Asthma Pathogenesis
Patogênese da Asma

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The authors declare that they do not have any potential conflict of interest.

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RESUMO
A asma resulta de uma interação complexa entre genes e meio ambiente que leva à tríade característica de obstrução variável do fluxo aéreo, hiper-responsividade e inflamação da via aérea.

Estímulos ambientais, como alérgenos e vírus, agindo em estágios críticos do desenvolvimento, promovem o início e a progressão da doença em pessoas geneticamente suscetíveis. O epitélio, ao interagir com estímulos ambientais e sinalizar para o mesênquima subjacente, direciona para o remodelamento da via aérea. Interações complexas entre subclasses de células T CD4+ efetoras, incluindo as tradicionais Th2 e as mais recentemente descobertas Th9 e Th17, células imunes e estruturais, desencadeiam inflamação e remodelamento da via aérea e são cruciais para a compreensão dos diversos fenótipos de asma. Novos fenótipos, como o de obesidade, podem ajudar a esclarecer mecanismos patogenéticos recentemente descritos na asma.

A patogênese de fenótipos distintos de asma está começando a ser descoberta; esse esclarecimento será crucial para a compreensão dessa doença complexa. O desenvolvimento de uma abordagem biológica e sistêmica, integrando biologia molecular e características clínicas, poderá levar a definição de alvos terapêuticos, especialmente na asma grave, e também avançar em busca de um tratamento personalizado na asma.

Descritores: Asma/patologia; Asma/genética; Inflamação/patologia; Remodelação das vias aéreas; Interação gene-ambiente.

ABSTRACT
Asthma arises from complex gene-environment interactions that drive the characteristic triad of variable airway obstruction, airway hyper-responsiveness, and airway inflammation.

Environmental stimuli (e.g., allergens and viruses), acting at critical stages of development, lead to the initiation and progression of disease in genetically susceptible individuals. The epithelium, by interacting with environmental stimuli and with the underlying mesenchyme, directs airway remodelling. Complex interactions between subsets of CD4+ effector T cells, including classical Th2 cells and the more recently discovered Th9 and Th17 cells, as well as immune and structural cells, drive airway inflammation and remodelling. Understanding such interactions is crucial to our understanding of the various asthma phenotypes. Descriptions of newer asthma phenotypes, such as the obesity phenotype, might clarify novel pathogenetic pathways in asthma.

The pathogenetic mechanisms of distinct asthma phenotypes are beginning to be unravelled; clarification will be crucial to our understanding of this complex disease. A systems biology approach integrating genetics, molecular biology, and clinical assessment is needed in order to develop targeted therapeutics, especially for patients with severe asthma, and advance toward tailored treatment of this disease.

Keywords: Asthma/pathology; Asthma/genetics; Inflammation/pathology; Airway remodeling; Gene-environment interaction.
arsenal of cytokines they secrete, which reflect the signature expression of transcription factor profiles.

The Th1/Th2 paradigm has underpinned research into the contribution of T cells to airway inflammation for many years. Consequently, the roles that IL-4, IL-5, and IL-13 play in atopy and asthma are well documented: IL-4 promotes allergic sensitisation and IgE production; IL-5 influences the differentiation, maturation, and survival of eosinophils; and IL-13 mediates mucus production, remodelling, and AHR. However, a more extensive array of effector T-cell subsets has emerged (9).

A third major subset of CD4+ effector T cells is that composed of Th17 cells, which play roles in host defence and auto-immunity. The characteristic Th17 cytokines are IL-17A and IL-17F, and Th17 cells primarily influence neutrophil recruitment and activation (10).

Interest in Th9 cells, characterised by IL-9 secretion, is also growing. Although IL-9 is considered a Th2 cytokine, a distinct population of IL-9-producing Th9 cells can arise in chronic diseases. The contribution of Th9 cells to chronic airway inflammation has only begun to be elucidated (11,12). The emergent hypothesis is that CD4+ effector T-cell subpopulations differentially contribute to asthma phenotypes. For example, Th17 cells might be more involved in neutrophilic rather than eosinophilic asthma (10).

Other key T-cell subsets postulated to play a role in airway inflammation are regulatory T (Treg) cells, including the naturally occurring CD4+CD25+FoxP3+ subset and induced adaptive CD4+ Treg cells (13,14). In
individuals without asthma, Treg cells promote immunological tolerance to aeroallergens. Changes in the number, phenotype, or function of Treg cells, including those present in the lungs, have been described in upper and lower airway disease (13,14). Early life events seem to be critical in programming immunoregulatory pathways that underpin immune homeostasis in the airways and other tissues (15,16). Immunoregulatory invariant natural killer T cells, which are reactive to CD1d-presented glycolipids, are also of interest. Such cells are found in human airways where they are relatively rare, but numbers are similar between mild/moderately severe asthma, COPD and controls (17). Additional T-cells subsets implicated in airways inflammation and asthma include CD8+ T cells and gamma-delta T cells (9).

Effector CD4+ T-cell subsets mediate their effects via the release of cytokines that then modulate, either directly or indirectly, the activity of other cell types—including eosinophils, neutrophils, and mast cells, all of which in turn augment the inflammatory response. High numbers of eosinophils are observed in the airways of many asthma patients. However, non-eosinophilic asthma occurs across a range of asthma severity, and there is particular interest in the role of neutrophils in severe asthma. The release of bioactive molecules such as histamines and leukotrienes from degranulated mast cells contributes to airway inflammation and the clinical symptoms of asthma.

The prime function of a barrier is to discriminate between relatively innocuous environmental antigens (including allergens) and infectious pathogens. Various stimuli drive cytokine production at barriers and this creates a local cytokine milieu that further informs the innate immune response and educates the adaptive immune response. Pattern recognition receptors, including Toll-like receptors (TLRs), nucleotide-binding oligomerisation domain-like receptors, and retinoic acid-inducible gene I-like receptors, are critical to that process. The repertoire of pattern recognition receptor expression differs by cell type, is developmentally programmed, and is further influenced by genetic variation and the local microenvironment. Dendritic cells are exquisitely placed, both physically and functionally, to bridge innate and adaptive immunity: they are in intimate contact with the epithelium where they can interact with environmental cues that shape the repertoire of cytokines, chemokines, and co-stimulatory molecules, which they express during antigen-specific priming of the immune response. This determines the nature of the allergen-specific CD4+ effector T-cell response generated.

Epithelium-derived cytokines and chemokines orchestrate the recruitment and activity of multiple cell types. Epithelium-derived eotaxin and IL-8 direct the recruitment of eosinophils and neutrophils, respectively, to the airways. Currently, there is much focus on IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), all of which have been implicated in allergic airway disease (and anti-helminth immune responses) but are not alone in demonstrating such properties (18). Models of airway over-expression are typically used to reveal their role but immunohistochemical and other analyses demonstrate the relevance of IL-25, IL-33, and TSLP to airway inflammation in humans. It has been shown that IL-25 plays a role in regulating IL-9 expression by CD4+ T cells (19), and IL-33 is a chromatin binding nuclear cytokine of the IL-1 family, implicated in classical Th2 cell- and mast cell-mediated asthma and anaphylaxis (20). However, IL-33 is an alarm released by necrotic cells to recruit and activate immune cells, i.e., to signal damage and amplify the innate immune response (21). Given the recent identification of neutrophil-derived enzymes as critical to the generation of mature bioactive IL-33 (22), neutrophil infiltrates might amplify IL-33 bioavailability in the airways. For its part, TSLP can promote Th2 cytokine-associated inflammation, modulate activity of granulocyte populations, limit the expression of dendritic cell-derived proinflammatory cytokines, and promote Treg responses (23). The recently identified natural helper cells have also been shown to play a role in Th2-dependent immune response. Natural helper cells are non-B, non-T innate effector cells that are activated via IL-25 or IL-33 to promote Th2 cytokine responses and might represent an ancient evolutionary conserved pathway (24,25).

Neuro-effector mechanisms have also been implicated in airway inflammation, with loss of pre-ganglionic, auto-regulatory muscarinic 2 receptors observed after exposure to allergens and viruses. These receptors normally limit the release of the neurotransmitter acetylcholine, which causes bronchoconstriction. Non-adrenergic, non-cholinergic systems might also play a role in airway bronchoconstriction, with substance P and tachykinins causing bronchoconstriction via the natural killer cell receptors 1 and 2, respectively (18).

**The Epithelium and Remodelling**

There is compelling evidence to support a fundamental role for the airway epithelium and the underlying mesenchyme (the epithelial-mesenchymal trophic unit) in the pathogenesis of asthma. It has been suggested that genetically susceptible individuals have impaired epithelial barrier function with disrupted tight junctions and defective anti-oxidant and innate immune defences (7,26). The epithelium is therefore vulnerable to viral infection in early life, conditioning immature dendritic cells to drive a Th2 “allergic” phenotype. A dysfunctional epithelium is susceptible to allergen sensitisation, and further environmental insults (e.g., exposure to viruses or pollutants), acting in concert with a susceptible genotype during the critical stages of immune system development, are critical to the development and persistence of asthma. In asthma sufferers, bronchial epithelial cells are more
susceptible to rhinovirus infection due to reduced IFN-β production and defences are restored by exogenous IFN-β (27). Susceptibility to recurrent exacerbations is associated with an O-secretor mucin glycan phenotype (28). The concept of epithelial dysfunction provides an explanation for certain aetiological factors in asthma (Table 1) and of exacerbation in response to environmental insults such as exposure to pollutants.

Table 1 - Summary of the main environmental factors (exposures) implicated in the aetiology of asthma.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Example(s)</th>
<th>Study type</th>
<th>Findings</th>
</tr>
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<tbody>
<tr>
<td>Allergens</td>
<td>House dust mite</td>
<td>Prospective</td>
<td>Sensitisation increases asthma risk</td>
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<td>Early childhood exposure increases asthma risk</td>
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<td></td>
<td>Cockroach allergens</td>
<td>Case control</td>
<td>Minimal threshold level of allergen exposure</td>
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<td>Animal allergens: cat/dog</td>
<td>Prospective cohort</td>
<td>Increased sensitisation in asthmatics</td>
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<td></td>
<td></td>
<td>Exposure decreases sensitisation to other aeroallergens</td>
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<td></td>
<td></td>
<td></td>
<td>No protective effect on asthma</td>
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<tr>
<td>Pollutants</td>
<td>Nitrogen dioxide (NO₂)</td>
<td>Cross-sectional, prospective</td>
<td>High NO₂ - increased asthma prevalence</td>
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<td>Indoor gas stove use associated with asthma symptoms</td>
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<td></td>
<td>Diesel exhaust particles</td>
<td>Mechanistic</td>
<td>Proximity to roads/elevated NO₂ - increased asthma risk</td>
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<td>Diesel exhaust particles promote dendritic cell maturation</td>
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<td></td>
<td>Diesel exhaust particles cause airway epithelial activation and pro-inflamatory cytokine release</td>
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<tr>
<td>Viral infections</td>
<td></td>
<td>Prospective cohort</td>
<td>High number of viral infections in infancy - reduced risk of asthma and atopy</td>
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<tr>
<td>Smoking</td>
<td>Active smoking</td>
<td>Prospective cohort</td>
<td>Smoking increases risk of asthma development</td>
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<td></td>
<td>Second hand smoking</td>
<td>Cross-sectional</td>
<td>Pre-natal maternal smoking - increased asthma risk</td>
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<td>Post-natal maternal smoking - increased asthma risk</td>
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<td>Adult passive smoking - increased physician-diagnosed asthma</td>
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<td>Medication use</td>
<td>Antibiotic use in childhood</td>
<td>Meta-analysis of prospective and retrospective studies</td>
<td>Antibiotic use in first year of life - increased asthma risk</td>
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<td></td>
<td>Hormone replacement therapy (HRT)</td>
<td>Cross-sectional, prospective</td>
<td>HRT use - increased asthma incidence</td>
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<td>Obesity</td>
<td></td>
<td>Prospective</td>
<td>Dose-dependent association between body mass index and asthma risk</td>
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<td>Weight loss studies improve disease control</td>
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<td>Early menarche</td>
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<td>Cross-sectional, longitudinal</td>
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<td>Peri-natal</td>
<td>Maternal diet</td>
<td>Prospective cohort</td>
<td>Maternal vitamin E - ↓ childhood asthma risk</td>
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<td>Prematurity</td>
<td>Retrospective meta-analyses</td>
<td>Maternal vitamin D - ↑ childhood asthma risk</td>
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<td>Breastfeeding</td>
<td>Prospective cohort</td>
<td>Prematurity - higher asthma risk</td>
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<td>Breastfeeding for 3-6 months - reduced wheeze</td>
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Sustained epithelial injury leads to disordered communication with the underlying mesenchyme, thereby triggering airway remodelling (29). The inhibition of epithelial repair results in the release of growth factors, including TGF-β2, which activate subepithelial fibroblasts to form myofibroblasts and promote mucous metaplasia. Myofibroblasts deposit extracellular matrix, thickening the epithelial lamina reticularis, and secrete mitogens causing smooth-muscle hypertrophy. Remodelling, including angiogenesis, can occur in childhood asthma, even before a clinical diagnosis of asthma has been made (30-32).

Airway remodelling represents a crucial part of AHR in established asthma and is a major cause of fixed airflow obstruction and declining lung function in more severe asthma. Repeated airway exposure to environmental insults promotes a milieu of persistent inflammation and remodelling associated with progressive disease. Targeting therapeutics toward enhancing epithelial barrier function, as well as exploring novel...
anti-inflammatory targets, presents an opportunity to advance asthma treatment.

NEW INSIGHTS – ASTHMA PHENOTYPES AND “ENODOTYPES”

The heterogeneity of asthma is evidenced by the identification of distinct phenotypes, including the early-onset “extrinsic” allergic phenotype, the late-onset “intrinsic” eosinophilic phenotype, and the late-onset, non-eosinophilic female version of the obesity phenotype (33). Despite sharing the common defining feature of variable airflow obstruction, the underlying pathophysiology is likely to differ. Recently, there has been a move toward describing asthma “endotypes”, subtypes defined by distinct pathophysiological mechanisms. Several asthma endotypes have been described, including aspirin-sensitive asthma, allergic bronchopulmonary aspergillosis, allergic adult asthma, predictive indices of asthma in childhood, late-onset eosinophilic asthma, and asthma in cross-country skiers (34).

SEVERE ASTHMA

Severe asthma encompasses the early-onset, eosinophilic, neutrophilic, and obesity phenotypes (35). Neutrophilic asthma with no evidence of eosinophilic inflammation is often seen in individuals with severe disease on high-dose steroids. Neutrophilic asthma shows features of innate immune activation within the airways, including upregulation of TLR2 and TLR4 and soluble CD14, as well as enhanced expression of proinflammatory cytokines such as IL-1β and IL-8 (36). This asthma phenotype might also involve systemic changes in innate immune function with upregulation of genes promoting neutrophil survival observed in peripheral blood (37). Upregulation of TNF-α within the airways has also been implicated and identified as a potential therapeutic target (38). Although early studies in steroid-resistant disease, using the anti-TNF-α drug etanercept, have produced promising results (39), those results have not been replicated in larger multi-centre studies (40). Adaptive immune mechanisms, including neutrophil inflammation promoted by Th17 cells, have also been implicated (10).

REFERENCES


Figures 1-2

Figure 1 - A systems biology approach integrating genetics, molecular biology, and clinical assessment is needed in order to develop targeted therapeutics, especially for patients with severe asthma.

Figure 2 - Diagram illustrating the mechanisms that might link obesity and asthma. GORD: gastro-oesophageal reflux disease; CRP: C-reactive protein. Note: Some of these factors could interact with each other: adipokines are known to have many immunomodulatory effects and might promote reactive oxygen species generation; metabolic factors such as insulin resistance might play a role in systemic inflammation; and fatty acids might moderate inflammation via Toll-like receptor signalling.
41. Boulet LP, Franssen E Influence of obesity on response to fluticasone with or without salmeterol in moderate...


