Bacteria in Asthma Pathogenesis

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Abstract

The airways are under continuous assault from aerosolized bacteria and oral flora. The bacteria present in the airways and gastrointestinal tract of neonates promote immune maturation and protect against asthma pathogenesis.

Later bacterial infections and perturbations to the microbiome can contribute to asthma pathogenesis, persistence, and severity.

INTRODUCTION

Many researchers initially believed that bacteria do not contribute to asthma because antibiotics did not seem to improve asthma symptoms.[1]

Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia trachomatis, Staphylococcus aureus, and Haemophilus influenza have all been identified as contributors to asthma.

These findings led to a reexamination of the role of antibiotics in asthma with interesting results. More recently, advancements in profiling the respiratory microbiome continue to provide insights into the role commensal and pathogenic bacteria play in asthma pathogenesis

Asthma

Asthma is a common chronic condition affecting both children and adults, and is characterized by chronic airway inflammation leading to bronchial hyper-responsiveness and mucous hypersecretion.

Asthma can be triggered by a variety of stimuli, leading to recurrent and reversible episodes of wheezing, shortness of breath, chest tightness, and coughing [1]. Asthma prevalence has increased dramatically both in the United States (US) and worldwide. Recent statistics from the National Health Interview Surveys (NHIS) and the US Centers for Disease Control and Prevention (CDC) estimated that 26.5 million people in the US, including 6.1 million children, have asthma .[2]

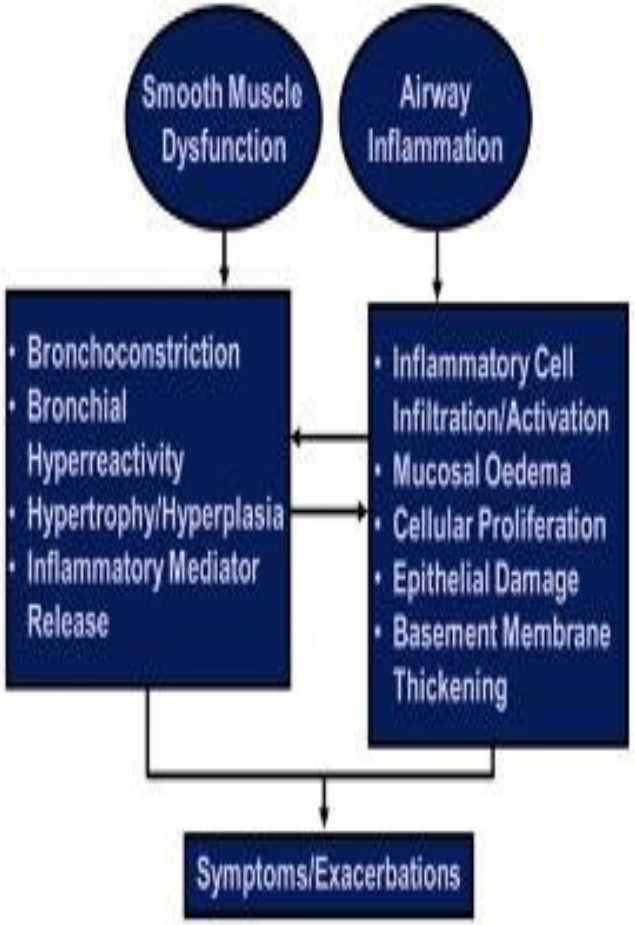
Pathophysiology of Asthma?

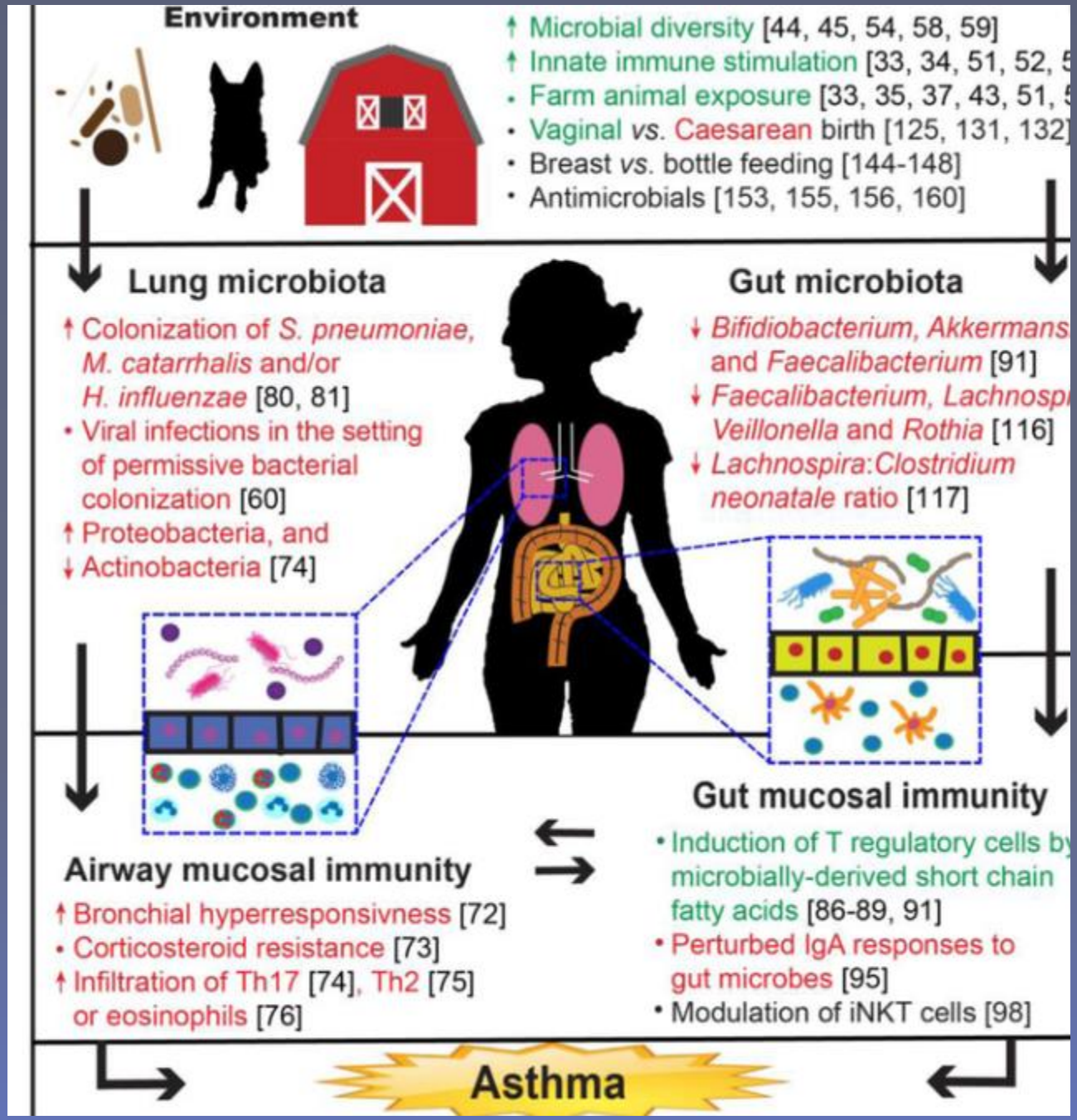
Increase **mucus production** - from goblet hyperplasia, hypertrophy of mucus glands.

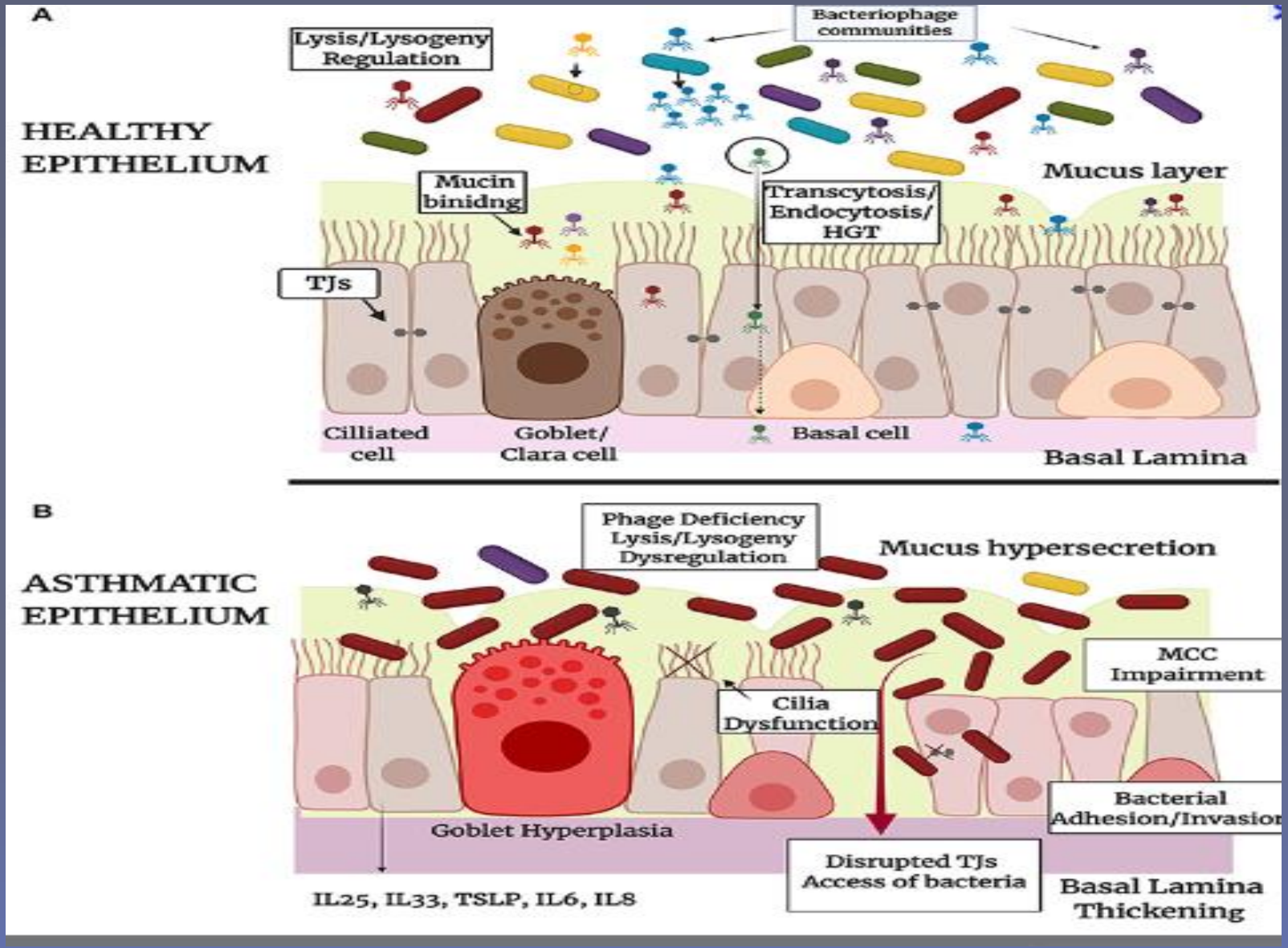
Airway thickening - fibrosis of bronchial wall.

Bronchoconstriction - smooth muscle hypertrophy.

Inflammation - mast cell degranulation, Eosinophil infiltration, inc. permeability, oedema.




Environment
↑ Microbial diversity [44, 45, 54, 58, 59]
↑ Innate immune stimulation [33, 34, 51, 52,
• Farm animal exposure [33, 35, 37, 43, 51,
• Vaginal vs. Caesarean birth [125, 131, 132]
• Breast vs. bottle feeding [144-148]
• Antimicrobials [153, 155, 156, 160]
Lung microbiota
↑ Colonization of S. pneumoniae, M. catarrhalis and/or H. influenzae [80, 81]
• Viral infections in the setting of permissive bacterial colonization [60]
↑ Proteobacteria, and
↓ Actinobacteria [74]
Gut microbiota
↓ Bifidiobacterium, Akkermans and Faecalibacterium [91]
↓ Faecalibacterium, Lachnospi Veillonella and Rothia [116]
↓ Lachnospira:Clostridium neonatale ratio [117]
Airway mucosal immunity
↑ Bronchial hyperresponsivness [72]
• Corticosteroid resistance [73]
↑ Infiltration of Th17 [74], Th2 [75] or eosinophils [76]
Gut mucosal immunity
• Induction of T regulatory cells by microbially-derived short chain fatty acids [86-89, 91]
• Perturbed IgA responses to gut microbes [95]
• Modulation of iNKT cells [98]
Asthma


A
HEALTHY EPITHELIUM
Lysis/Lysogeny Regulation
Bacteriophage communities
Mucus layer
Mucin binidng
Transcytosis/ Endocytosis/ HGT
TJs
Cilliated cell
Goblet/ Clara cell
Basal cell
Basal Lamina
B
ASTHMATIC EPITHELIUM
Phage Deficiency Lysis/Lysogeny Dysregulation
Mucus hypersecretion
MCC Impairment
Cilia Dysfunction
Bacterial Adhesion/Invasion
Goblet Hyperplasia
Disrupted TJs Access of bacteria
Basal Lamina Thickening
IL25, IL33, TSLP, IL6, IL8

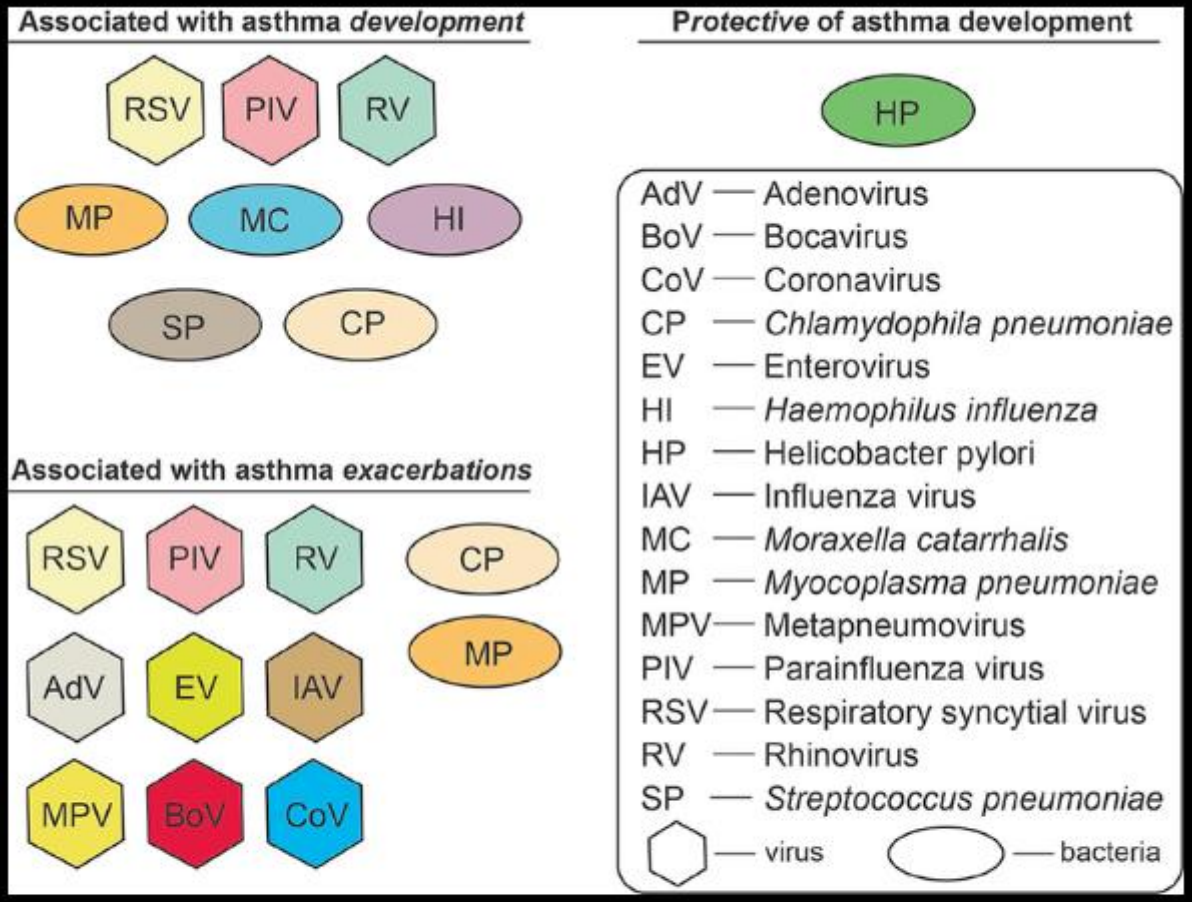


Figure 1.. Pathogens associated with asthma development and exacerbation. Early life infections play a role in the development of asthma and disease exacerbation. This figure lists

Atypical bacterial infection and development of asthma

Infections with atypical bacteria also appear to play a role in the induction and exacerbation of asthma in both children and adults. Several studies suggest that atypical respiratory pathogens such as Chlamydophila pneumoniae (CP) and Mycoplasma pneumoniae (MP) and fungi like Aspergillosis may contribute to the pathogenesis of asthma[55–59].

Chronic CP infections are more frequent in asthmatic patients and have been associated with poor asthma control[60, 61].

Role of Respiratory Microbes in Asthma.

The upper airway, especially the oropharynx and sinuses, has long been recognized to harbor communities of microbes that influence human health, have revolutionized our understanding of microbial communities that reside within the lower airway.

Further microbial community specialization to regions within the lung are also likely: lung explants and post-mortem analyses of patients with cystic fibrosis and chronic obstructive pulmonary disease have demonstrated that unique communities can be discerned between different segments of the lung [56, 57]. The effect of these biogeographical variations in microbial community composition within the airway is not fully understood but have practical and function implications that are important to understanding their role in asthma.

Acquisition of upper airway microbes commences at birth, where early seeding of the respiratory tract (e.g. naso- and oropharynx) occurs during delivery. The types of microbes that initiate early colonization depend on the mode of delivery, with children born vaginally harboring a different consortium of microbes than babies born by Caesarian section [58]. After birth, respiratory microbial community assembly continues to occur over the first two years of life, with stable nasopharyngeal bacterial community structures associated with Dolosigranulum and Moraxella species [59]. Additionally, daycare exposure, viral infections and antibiotic treatment can modulate the composition of the nasopharyngeal microbiota [60].

Obtaining samples from the lower airway requires either invasive bronchoscopy or induced sputum, which requires additional analysis and processing to account for contamination by the upper airway microbiota.

The constituents of the lung microbiota are thought be delivered from the oropharynx through micro-aspiration events and/or mucosal dispersion from contiguous tissues [62]. Microbial density within the lungs is low, with estimates of the densities of microbes within the lower airway being approximately [103-104]

These findings have led to the notion that the bacterial community ecology of the lungs in healthy individuals is determined by the equilibrium established by of immigration of microbes from the upper airway and their elimination, rather than microbial persistence and proliferation in the lower respiratory tract [64].

Changes in the airway microbiota may precede the development of asthma in early childhood [60, 80, 81]. Early colonization with Streptococcus pneumoniae, M. catarrhalis and/or H. influenzae at one month predicts later wheezing, hospitalization and ultimately, the diagnosis of asthma at five years of age [80]. Enrichment of these same taxa within the upper airway microbiota also appears to occur during acute wheezing episodes in children and is a risk factor for wheezing episodes, independent from viral infections [81].

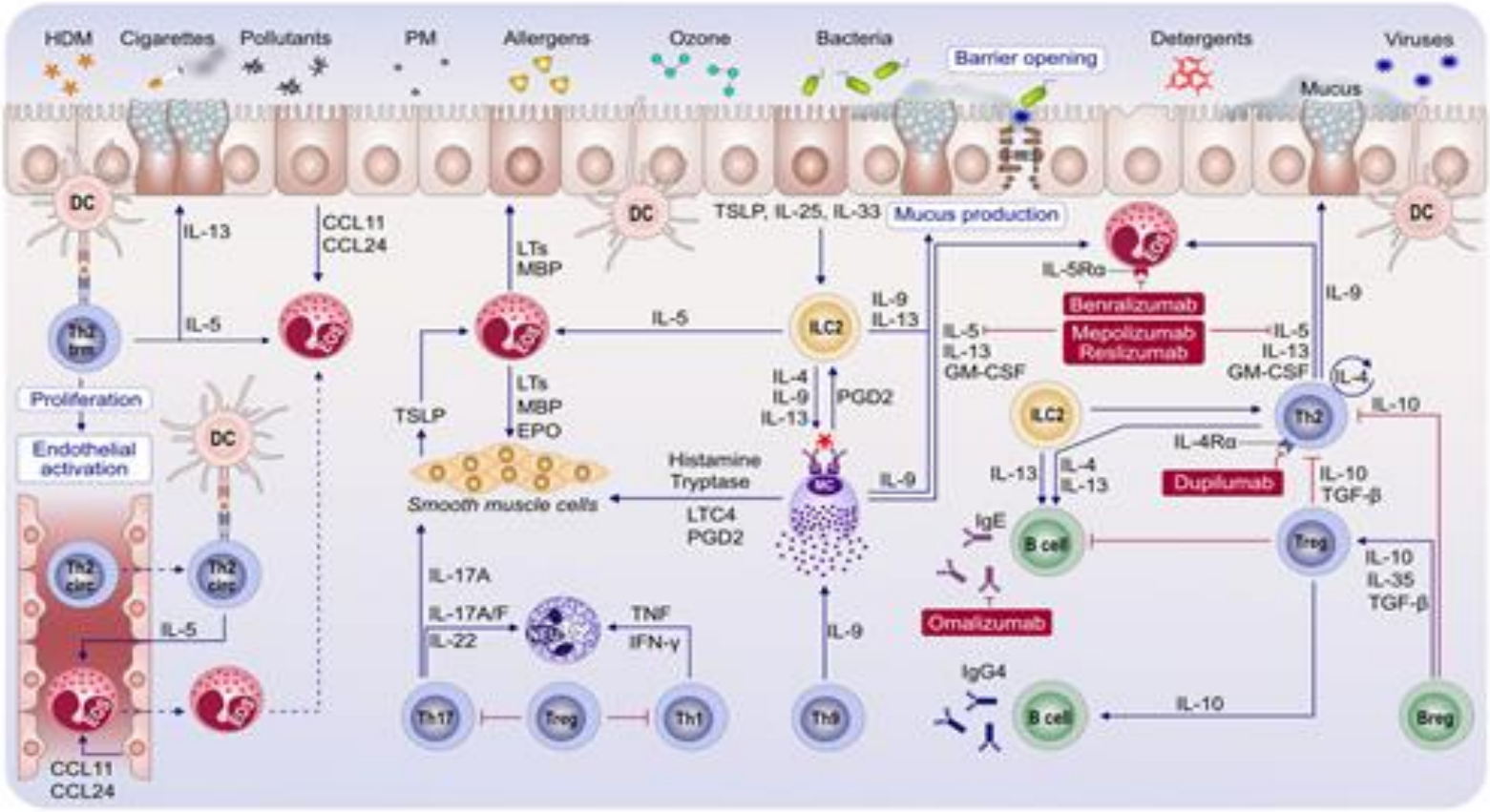
Bacterial colonization also modifies the risk and severity of viral infections--airway microbiota dominated by Moraxella predisposes to lower respiratory tract infections and increases the risk of fever when in the presence of respiratory syncytial virus (RSV) [60].

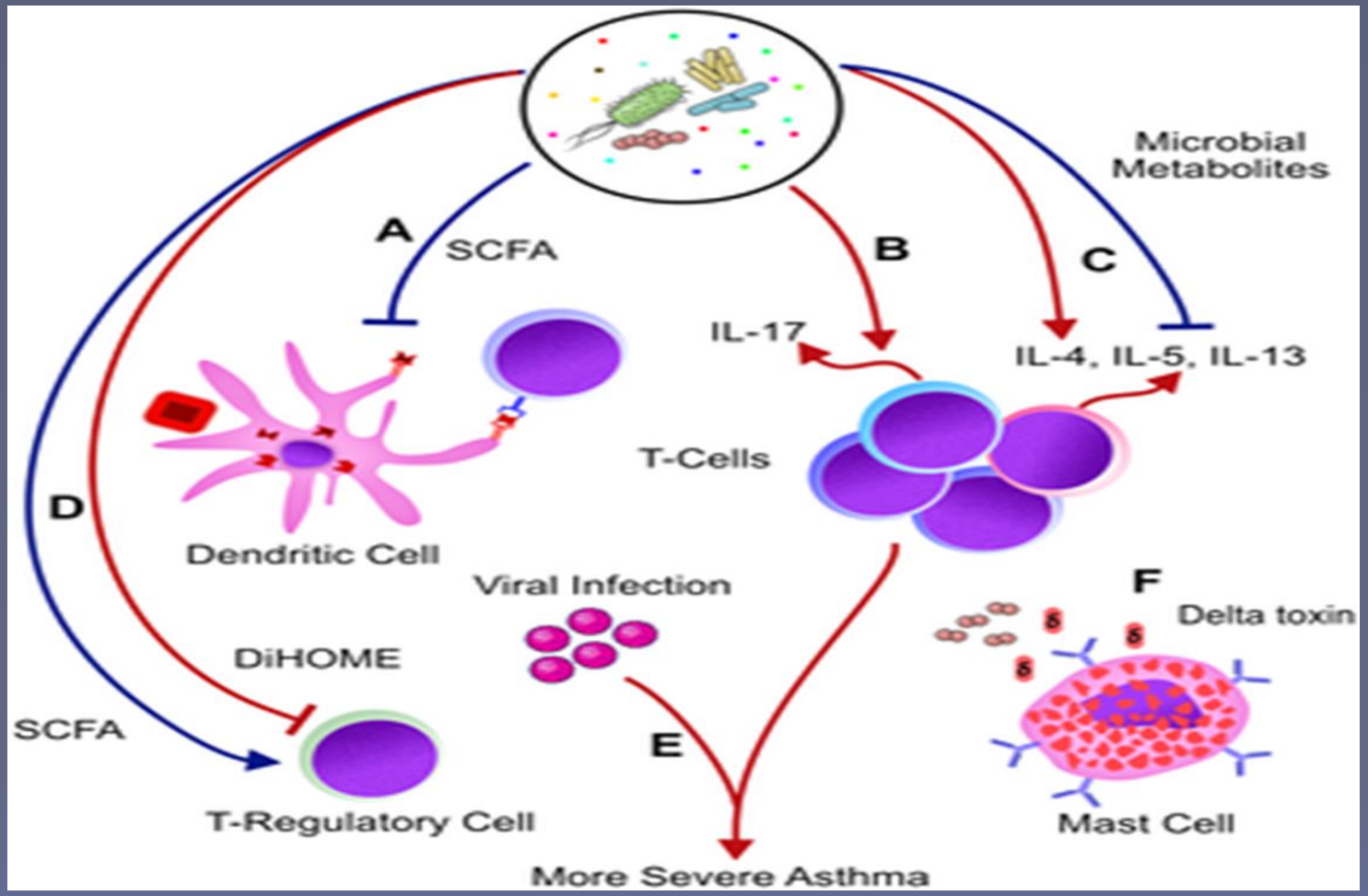
microbes and viruses contribute to the risk of later wheeze.

The Gut Microbiota and Asthma

While the potential for airway microbes to modulate asthma is readily appreciated due to the close proximity of respiratory microbial communities and the sites of allergic inflammation, gut microbes, despite their anatomical separation, are now appreciated to play important roles in asthma.

This crosstalk between the gut and the lungs has been termed the gut-lung axis, which emphasizes the interconnection between gut and lung function [83, 84]. Although a comprehensive understanding of the mechanisms underlying this axis has not yet been achieved, the gut microbiota is thought to play an important role in altering lung function and several contributing pathways have been identified.


HDM
Cigarettes
Pollutants
PM
Allergens
Ozone
Bacteria
Barrier opening
Detergents
Viruses
Mucus
DC
IL-13
CCL11
CCL24
LTs
MBP
TSLP, IL-25, IL-33
Mucous production
IL-5Rα
Benralizumab
Mepolizumab
Reslizumab
IL-9
IL-5
IL-13
GM-CSF
Th2 trm
IL-5
ILC2
IL-9
IL-13
Proliferation
Endothelial activation
LTs
MBP
EPO
TSLP
IL-4
IL-9
IL-13
PGD2
IL-4
IL-10
IL-4Rα
Dupilumab
IL-10
TGF-β
Histamine
Tryptase
LTC4
PGD2
Smooth muscle cells
MC
IL-9
IL-13
IL-4
IL-13
IgE
B cell
Treg
IL-10
IL-35
TGF-β
Th2 circ
IL-5
IL-17A
IL-17A/F
IL-22
TNF
IFN-γ
Omalizumab
IgG4
Th17
Treg
Th1
Th9
B cell
IL-10
Breg
CCL11
CCL24



Short-chain fatty acids (SCFAs) are the main metabolites produced by the microbiota in the large intestine through the anaerobic fermentation

Treg cells

T regulatory cells (Tregs) play a crucial role in immune homeostasis, particularly in allergy. In mice, blockade of peripheral Treg induction results in Th2-type inflammation at mucosal sites in model systems [85].

In humans, Treg responses directly mediate tolerance to allergens [90]. The gut microbiota and their metabolites have been implicated in allergy, in part, due to their ability to modulate the differentiation of Treg cells [91].

Tregs also modulate production of the major mucosal antibody, IgA, through the production of TGfβ. In healthy mice, Tregs direct IgA secretion at mucosal surfaces to exclude microbial ligands, which lowers systemic inflammation due to decreased overall CD4+ T cell activation [92

iNKT cells

Induced NKT (iNKT) cells fill an important niche, bridging both innate and adaptive immune functions. They are capable of massive cytokine release that, depending on the context, can be either Th1 or Th2 predominant, and iNKT dysfunction is implicated in multiple inflammatory disorders [96, 97]. In animals lacking a gut microbiota (germ-free mice), iNKT cells accumulate in the intestines and lungs and confer increased susceptibility to inflammation at these sites compared animals harboring a normal intestinal microbiota [98].

While the role of iNKT cells in the pathogenesis of asthma remains somewhat unclear in humans [99, 100],

Th17 cells

The Th17 axis is important for maintaining barrier function and clearing pathogens at mucosal surfaces, while on the other hand its dysregulation has been implicated in a range of inflammatory disorders [101]. In asthma, Th17 activation reciprocally regulates Th2 inflammation in mice and humans [102] and is associated with a separate endotype of asthma characterized by neutrophilic inflammation and decreased responsiveness to steroids. Hence, it is a potential therapeutic target in severe asthma [103, 104], although the only clinical trial completed to date targeting the Th17 axis showed no treatment effect [105].

The gut microbiota plays a key role in the early development and conditioning of the Th17 axis. Much of the data available linking the influence of the microbiota on Th17 responses comes from animal studies. In mice, a single species of Firmicute, Segmented Filamentous Bacteria, is sufficient to induce Th17 development in the gut [106], which in turn confers protection from subsequent mucosal infections. Th17 inflammatory responses are an example of the gut-lung axs where immune responses originating in the gut lead to lung pathology [107], while respiratory infections inducing a Th17 response can result in intestinal injury [108].

Early establishment of the gut microbiome

Birth Mode

Breastfeeding

Type organism

Birth Mode

Differences in the gut microbiota based on birth mode are associated with development of asthma and allergy.

In children born via vaginal delivery, the first microbial contact occurs during the descent through the vaginal tract, along with incidental exposure to the maternal fecal microbiota. This results in an overall increase in microbial diversity in the infant gut microbiota that is enriched, among others, for Lactobacillus, Prevotella, and Bacteroides,

In contrast, colonization patterns in caesarean-delivered neonates most closely resemble the skin microbiota, and may be no more specific to the birth mother's skin microbes than to those of other caesarean-delivered neonates [58].

Modern trends of increasing rates of caesarean section both in the U.S. [128] and worldwide [129] may be causally linked to rising rates of autoimmune and allergic conditions [130].

Meta-analyses of these studies have found about a 20% increased risk of asthma associated with delivery by caesarean section [131, 132].

Breastfeeding

Breastfeeding plays an important role in shaping the early gut microbiota [112, 113, 133]. In addition to the marked difference between breast-fed and bottle-fed infants, there is a rapid shift in the microbiome of breast-fed infants to a more “adult-like” composition after weaning, suggesting a dominant effect of breast milk components on microbiota composition [112].

Breast milk can also guide the development of the infant gut microbiota by serving as a source of nutrients for microorganisms [134],

delivering immune-active compounds, including maternally secreted IgA, to the infant gut [135-137] and transmitting microbes present in the breast milk itself to the nascent microbial community [138-141]. While decreased rates of breastfeeding [142, 143] show a similar temporal association with increased prevalence of autoimmune and allergic disorders,

Similar to caesarean section, there are tantalizing associations between breastfeeding, the microbiota and asthma.

Antimicrobials

Antibiotics profoundly affect the microbiota [149-151] There is intense interest in the effect of antibiotic use in infancy or early childhood and subsequent asthma risk [153-156]. Currently, no universal agreement exists regarding the role of antibiotics in the risk of asthma in humans, but the potential negative effects of antibiotics on the microbiome and physiology have been demonstrated in mice. Antibiotic exposure during a "critical window" of gut microbial development can result in lasting consequences for the host [157-159]. This critical window is known to be important for allergic airway inflammation: antibiotic treatment of neonatal mice increases susceptibility to asthma, while treatment of adult mice does not[160]. This effect also extends to the perinatal period, where treatment with antibiotics can increase susceptibility to allergic asthma [161, 162].

Do bacteria have a role in asthma development?

The clearest evidence stems from studying asthma exacerbations or wheezing episodes. In clinical studies viruses can be detected in up to 90% of such episodes [1], with rhinovirus being most commonly identified, followed by respirator syncytial virus (RSV) in the first years of life. Other virus such as parainfluenza, metapneumovirus, coronavirus, adenovirus, influenza and enteroviruses have also been implicated,mostly in older patients. In ,10% of episodes multiple viruses were found [2].

In a Danish birth cohort, colonisation with H. influenzae early in life was a risk factor for subsequent asthma.

Obtained aspirates from the hypopharyngeal region of healthy infants at the age of 1 month, cultured the aspirates for H. influenzae, S. pneumoniae, M. catarralis and Staphylococcus aureus and prospectively followed the children until 5 yrs of age.Colonisation of the upper airways with S. pneumonia, H. influenzae or M. catarrhalis, but not S. aureus, was a predictor of recurrent wheeze and asthma at 5 yrs of age [15].

In this issue of the European Respiratory Journal, HOLLAMS et al.[16] report an association between asthma and levels of specific IgE antibodies against S. aureus enterotoxin (SAE) and surface antigens of H. influenzae and S. pneumonia.

Furthermore, these authors showed that this IgE response to RSV early in life was related to recurring wheezing, but not to lung function and allergic sensitisation at age 7–8 yrs [18]. Thus, these findings may suggest that IgE antibodies to RSV occur independently of atopy and may beindicative of an ongoing asthmatic process. IgE antibodies towards bacterial antigens have also been described previously.

In the study by HOLLAMS et al. [16] a positive association between IgE levels against SAE and an inverse relationship between IgE levels to H. influenzae and S. pneumonia surface antigens and asthma in a cohort of 1,380 teenagers is reported.

SAE and H. influenzae and S. pneumonia surface antigens interact quite differently with the immune system. SAE acts as superantigen which can directly activate T-cells and can shift the cytokine pattern towards a T-helper (Th)2 profile. Thus, IgE antibodies to SAE may be regarded as seconding the atopic process as suggested by the authors. In turn, H. influenzae and S. pneumonia surface antigens have to be processed andpresented by antigen presenting cells (APC) to activate T-cellsand, thus, may not directly induce a Th2 response

The effects of Th2 cytokines, such as IL-4 and IL-13,

seem far more complex than just impacting on IgE production

[20]. As HOLLAMS et al. [16] discuss there is some evidence that

Thus, bacterial IgE to H. influenzae and S. pneumonia surface antigens might merely reflect such a downregulating Th2 response and exacerbations induced by viral infections. In this scenario a Th2 response would merely be indicative of an augmented Th1 response brought about by certain bacterial exposures in the airways .

Thus, indirectly corroborate the notion of an increased asthma risk by airway colonisation with“asthmatogenic” bacterial species.

KEY POINTS

Common atypical and non atypical bacterial infections are associated with asthma symptoms and onset.

Antibiotics mitigate asthma severity.

The microbiome in infancy and adult life play an integral role in asthma pathogenesis and persistence.