



Environmental and genetic contribution in airway epithelial barrier in asthma pathogenesis

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Purpose of review

To examine the recent, most relevant genetic and epigenetic modifications of the epithelial barrier in response to the environmental factors, including allergens, viruses, and pollutants, susceptible to participate to asthma.

Recent findings

IL-33 and *TSLP* gene polymorphisms are found in almost all asthma studies. Recent data have highlighted a new population of innate lymphoid cells, activated by these two cytokines, and mediating type 2 innate immunity dependent asthma. Gene variants of innate pattern recognition receptors associated with asthma have been evidenced in early viral infected high-risk birth cohorts, as well as polymorphisms in pathways involved in type I interferon (IFN) production, giving further insight into the role of viruses in asthma development. Novel epigenetic mechanisms have been evidenced in asthma and in response to the environmental pollutants, and point out genes like *TSLP*, which may link environmental pollution and asthma.

Summary

Genetic data support the role of a specific set of epithelial-derived proTh2 cytokines, including *IL-33* and *TSLP*, as well as the role of decreased type I IFN in virus-induced impaired epithelial barrier. Epigenetic modifications of epithelial genes are promising mechanisms that warrant further investigation.

Keywords

asthma, environment, epigenetics, epithelium, genetics

INTRODUCTION

Asthma is an inflammatory disorder of the airways associated with Th2-driven immunity, leading to bronchial hyperreactivity and airway obstruction. Epithelial cells express pattern recognition receptors (PRRs) that detect environmental stimuli, secrete danger signals, and orchestrate defence against inhaled microorganisms and pollutants. In asthma, the epithelial barrier integrity is compromised failing to repair properly and has immune deviation in mediator production, resulting in inappropriate recruitment and skewing of downstream adaptive immune responses. Continued epithelial susceptibility to environmental insults and altered repair responses lead to asthma persistence, and provide microenvironment for airway wall remodelling.

The focus of this article is to review the recent data on how genetic and epigenetic modifications of the epithelial barrier, in relation with environmental factors, potentially contribute to the asthma pathogenesis. In particular, we will focus on the mechanisms involving allergens, viruses, and air pollutants.

ALLERGENS AND ACTIVATION OF THE EPITHELIAL BARRIER

Epithelial cells, as a direct target of allergens, have been directly implicated in Th2 responses, serving as a critical interface between innate immune responses and Th2 immunity. Emerging studies have revealed the mechanisms by which the epithelium modulates Th2 responses through the production of cytokines, including interleukin-25 (IL-25), *IL-33*, and thymic stromal lymphopoietin (*TSLP*).

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KEY POINTS

- Innate pathways involving *IL-33* and *TSLP* epithelial genes are able to activate the recently discovered ILC2, as well as Th2 cells, which may account for the strong genetic association between these genes and asthma.
- Genetic variants in the key signalling molecules of the type I IFN pathway in epithelial cells add further weight to the hypothesis of impaired epithelial barrier function in virus-induced asthma.
- Epigenetic regulation of epithelial genes by miRNA have been reported in asthma and in response to the environmental pollutants, but further studies are needed to decipher whether epigenetics connects environment and asthma.

IL-33 and its receptor IL-1RL1/ST2

IL-33 is a cytokine of the IL-1 family constitutively expressed in the nucleus [1], produced by the airway epithelial cells activated by house dust mite and alternaria allergens [2], and also in response to multiwalled carbon nanotube exposure [3]. IL-33 signals through a heterodimer receptor consisting of an IL-1R-like subunit, also known as ST2 (IL-1RL1/ST2) and IL-1R accessory protein (IL-1RAcP). Functionally, IL-33 induces the production of IL-5 and IL-13 by Th2 cells, as well as activation of IL-1RL1/ST2 expressing cells such as epithelial cells, mast cells, eosinophils, and basophils, suggesting a predominant role in allergen-induced Th2 responses. Amongst all genome-wide association studies (GWAS) performed in asthma, single-nucleotide polymorphisms (SNPs) in *IL-33* and *IL-1RL1/ST2* have been constantly associated with asthma. In the GABRIEL study (A Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community) performed on asthmatics and controls recruited from 23 studies, 1 SNP on chromosome 9 flanking *IL-33* has been associated with asthma [4[¶]]. A subsequent GWAS study combined with published GWAS [5] identified a total of 59 SNPs, amongst which *IL-33* was one of the top hits for asthma. The majority of the asthma-associated *IL-33* SNPs are located in the first intron of the gene, suggesting that these SNPs affect *IL-33* transcription and that asthma susceptibility alleles are associated with increased IL-33 production. Different SNPs for IL-1RL1 scattered throughout the gene have also been reported associated with asthma in many studies [6]. An asthma-associated polymorphism is located in exon 3, resulting in an amino acid substitution probably affecting IL-33 binding to the IL-1RL1 protein. Another SNP results in a change

of a residue involved in the interaction of IL-1RL1 with an adaptor protein, probably affecting IL-33-induced signalling [6]. Although the functional consequences of these SNPs warrant further exploration, *IL-33* and *IL-1RL1* genes appear the most promising gene association with asthma. Recent progress made in the functional studies in humans and mouse models of allergic airway disease indicate a central role of IL-33 signalling in driving Th2 inflammation in asthma. Studies in asthmatic patients have shown that increased IL-33 protein in bronchoalveolar lavage fluid (BALF) and in airway epithelial cells correlates with the asthma severity [7[¶]]. In murine models, IL-33 is released after allergen challenge in sensitized mice. On release, IL-33 activates a recently discovered innate population of IL-5-producing and IL-13-producing cells, referred to as innate lymphoid cells type 2 (ILC2) [8], present in the lungs, and contributing to allergic airway inflammation and airway hyperresponsiveness (AHR) [9[¶],10–12]. These cells also respond to IL-25 and TSLP, other epithelial-derived mediators induced by allergen stimulation. The relevance of these cells in asthma is underlined by the identification of retinoic-acid-related orphan receptor α (ROR α), a transcription factor critical for their differentiation [13,14], as another asthma gene in GWAS [4[¶]]. Therefore, genetic variation at the *IL-33* and *IL-1RL1* loci may translate into increased susceptibility for asthma through the mechanisms involving both innate and adaptive immunity.

Thymic stromal lymphopoietin

TSLP is an IL-7-like cytokine derived mainly from the damaged epithelial cells that activates immature dendritic cells and causes preferential differentiation of naive T cells into Th2 cells [15]. TSLP expression has been associated with Th2-mediated diseases, including asthma, but is also able to inhibit T regulatory functions, underscoring the importance of airway epithelium in breaking tolerance in asthma [16]. TSLP is released from the airway epithelial cells in response to a wide range of environmental factors such as proteolytic allergens, pathogens, diesel exhaust particles, and cigarette smoke, and causes dendritic cell activation. *TSLP* is an established susceptibility gene for asthma across different ethnicities [4[¶],17–19] and its association with asthma has been confirmed in recent studies [5]. A stronger association between *TSLP* and asthma was noted in individuals with a history of smoking, indicating a complex interaction between genetic impacts of *TSLP* and smoking, and suggesting that in addition to allergic inflammation, TSLP may also play a role

in nonallergic airway inflammation [20]. In humans, TSLP protein expression was significantly increased in airway epithelium of patients with severe asthma [21]. In mice, blockade of TSLP reversed the established chronic allergen airway inflammation and reduced airway remodelling [22]. These findings suggest that TSLP may represent a key molecule in the initiation of allergic and nonallergic inflammation through epithelial–dendritic cell interface.

Altogether, these data highlight a previously unrecognized role of innate pathways induced at the epithelial level, able to trigger Th2-type polarization, which may participate in the strong genetic association between genes such as *IL-33* and *TSLP* and asthma. These genes are induced by a plethora of environmental factors, including allergens, pathogens, and pollutants, highlighting their potential as asthma susceptibility danger signals.

VIRUSES AND ALTERATION OF THE EPITHELIAL BARRIER

In addition to allergens, the asthmatic airway is particularly sensitive to respiratory viral infection, leading to 40–80% of asthma exacerbations both in children and in adults. Epithelial cells sense viruses as well as bacterial components through PRRs, including Toll-like receptors (TLRs), and trigger innate inflammatory responses. Viral infections are recognized as environmental risk factors for both development and exacerbations of asthma. To identify the potential gene–environment interactions between innate immunity genes and early viral infections in the first 12 months of life, high-risk birth cohorts were evaluated at 7 years of age for association between 26 innate immunity genes and atopy, asthma, atopic asthma, and AHR [23²⁴]. Six SNPs showed significant effects on both the phenotype and SNP–virus interaction analyses, including for atopic asthma TLR1 and TLR3. The *TLR1* variant was associated with respiratory syncytial virus and parainfluenzae virus infections and with atopic asthma and AHR, whereas the *TLR3* variant was associated with atopic asthma and picornavirus infection. TLR3 is an intracellular receptor able to bind virus-derived double-stranded RNA and makes sense in the context of viral infection, whereas TLR1 functions as a heterodimer with TLR2 and recognizes bacterial lipoproteins only, suggesting that bacterial co-infections may also play a role in asthma pathogenesis. Although these data convey preliminary epidemiological evidence for a relationship between viral exposure, innate immunity, and phenotypes of asthma, replication in other cohorts must be performed. Recent studies have evaluated TLR signalling pathways associated

with childhood asthma. TLRs activate complex signalling cascades involving both MyD88-dependent and MyD88-independent pathways. Association between 41 genes selected from known TLR-mediated signals and atopic and nonatopic asthma was analysed in a genome-wide association dataset [24²⁵]. The association of almost 10% of the investigated SNPs and more than 45% of the genes with asthma suggests a relevant contribution of the *TLR* pathway genetic variability to asthma susceptibility. Interestingly, association of signal clustering showed that MyD88-independent pathway SNPs were associated with nonatopic asthma and MyD88-dependent SNPs with atopic asthma. One of the strongest regulated genes in asthma was IL-1 receptor-associated kinase 1 (*IRAK1*), which activates nuclear factor κ B and interferon-regulatory factor 5 and 7 (*IRF5* and *IRF57*) leading to the production of type I interferon (IFN), involved in innate antiviral immunity. Accordingly, another study [25] has shown that *IRF5* polymorphisms, resulting in lower expression of *IRF5*, were associated with asthma, in particular nonatopic asthma. Defective IFN- β and IFN- λ production has been observed in epithelium from asthmatic patients [26], which may explain highest susceptibility and damage of asthmatic epithelium to viruses through lack of viral clearance.

POLLUTANTS AND EPIGENETIC MODIFICATIONS OF THE EPITHELIAL BARRIER

Air pollution has been associated with asthma exacerbations and possibly with asthma onset through genetic variations and epigenetic changes. Such epigenetic mechanisms including DNA methylation and microRNA (miRNA) were evaluated in epithelial cells.

DNA methylation

DNA methylation is characterized by the addition of a methyl group to a cytosine base in a cytosine–guanine dinucleotide resulting in gene silencing or repression. Several environmental factors have proved to influence the methylation patterns [27]. DNA methylation profiles were assessed in airway epithelial cells from healthy, atopic, and asthmatic children at baseline, and showed eight genes differentially methylated in asthmatics [28]. One of the most significant genes was the transcription factor *STAT5A*, recently implicated in Th2 cell differentiation [29]. In nasal epithelial cells from asthmatic children, a correlation was observed between promoter hypomethylation of inducible nitric oxide synthase and IL-6 and increased fraction

of exhaled nitric oxide [30]. Although these modifications have been previously related to particulate pollution [31], there was no correlation between methylation changes and traffic intensity in the street of residence in this cohort [30].

MicroRNA regulation of epithelial cells

Another epigenetic mechanism is represented by miRNAs, which are small noncoding RNAs, of about 20 nucleotides, that generally bind to the 3'-untranslated region of target mRNAs, able to switch genes 'off' in response to endogenous and exogenous signals. Over 1000 human miRNAs have been discovered and these are able to regulate over 60% of human genes. Most studies in asthma have evaluated the miRNA profiles in inflammatory cells [32]; however, recent publications have evaluated miRNA expression in epithelial cells. At baseline, one study found 66 miRNAs differentially expressed between healthy and asthmatic donors [33], including decreased expression of miR-203 in asthmatic patients, a miRNA previously shown to down-regulate IL-8 [34]. A second study [35] found 217 miRNAs, different from those of the first study, differentially modulated between asthmatic patients and healthy donors. What was relevant in this study was the decreased expression in asthmatics with or without inhaled corticosteroid therapy of four members of the miR-34/449 family, involved in the regulation of epithelial cell differentiation through the inhibition of IL-13-induced mucus metaplasia [36]. In-vitro stimulation of bronchial epithelial cells by IL-13 recapitulated the miRNA deregulation profile observed in asthmatic patients [35], suggesting a link between these miRNAs and mucus metaplasia. Exosomes are nanosized vesicles of endosomal origin mainly released by the lung structural cells, in particular by the epithelial cells in asthma [37]. Interestingly, miRNAs are present in exosomes and can be transferred to the nearby cells [38]. In agreement with the results obtained by Solberg *et al.* [35], the miRNA profile in exosomes from BALF from mild asthmatic patients compared with healthy individuals showed inhibition of miR-34 family members, as well as decreased miR-21 and let-7 family in asthmatic patients [39], as also recently shown in breath condensates of asthmatics [40]. Exosomes from asthmatics exposed to subway air pollutants (containing mostly iron oxides) showed only three miRNAs differentially modulated, including miR-203 [39]. Recently, the effect of ambient particulate matter and diesel exhaust particles was evaluated on miRNA expression by human bronchial epithelial cells [41]. Pollutants induced

miR-375 upregulation, which induced TSLP expression. Moreover, the aryl hydrocarbon receptor, a transcription factor able to bind exogenous pollutants, was evidenced as a target of miR-375. All these data suggest a complex interplay of the epigenetic mechanisms in response to pollutants, leading to the release of TSLP and to Th2-type-associated inflammation.

Therefore, although environmental factors known to increase asthma risk affect the epigenetic patterns in epithelial cells, the link to subsequent asthma development is not yet established and will need further investigation.

CONCLUSION

The mechanisms involved in the pathogenesis of asthma have strongly evolved in the last years from a purely adaptive immunity view to a diversity of innate triggers linked to environmental factors, and to a diversity of asthma phenotypes. This may explain why the therapeutic efforts directed at dampening the allergic adaptive immunity have so far achieved little success. In this context, the epithelium initially considered as a simple barrier has gained further interest with the understanding of its role as a key interface between innate and adaptive immunity [42]. GWAS have revealed new asthma susceptibility genes mostly expressed in the epithelium and innate immune pathways, including *IL-33* and *TSLP*. The recent discovery of antigen-independent innate lymphoid populations activated by these cytokines, able to produce type 2 cytokines, opens new insights into the pathogenesis of asthma phenotypes related to environmental triggers, although it is unlikely that a few functional gene variants will explain all the pathophysiological mechanisms of asthma. However, much is still to be learned from these cells, as in addition to cytokines, it is not clear what activates them [43].

The hypothesis that type I IFN genetic deficiency may underlie the increased sensitivity of epithelium to viruses and to asthma development gains further insight with the recent studies showing gene polymorphisms in different pathways involved in type I IFN production. This idea is further supported by the studies in asthmatic children, showing that sputum airway cells have impaired IFN signalling [44] and that exogenous IFN- β treatment of asthmatic epithelial cells suppresses the release of proinflammatory mediators [45].

Epigenetic modulation of epithelial genes, in particular those highlighted in GWAS, may provide a link between environmental factors and asthma; however, more studies are needed to confirm this connection.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 580).

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