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Gene–environment interactions in primary atopic disorders

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Environmental factors modify disease presentation and severity in allergic disorders. Primary atopic disorders (PADs) are a heterogenous group of single gene disorders that lead to significant atopic and allergic disease manifestations. However, a number of these monogenic diseases have variable penetrance suggesting that gene–gene and/or gene–environment interactions could modulate the clinical phenotype. Environmental factors such as diet, the microbiome at the epithelial–environment interface, the presence and/or extent of infection, and psychologic stress can alter disease phenotypic expression of allergic diseases, and PADs provide discrete contexts in which to understand these influences.

We outline how gene–environment interactions likely contribute to a variable penetrance and expressivity in PADs. Dietary modifications of both macronutrients and/or micronutrients alter T-cell metabolism and may influence effector T-cell function. The mucosal microbiome may affect local inflammation and may remotely influence regulatory elements, while psychologic stress can affect mast cell and other allergic effector cell function. Understanding gene–environment interactions in PADs can hopefully provide a foundation for interrogating gene–environment interactions to common allergic disorders, and also present opportunities for personalized interventions based on the altered pathways and environmental influences in affected individuals.

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Introduction

It is well established that gene–environment interactions influence the clinical presentation, disease severity and treatment response of common allergic diseases such as asthma and atopic dermatitis [1,2]. Observations from such common allergic diseases underlie the influence of environmental factors on polygenic allergic diseases with a complex multifactorial etiology. Primary atopic disorders (PADs) are a series of monogenic causes for symptoms associated with allergy and hypersensitivity, whether triggered or spontaneous activating any element of allergic effectors [3]. Such diseases have provided insights into immune pathways of common atopic and allergic diseases [3,4]. They can be distinct from common allergic diseases in that the clinical phenotype is largely influenced and attributed to one gene variant that promotes allergic inflammation. However, monogenic atopic diseases also tend to show variable penetrance suggesting that gene–environment interactions modulate their clinical phenotype [3]. Therefore, lessons from gene–environment interactions observed in PADs provide a different type of opportunity—by fixing the genetic cause, to study the such interactions.

Environmental factors including changes in skin and gut microbiota, dietary modifications, and concomitant infections have been shown to influence the presentation and severity of the allergic phenotype in atopic individuals [5]. For example, exposure to pollutants, such as cigarette smoke and urban pollution increases the risk of developing asthma [6–8]. Conversely, an upbringing on a farm protects from developing allergic rhinitis and asthma in individuals with single nucleotide polymorphisms associated with allergy and asthma risk [9]. Further, dietary intake influences the severity of allergic inflammation [10]. Environmental factors can impair epidermal barrier function in genetically-predisposed individuals for atopic dermatitis [2]. Exogenous proteases of *Staphylococcus aureus* and house dust mites disrupt the epidermal skin barrier [11,12]. Chronic topical corticosteroids, and washing with soap and detergents increase production of chymotryptic enzyme also impairing epidermal barrier function [13]. Physiologic and psychologic stress can trigger eczema flares, urticaria, and other allergy-related symptoms in some individuals but not others [14,15•,16].

This review proposes observations and questions regarding potential gene–environment interactions in a number of PADs. We refer to specific cases where putative environmental factors may influence phenotypic expression of PADs. Some mechanisms may also draw from our current understanding of gene–environmental interactions in polygenic allergic diseases. Understanding such interactions could enlighten new mechanistic approaches

to prevention of disease exacerbations and treatment in allergic diseases of myriad etiologies.

Nutrient influence on T-cell metabolism and dendritic cells may modulate clinical phenotype

CARD11 (also known as CARMA1) encodes a membrane-associated guanylate kinase (MAGUK) that forms a CBM complex protein by associating with BCL10 and MALTI1 [17,18]. The CBM complex is a scaffold required for IκB kinase (IKK) and nuclear factor-kB (NF-κB) activation following lymphocyte receptor ligation [19]. Hypomorphic dominant-negative *CARD11* mutations cause severe atopic disease (atopic dermatitis, asthma and food allergies) with variable penetrance and no gender bias [20]. Dominant-negative heterozygous mutations in *CARD11*(CARD11DN) may also present with elevated IgE levels and eosinophilia [20]. In a cohort of 60 patients carrying heterozygous *CARD11* variants, 73% had severe atopic dermatitis, 55% had asthma and food allergies were present in 32%. Rhinitis and eosinophilic esophagitis were less frequent ([21••]. This Th2-driven clinical phenotype is due to decreased T-cell and B-cell receptor signaling via NF-κB which decreases T regulatory cell function while preserving Th2 effector cells [22]. The data show that frequency and severity of atopy and allergic inflammation in such patients are variable. The magnitude of IgE elevation and eosinophilia is also variable with some patients having serum IgE and/or peripheral eosinophil counts within reference range. It is noteworthy that even within individual patients, atopic disease can wax and wane, and new phenotypes can emerge later in life. This variability therefore highlights the point that gene–gene, and, more likely, gene–environment interactions must occur in this monogenic disorder.

Disrupted cellular metabolism may play a key role in immune dysregulation of *CARD11* deficiency [19,23]. While some of the pathology seen in *CARD11* mutations is likely due to poor NFkB activation, defects in other CARD11-dependent pathways may explain the atopy observed. T-cell receptor (TCR) and co-stimulatory CD28 signaling is required for glutamine and leucine influx which is required for normal mTORC1 signaling [24]—which promotes Th1 responses and may repress Th2 responses. TCR and CD28 signals converge on the CARD11-BCL10-MALT1 (CBM) complex which promotes activation or expression of alanine, serine, cysteine-preferring transporter 2 (ASCT2) on the cell surface [17,25] which enables glutamine import [24] and mTORC1 activation [24]. Deletion of ASCT2 or mTORC1 components increases Th2 but limits Th1/Th17 phenotypes [24]. This occurs through suppression of mTOR1 signaling. Leucine and glutamine supplementation rescue defective mTORC1 activation when ASCT2 expression is decreased [20,24]. Furthermore, glutamine deprivation of human T-cells during T helper differentiation skews away from Th1 and towards Th2 and regulatory T-cell phenotypes. Patients with dominant-negative CARD11 deficiency have reduced mTORC1 activation as CD4+ lymphocytes fail to upregulate ASCT2 [20]. Further, exogenous glutamine administration partially restores mTORC1 activation and Th1 cytokine IFNγ production [20]. Notably, glutamine supplementation in otherwise healthy premature infants was associated with a significant primary prevention of atopic dermatitis [26,27], and mouse studies have shown that among amino acids, maximal glutamine absorption is unique in that it requires a normal gut microbiome [28]. Glutamine intake and absorption may therefore be one way that environmental factors could modulate an atopic phenotype in the context of CARD11 deficiency, and perhaps far more broadly. Future studies in the CARD11DN patients, and in the general population, around glutamine availability, absorption and intake, as well as interventional trials, will establish the relevance of these initial findings.

Diet may also influence the allergic phenotype through changes in intestinal microbiota. In mouse models, a high fiber diet increases the proportion of Bacteroidetes in relation to Firmicutes in both the gut and the lung [29]. This change in colonization leads to bacterial populations generating short chain fatty acids which enhance hematopoiesis of dendritic cell precursors in the bone marrow. These dendritic cells have a decreased ability to activate Th2 effector cells in the lung suggestive that a high fiber diet may protect from developing allergic inflammation [29]. It is unclear as to what extent CARD11 signaling would feature in this particular pathway; however, it is known that loss of glycolysis impairs dendritic cell migration as CCR7 oligomerization is impaired [30]. Dysregulated glycolysis in CARD11 deficiency may implicate decreased tolerogenic dendritic cell activity that allows Th2 effector cell inflammation to develop and persist. This mechanism may have implications in other PADs that have intrinsic immune dysregulation especially at mucosal surfaces. In the case of STAT3LOF, epithelial cells (which are non-professional antigen-presenting cells) do not elicit effective antimicrobial responses via IL-22. This is both due to IL-22 production being impaired by *STAT3* mutations and because any residual IL-22 signals via STAT3 [31]. Thus, the role of diet may be more pronounced in other PADs whereby dysregulated antigen presentation exists.

Finally, it should of course be pointed out that the type of infections themselves, independent of diet, may modulate the risk for allergic disease. As noted in Dorjbal *et al.*, while in the context of a small sample size, the lack of atopy in CARD11DN patients was seen most commonly in the context of neutropenia—a state which could lead to a distinct set of infectious predilections [21••].

Chronic skin inflammation is influenced by skin barrier function and antimicrobial triggers

Physical and perhaps chemical defects in the skin barrier promote skin inflammation and numerous gene association studies have shown that skin structure genes play a major role in atopic dermatitis risk [2,32]. Similarly, individuals with monogenic defects in proteins critical for skin integrity can present with severe atopic dermatitis, psoriasiform dermatoses or skin infection. The nature of skin inflammation is variable and may be related to the underlying monogenic variant. For example, individuals with gain of function variants in *CARD14* develop pustular psoriasis pityriasis rubra pilaris and related skin disorders, while dominant-negative *CARD14* variants are predisposed to atopic dermatitis. In both cases, among individuals with gain or loss of function variants, there is variability in presentation of the inflammatory skin phenotype. Interestingly, patients with *SPINK5* mutations, who were initially thought to only develop ichthyosis and atopic dermatitis-like presentations, can also present with psoriasiform-like skin inflammation distinct from an atopic phenotype. The role of the skin microbiome's interaction with the host immune system in PADs may also contribute to differential phenotypic presentations such as severity of skin inflammation, and the presence and severity of skin infections.

SPINK5 (serine protease inhibitor Kazal-type 5) is a kallikrein family protease crucial in maintaining the balance between desquamation while ensuring an intact skin barrier with the outside environment [33]. Autosomal recessive loss-of-function mutations in *SPINK5* lead to desmosomal instability due to increased protease activity [34]. This leads to excessive desquamation and decreased thickness of the outer skin layer-the stratum corneum. Patients with autosomal recessive *SPINK5* mutations present with a syndromic phenotype (the Netherton Syndrome) of ichthyosis and erythroderma, atopy, elevated IgE and trichorrhexis vaginatum (Bamboo hair). Patients with Netherton Syndrome do not classically present with superficial skin infections [35]. This is contrary to other atopic patients without an identifiable monogenic defect who have an increase in superficial staphylococcal and cutaneous viral infections. The predisposition to infection in atopic dermatitis is attributed to high levels of IL-4 and IL-13 acting on keratinocytes to downregulating antimicrobial peptides on the skin surface (including cathelicidin, human beta defensins [HBD]-2, and HBD-3) [36,37]. It is known that keratinocytes in patients with dominant-negative *CARD14* deficiency also have decreased antimicrobial peptide secretion which may explain a functionally impaired skin barrier [38••]. CARD14 is expressed in keratinocytes having analogous functions to CARD11 in hematopoietic cells [17]. Patients with dominant-negative mutations in *CARD14* present with atopic dermatitis while dominant gain-of-function mutations in *CARD14* are associated with psoriasis and Th17-mediated diseases [38••,39].

In addition to suppressing antimicrobial peptides Th2 cytokines IL-4, IL-13 and IL-25 suppress filaggrin expression [40]. Filaggrin is a filament-associated protein that binds to keratin fibers in keratinocytes [41]. In so doing, it contributes to skin barrier function. Filaggrin is broken down to natural moisturizing factor in the stratum corneum which is essential for skin hydration [42]. Filaggrin gene expression is reduced in nonlesional skin of patients with atopic dermatitis [43]. Homozygous loss-of-function mutations in filaggrin lead to ichthyosis vulgaris which is characterized by elevated IgE, and severe dry, flaky and pruritic skin [44]. Heterozygous loss-of function mutations are associated with early onset atopic dermatitis, allergic asthma and food allergy [45,46]. Filaggrin expression is retained in skin keratinocytes of patients with Netherton syndrome likely due to increased Th17/IL-23 responses when compared to atopic controls [47••].

As noted above, recurrent infections and/or autoimmunity, in addition to atopic dermatitis, are highly prevalent in patients with dominant-negative *CARD11* deficiency [19,21••,48]. While CD4 + IFNγ production was reduced in CARD11DN patients, the presence of infection and/or autoimmunity could, under certain conditions, alter Th2 effector cell function partly due to direct suppressive effects of effector cytokines which oppose Th2 development [49]. Further, certain types of inflammation could actually enhance expression of antimicrobial peptides and filaggrin in dominant-negative *CARD11* deficiency which would decrease the clinical severity of atopic dermatitis.

In addition to physical structural defects, signaling proteins are critical in modulating skin inflammation. For example, A20 expression (encoded by *TNFAIP3)*, which regulates NF-κB-dependent expression of proinflammatory genes, can decrease skin inflammation in both atopic dermatitis and psoriasis [50••] while A20 gene polymorphisms are associated with an increased risk of asthma [9]. The protection against asthma afforded by growing up on a farm is heavily influenced by A20 polymorphisms which maintain A20 function, especially within the epithelium [9]. As such it is interesting that a monogenic disease associated with autoinflammation, haploinsufficiency of A20 (HA20) does not have a substantial atopic component [51].

The type of microbial stimulants might influence atopic disease phenotype in the context of monogenic lesions. In several mouse models of NFkB pathway disruption, there is no phenotype at baseline, but atopy develops after introduction of viral infection or products. *RelB* deficient mice develop severe eczema following exposure to the smallpox vaccine and vaccinia virus [52] and *Trim32* knockout mice develop atopic dermatitis-like lesions

and skin infiltration after administration of TLR7 agonist imiquimod [53••]. While it is often thought that the Th2 milieu is the cause of susceptibility to viral skin infection, these data suggest it is also quite possible that the underlying lesion predisposes to viral infection which trigger the Th2 response. Thus in many CARD11 mutant patients, in whom NFkB signaling is impaired, the environmental trigger of viral skin disease seen could drive the development of atopic dermatitis. Another potential example of the modulation of atopy by viral skin disease may be found in patients with Dedicator of cytokinesis 8 (DOCK8) deficiency. DOCK8 deficiency is a primary immune deficiency (due to actin cytoskeletal dysregulation) presenting with severe atopy, recurrent and severe skin viral infection, systemic infection and cancer in the setting of elevated IgE and severe allergy and atopic dermatitis [54,55]. As with many of the other diseases discussed, the presence and severity of atopy is variable Patient with DOCK8 deficiency have increased eukaryotic viral colonization and diversity compared with healthy volunteers and hundreds of novel human papillomavirus genomes identified, some of which contributed to clinical manifestation of warts [56••].

Environmental triggers for development of Omenn syndrome

Omenn syndrome is a monogenic disorder of severe combined immune deficiency complicated by eosinophilia, elevated IgE, erythroderma, and massive expansion of oligoclonally activated T cells [57]. Patients present in infancy with failure to thrive, pneumonitis and chronic diarrhea, with co-existing manifestations of allergic inflammation which typically manifests as severe erythroderma in the setting of eosinophilia and elevated IgE. It is important to note that unlike a number of other congenital inflammatory diseases (including another primary atopic disorder —STAT3 loss-of-function [58]), inflammation is not present at birth but develops later in infancy [59], and interestingly it has been demonstrated that individuals bearing the same causal mutation can either have SCID alone or SCID with Omenn syndrome. There is a genetic predisposition, but it is not sufficient to explain the variable development of this striking phenotype. Patients with SCID generally require timely hematopoietic stem cell transplantation for this otherwise fatal disease, and longer waits may predispose to developing OS in susceptible individuals which complicates the process even further [60]. Mutations in genes known to cause severe combined immune deficiency (SCID) are associated with Omenn Syndrome; including *RAG1* [61], *RAG2* [62], *LIG4* [63], *ZAP70* [64] and *FOXN1* [65], *IL7RA* [66], *DCLRE1C* [67], *ADA* [68], *CARD11* [69] and *RMRP* [4,70]. In the case of *RAG1* gene mutations, residual enzymatic activity can be used to predict the development of Omenn Syndrome [61].

Patients with RAG-deficient Omenn syndrome have poor autoimmune regulator (AIRE) expression in the thymus leading to a significant proportion of autoreactive peripheral T-cells within the oligoclonal T-cell population [71,72]. Such an observation argues for a possible autoantigen triggering the inflammatory process. However, an infectious trigger, perhaps even concurrent with the presence of autoantigen is also possible since it is unlikely that the autoantigen would not emerge until several months postnatally. To reinforce the notion of potential infectious triggers, in three related patients presenting with features of T-B-NK + SCID due to a homozygous mutation in the core domain of *RAG2* (1305 G > T), one of the patients developed a classic phenotype of Omenn Syndrome one month following a parainfluenza type 3 lower respiratory infection [73].

Stress and mast cell activation

Psychological stress is considered an inciting factor of acute flares in chronic relapsing-remitting inflammatory disorders, including inflammatory bowel diseases and atopic dermatitis [74–76]. Stress is associated with the inducing disease flares due to mast cell activation [77] and influences the severity and recurrence of chronic idiopathic urticaria [16,78]. The precise mechanistic underpinnings of such interactions are not well defined. Mast cells are strategically positioned close to neurovascular units and at mucosal barriers which are host–environment interfaces [79]. Activated mast cells release preformed mediators through degranulation which trigger rapid physiologic changes including local vasodilation, endothelial and epithelial permeability and immune activation [79,80]. Activation of mast cells has been associated with the onset and severity of asthma, atopic dermatitis, irritable bowel syndrome and inflammatory bowel disease [81–84]. Patients with atopic dermatitis who experienced acute psychological stress had increased allergen-induced skin wheals, increased levels of substance P, vasoactive intestinal peptide (VIP) and nerve growth factor [84]. Keratinocyte transcriptomic analysis in children with atopic dermatitis due to filaggrin haploinsufficiency showed upregulation of type 1 interferon-mediated stress genes [32]. Further, the density of mast cells and neurofilament fibers are significantly increased in lesional skin of atopic dermatitis suggesting a morphologic basis for mast cell–neural interactions in atopic dermatitis [84].

Psychological stress activates the sympathetic and adrenomedullary system and the hypothalamo-pituitary-adrenocortical axis [85]. During the acute stress response, the paraventricular nucleus of the hypothalamus releases corticotropin-releasing factor which stimulates anterior pituitary corticotrophs to produce adrenocorticotrophic hormone (ACTH) thereby activating the hypothalamopituitary-adrenal (HPA) axis [86]. Mast cells express two corticotrophin releasing factor receptors; CRF_1 and CRF_2 [87,88]. CRF binding to

CRF_1 on mast cells potentiates mast cell degranulation in response to external stimuli. Signal transduction through the CRF_2 receptor leads to inhibitory responses to mast cell degranulation [89]. Selective inhibition of CRF_1 reduces mast cells responses to stimulation in $CRF_2^{-/-}$ mice suggesting that both receptors play a key antagonistic role in regulating mast cell-dependent processes [90••]. One study of normal volunteers even showed that psychological stress, but not physical stress, could trigger stress hormone release and mast cell-dependent gut permeability [91].

Mast cells and basophils contain tryptase; a serine protease that leads to allergic inflammation when enzymatically active [92]. Tryptase inhibition in animal models suggests a role for the enzyme in promoting vascular permeability, inflammatory cell recruitment, and airway hypersensitivity. Hereditary alpha tryptasemia is a monogenic trait of elevated basal serum tryptase associated with multisystem symptoms, including those seen in the context of mast cell activation such as urticaria, anaphylaxis, pruritis and flushing. This dominant trait is due to increased genomic copies at *TPSAB1* of alpha-tryptase allele [93]. There is quite a variation in phenotype among those with increased *TPSAB1* copy number, [94•] which is not surprising given that elevations of serum tryptase in the Caucasian population — which are largely explained by these copy number increases — are present in up to 5% of the Caucasian population. Therefore, *TPSAB1* copy number increase is likely a risk allele for symptoms such as functional gastrointestinal complaints, flushing, pruritus and increased likelihood for systemic reaction to venom [92]. It is not clear what the precise mechanism of increased tryptase may have on mast cell activity. Anecdotally, many patients often report that a major stressful incident could trigger initiation or worsening of symptoms. Given the way by which stress modulates mast cell degranulation, such stimuli and responses may be one environmental factor to underlie variable expressivity on hereditary alpha tryptasemia.

Conclusion

A number of PADs present with variable penetrance of the allergic phenotype, suggesting that gene–gene or gene–environmental interactions play a crucial role in determining a clinical phenotype and disease burden [3]. From variations in diet and metabolism, to microbiome and overt infection, and to psychologic and physiologic stress, distinct immune effector mechanisms are produced. PADs provide an opportunity for a rigorous analysis of gene–environment interactions in atopy and allergic inflammation; in that one gene variant largely influences the clinical phenotype. It is evident that other gene variants, comorbidities, infections, and the microbiome are active players in genotype–phenotype interactions within the domain of PADs. Further characterization of the pathways highlighted by PADs and examination of various tissues in patients with and without certain environmental exposure will help even better deconvolute these powerful interactions and their impact upon allergic disease.

Declaration of interests

Nothing declared.

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- • of special interest
- •• of outstanding interest

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