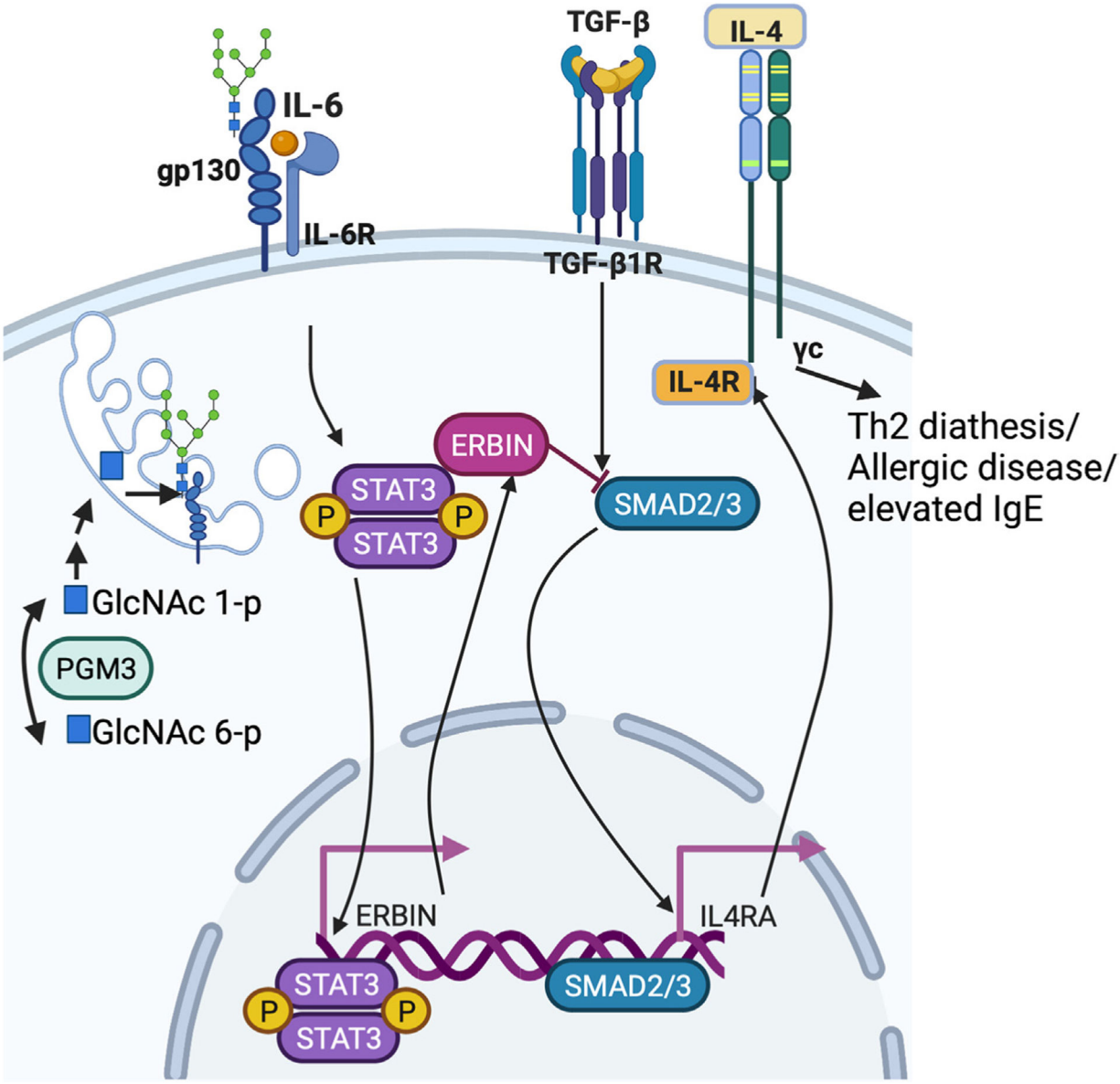

Figure 1.

Il-6-mediated signaling via IL-6R and gp130 leads to activation of STAT3, which leads to transcription of ERBIN and physical complexing of STAT3/ERBIN/SMAD2/3, sequestering SMAD2/3 away from the nucleus, and normally preventing IL-4 receptor upregulation on the surface of lymphocytes, and therefore Th2-related phenotypes. PGM3 produces a precursor sugar amine required for N-linked glycosylation that provides stability for surface gp130 expression. Created with BioRender.com.