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Inflammation and infections in asthma

Adrian Gillissen and Maria Paparoupa

Department of Pulmonary Medicine, General Hospital Kassel, Kassel, Germany

Abstract

Introduction: Asthma is driven by an inflammatory response against normally harmless environmental inorganic and organic compounds in the respiratory tract. Immune responses to airborne pathogens such as viruses and bacteria may reduce the allergic responses but are also known to trigger asthma attacks and eventually lead to severe disease condition.

Objective: To investigate the role of respiratory pathogens concerning the induction or protection against acute or chronic asthma manifestations.

Methods: We included 131 articles for the final review according to their relevance with the subject.

Results: There is apparently contradictory interaction of respiratory germs in the airways of asthmatics which may be protective on one angle but deleterious on the other.

Conclusion: The relationship between inflammation and remodeling and the pathogenic role of viral and bacterial infection in the airways of asthmatic patients is still highly debatable and incompletely understood.

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Correspondence
Adrian Gillissen, MD, PhD, MSc, Department of Pulmonary Medicine, Kassel School of Medicine, General Hospital Kassel, Mönchebergstr. 41-43, D-34125 Kassel, Germany.
Tel: +49 (0) 561 980 5263
Fax: +49 (0) 561 980 6795
email: adrian.gillissen@klinikum-kassel.de

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Introduction

The definition of asthma is based on the functional disparities and the underlying inflammation:

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction with the lung that is often reversible either spontaneously or with treatment (1). The asthma nomenclature as well as the definition of disease severity and management goals has changed substantially in recent years. It has moved away from a system predominantly based on lung function and symptoms towards one based on therapeutic methods and doses required to achieve disease control.

Airway inflammation is the central driver of the chronic intermittent nature of asthma symptoms eventually ending in severe asthma attacks (2, 3). The inflammation affects all airways from the upper respiratory tract up to the small airways although its physiological effects are believed to be most pronounced in medium-sized bronchi. If not prevented or therapeutically inhibited, inflammatory processes may lead to a deterioration of the disease. Asthma attacks are potentially life threatening. Acute worsening has many grounds like insufficient treatment, exercise, allergic triggers, cold air but also infectious microorganisms.

This review provides an overview of research published on the cellular basis of this disease, assesses the role of virus and bacteria in acute and chronic worsening.

Inflammation of the airways

Asthma is based on an aberrant immune response to non-pathogenic stimuli in the airways leading to a chronic inflammatory response relevant to the pathogenesis of the disease. The inflammation affects all compartments of the airways including the upper respiratory tract and the nose. The major physiological effect comprises the medium-sized bronchi and the small airways (4). Although the spectrum of clinical symptoms varies widely and typically occur episodically, the underlying chronic inflammation is always present even in the absence of continuous allergen exposure or in a period of relatively minor symptoms. The type of cells and the cellular components involved in the inflammatory processes appear to be comparable regardless of the asthma phenotype, the type of allergy or non-immunologic triggers like exercise or smoke or age. The complex interaction between the multi-cellular inflammatory infiltrate and parenchymal pulmonary cells is organised by a complex network of interacting bioactive mediators (5–7).

Mediators

Numerous cytokines, antibodies and growth factors stimulate or inhibit the immune response, and there is now increasing evidence that the deregulation of endogenous immune regulation processes are at least in part responsible for the manifestation and aggravation of this disease (8). Over 100 mediators have been identified to be involved, among those are:

- Chemokines which recruit inflammatory cells like eosinophils or Th2 cells from the blood vessels into the airways. Examples are eotaxin, thymus and activation-regulated chemokines (TARC) or macrophage-derived chemokines (MDC) (9).
- Cysteinyl leukotrienes which are potent bronchoconstrictors and having proinflammtory potency. They derive from mast cells and eosinophils (10).
- Cytokines orchestrate the inflammatory response. Interleukins (IL) like IL-1ß or tumour necrosis factor alpha (TNF-α) amplify the inflammation, whereas granulocyte macrophage – colony stimulation factor (GM-CSF) prolongs eosinophil survival. IL-5 mediates eosinophil differentiation and survival, and IL-4 is important for Th2 cell differentiation. IL-13 is required for IgE (immunoglobulin E) formation (11).
- Histamine is released from mast cells, and it has various pro-inflammatory functions leading, among others, to vasodilatation or to bronchoconstriction (12).
- Nitric oxide (NO) functions as a vasodilator. Allergic inflammation in the airways activates the inducible NO synthase in bronchoepithelial cells causing higher NO levels e.g. in asthmatic patients (13–15).
- Prostaglandin D2 is a potent bronchoconstrictor released from mast cells which has chemotactic properties on Th2 cells (16).

Structural changes of the airways

Chronic inflammation is often accompanied by remodeling of the tissues. Remodeling can be seen as an adaption to injury and mechanical demands by changing geometry, structure and properties within the airway wall. Patients with poorly controlled asthma develop progressive persistent airflow limitation with longer disease durations and insufficient or no anti-inflammatory therapy providing evidence that airway remodeling plays a crucial role in the impairment of lung function (17–20). It occurs in a wide range of tissues and organs and can be observed in almost all tissues susceptible to repeated chronic injury. In the asthmatic inflammation, it leads to structural changes of the airway which includes changes of the epithelium, subepithelial fibrosis, increased airway smooth muscle mass with hyperplasic and hypertrophic composition, decreased distance between the smooth muscles and the epithelium, thickening of the reticular basement membrane, dysregulated extracellular matrix, mucous gland and goblet cell hyperplasia, vascular changes and oedema (21–24). Some of these changes are related to the severity of the disease and may result in relatively irreversible narrowing of the airways or are related to airway hyperresponsiveness. The thickness of the reticular basement membrane has been correlated to airflow obstruction and increased airway hyperresponsiveness (25–27).

Many cells contribute to tissue injury and repair process. These include inflammatory and structural cells. Th-2 type cells dominate over Th-1 type cells promote subepithelial fibrosis and hyperplasia of airway smooth muscle cells (28).

- Regulatory T-cells exhibit cytokine-dependent suppressive mechanism via IL-10 and TGF-ß secretion. They induce via – among others – the transcription of IL-6, TNF-α and extracellular matrix proteins

(ECM) which leads to subendothelial fibrosis, collagen deposition and increased accumulation of actin-containing smooth muscle cells (29).

• Regulated by proinflammatory chemokines such as RANTES (regulation on activation, normal T cell expressed and secreted), IL-5 and eotaxin, eosinophils accumulate in the airways of asthmatics. They produce many proinflammatory and remodeling cytokines including IL-6, IL-11 or IL-17 (3, 30, 31).

• Airway epithelial cells and mesenchymal cells form a trophic unit. Epithelial damage occurs typically as a response to the environmental exposure, results in production of signals that act on the underlying mesenchyme to propagate and amplify inflammatory and remodeling responses in the submucosa. Allergen sensitisation may be the consequence of a defective airway epithelium leading to an activation of dendritic cells towards promoting a Th2 response. Activated epithelial cells produce, via STAT-6 activation (e.g. by infiltrating T lymphocytes), numerous chemokines including IL-8, RANTES and eotaxin. Further, they release growth factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), TGF-ß and vascular endothelial growth factor (VEGF). All of these advocate airway smooth muscle proliferation, angiogenesis and ECM protein deposition.

• The airway smooth muscle cells are the most important effort cells of the whole inflammatory process. Evidence of either hypertrophy, hyperplasia, or both is reported in mild, moderate and severe asthma, and it is correlated with the severity of the disease. Myocytes proliferate in response to growth factors and inflammatory mediators. They can also increase in size and shape and migrate. Airway smooth muscle cells not only respond to inflammatory processes, they themselves participate in the remodeling process through their release of cytokines like TGF-ß, TNF-α, IL-1ß, IL-8, Interferon-gamma (IFN-γ), chemokines like RANTES, eotaxin, MIP-1α (macrophage inflammatory protein 1alpha) and ECM proteins (2, 32–35). Many of those cytokines induce the expression of toll-like receptors (TLRs) on airway smooth muscle cells. Gram-negative bacteria were suggested to promote airway hyperresponsiveness through TLRs on those cells. Infections in general or viral/bacterial components activate TLRs and thus contribute to remodeling (36–38).

• Fibroblasts differentiate in response to various stimuli into myofibroblasts which secrete, among other inflammatory mediators, ECM proteins (39, 40). In severe asthma, or insufficiently with anti-inflammatory drug-treated asthma, subepithelial fibrosis occurs because of increases deposition of ECM proteins, including collagens I, III, V, proteoglycan, tenascin and fibronectin. The deposition of ECM proteins are regulated by myofibroblasts and the imbalance between matrix metalloproteinase (MMP-9), which degrades collagen 4 and tissue inhibitor of matrix metalloproteinase (TIMP-1) being both secreted by fibroblasts (41).

• Mucus glands are activated in asthma. Increase mucus hypersecretion because of goblet cell proliferation is a common feature in poorly controlled asthma. Predominantly IL-1ß, IL-9, IL-13, TNF-α and COX-2 and their associated intracellular signalling pathways have been shown to be involved in the upregulation of mucin synthesis further promoting goblet cell hyperplasia. However, goblet cell hyperplasia is not a general feature in asthma and only found in a subgroup of patients (42).

Environmental factors such as allergens but also virus and bacterial infection lead to the destruction of the epithelial barrier in the airways and thus contributing to remodeling (43). Vice versa inflammatory damage of the airways alleviates infection eventually leading to an asthma exacerbation. This explains the susceptibility of asthmatic airways to respiratory germs and the impact on the health of poorly controlled asthmatic patients (44, 45). Furthermore, inhaled (virus, bacteria) and even ingested germs (e.g. parasites) interact with the immune system which may enhance or restrain the immunogenic response utilising the same inflammatory pathways as described above (46–48). Infections in early life are linked with subsequent respiratory morbidity, but they were also protective towards the eventual development of allergic diseases and possible asthma as proposed by the hygiene hypothesis (49, 50). Wheezing illnesses including asthma exacerbations are associated with viral or bacterial respiratory infections in patients of all ages (51, 52).

The role of viral infections

Interestingly, viral infection can be both inducers of wheezing but also protectors against the development of allergic disease. Respiratory viral infections are associated with asthma exacerbations which are seen in children as well as in adults. It is not clear if respiratory infections instigate disease progression or intensify severity of the disease, because wheezing episodes due to respiratory infections may diminish with age, but for some individuals they start in early life marking the beginning of a life-long asthma carrier.

Virus trigger in children

There are many virus known to trigger wheezing events including respiratory syncytial virus (RSV), human rhinovirus (HRV), metapneumovirus, parainfluenza and coronavirus. The relation between viral infections and the prevalence in asthma has been best studied in RSV and HRV (53). Natural and experimental viral infection induces activation of transcription factors like NF-κB. This initiate gene transcription of cytokine and chemokine production such as IL-1ß, IL-6, IL-8, IL-11, membrane cofactor protein 1, MIP-1α and RANTES (28, 54–56). These mediators promote tissue infiltration by T cells, eosinophils and basophils. When activated they themselves, release mediators such as eosinophil cationic protein, histamine and with the immunological reaction also virus-specific IgE. The persistence and severity of the inflammation seem to be more pronounced in atopic asthma compared to healthy individuals which is because of an immunological imbalance in Th1- and Th2-type cytokines released during the inflammation.

This cascade of airway inflammation of the initial upper respiratory infection may result in bronchial hyperresponsiveness, (RSV-) bronchiolitis and persistence of asthma symptoms. Even relatively mild viral infections might induce more or less severe inflammation of the airways possibly accompanied by prolonged periods of bronchial hyperreactivity (44, 57, 58). One reason for that phenomenon is the absence of protective immunological memory, another might be a genetically determined premorbid abnormality, simply maternal smoking during pregnancy or involuntary second hand smoke exposure since early years are also known promoters (59).

About half of all patients developing RSV bronchiolitis suffer from persistent episodes of wheezing in early childhood. A child born at the peak of the winter bronchiolitis season has an apparent high risk for developing asthma. Another risk factor seems to be RSV-mediated wheezing illness in early life eventually lead to subsequent persistent wheezing and asthma when a child begins to go to school (57, 60). Various reasons have been discussed for that phenomenon:

- The immaturity of the immune system at the time of initial infections resulting in slower recovery. This might even cause severe symptoms in later years although the starting infection is relatively mild.
- Different genetic background and genetic susceptibility (61–63) or virus strain variability (64).

However, not all investigations have demonstrated such association. May be an additional genetic predisposition for the development of asthma in later years exists as discussed in a twin registry study from Denmark (65).

Also HRVs which trigger the common cold and respiratory tract infections can cause bronchiolitis and promote later asthma. Jackson et al calculated the risk factors for HRV or RSV-induced wheezing illness during the first 3 years of life and the probability of asthma development at the age of 6 with odds ratio 2,6 (95% CI 1,0-6,3) for RSV-related wheezing and 9,8 (95% CI 4,3-22,0) for HSV (57). HRV-related wheezing in the first 3 years was highest when the children acquired an additional aeroallergen sensitisation (60). In contrast, sensitisation during the first year of life had no promoting effect on asthma development. The knowledge of host virus interaction after viral infection during the early phase of their life is essential to understand why some children develop asthma, but others are protected from allergic sensitisation.

Viral infection promote asthma attacks

Sensitive diagnostic tests based on polymerase chain reaction (PCR) or microarray technology revealed that respiratory viral infections are associated with up to 85%–95% of exacerbations of wheezing or acute worsening of asthma (66, 67). Rhinovirus is probably the most important pathogen in triggering asthma attacks. RSV and HRV turned out in epidemiologic studies to be the most often detected viruses depending on season and geographic areas (68, 69). HRV infections peak with asthma hospitalisations in spring and autumn, while RSV is more likely to trigger acute asthma symptoms in the winter time (70, 71). Although there is clear evidence that virus infection is a trigger for asthma exacerbations, there is no clear evidence that asthma patients have more colds than healthy individuals. But asthmatics may suffer from extended duration of illness and increased severity of lower respiratory tract symptoms. This finding suggest that the response to a viral infection but not the frequency differ between susceptible and healthy patients (72, 73). Atopy promotes more severe illnesses than non-allergic asthma after infection with respiratory viruses (71). Delayed viral clearance and increased viral load in the upper respiratory tract are obviously not the reasons for that phenomenon. Authors suggested an abnormal antiviral activity e.g. by reduced generation of interferons to virus infections as a possible reason for increased susceptibility (73) or disruption of the innate immune host defence pathways through the antagonistic interaction between allergic inflammation and antiviral immunity (74).

Hygiene hypothesis

Epidemiological studies have demonstrated that infections within the first year of life protects against the development of atopy and allergy (75). The hygiene hypothesis is drawn from the observation that the individual susceptibility of allergic diseases is promoted by changes in the interaction between the immune system and microbes (76). The following findings hint that infections in early life may protect from atopy:

- Children with more siblings have less skin-prick test reactivity (50).
- The lack of wheezing lower respiratory tract infections in early life coincide with low IgE levels in serum (77, 78).
- The use of daycare centres correlates inversely with the prevalence of typical allergic symptoms (50).
- Children who grew up in close proximity to farms close to livestock within the first year of life or whose parents are farmers also have fewer allergies than those who grew up under cleaner or more hygienic conditions (79). A huge list of putative protective factors have been discussed such as high exposure to endotoxins, exposure to livestock especially cattle, traditional diet, ingestions of unpasteurised milk and many more (80).
- A strong Th1 response of delayed-type hypersensitivity to mycobacterium tuberculosis also reduces atopy incidence (81).

But the hygiene hypothesis has not been unanimously accepted because epidemiologic inconsistencies exist regarding the beneficial but also diseases promoting functions of microbes (82). Many observations seem to contradict the hygiene hypothesis: For example, regardless of the lack of cleanliness in inner cities, allergic sensitisation for example against cockroach allergen increases (83, 84). A more prevailing version of the hypothesis now focuses on the protective role of intracellular mild pathogens ingested through the faecally contaminated environment (water, food) which also includes microbes (85). All of these exposures vanguard a long-lasting immune response, and thus protecting from allergies (62, 82, 86).

The role of bacterial infections

While the importance of viral infections as a source of asthma exacerbations and chronic inflammation of the airways in children and adults is well demonstrated, the role of bacterial infections in the development of stable asthma and acute asthma exacerbations remains more controversial. Of all bacterial respiratory pathogens assumed to have a potential role in the pathogenesis of asthma, *Chlamydophila pneumoniae* (previously *Chlamydia pneumoniae*) and *Mycoplasma pneumoniae* are most commonly discussed in this context (68). Although the cascade of pathogenetic mechanisms between the atypical bacterial infection and airway inflammation in asthma is not yet completely understood, still enough data have been accumulated supporting such a hypothesis (87).

Detection methods of atypical bacteria

The greater limitation of confirming an association between atypical respiratory infection and asthma is the lack of standardised laboratory methods for the detection of these pathogens and the practical or even ethical difficulty of obtaining clinical samples of the lower respiratory tract in asymptomatic population (88, 89). Geographical and temporal variations in the natural history of these infections seem also to play a role. Commonly used methods like serological detection of IgG antibodies cannot distinguish between previous infection, chronic colonisation and reactivation of a chronic infection, while the prevalence of IgG antibodies against atypical bacteria is high among the general population, allowing no comparison between asthmatic patients and control group (90). On the other hand, acute infections and reinfections are not always accompanied by IgM antibodies production causing an even greater uncertainty.

However, molecular methods like PCR enabled over the recent years the detection of these pathogens with higher sensitivity, which is very important in case of chronic colonisation where the bacterial load is very low, and higher specificity, which is also important in order to avoid usually observed cross-reactions (90, 91). The most recently emerged reverse-transcriptase PCR based on the detection of messenger RNA allowed the discrimination between viable and non-viable organisms resulting to a better differentiation between chronic colonisation with viable bacteria and preceding infections with non-viable bacteria (92, 93). Additionally to the refined laboratory methods, numerous human studies have outlined the clinical relevance between atypical infections and asthma, while animal models highlighted the pathophysiological pathways by which these infections promote lung inflammation and airway remodeling.

Cellular changes due to atypical bacteria

C. pneumoniae is predominately implicated as a pathogen in community-acquired pneumonia, but as an

obligatory intracellular bacterium, it has also the potency to cause chronic infection of the affected cells. *C. pneumoniae* infection is associated with the production and release of several cytokines such as TNF-α, IL-8 and INF-γ (94, 95). The major role of these molecules is the attraction of immune cells, like TH-2 and macrophages, as a response against bacterial presence. However, the recruitment of immune cells within the airway wall may subsequently trigger inflammatory responses with tissue damage. The most predominant correlation between immune system activation and structural changes of the airways is mediated through MMPs. MMPs and their physiological inhibitors, tissue inhibitors of TIMPs, are produced by different structural and inflammatory cells mainly by smooth muscle cells of submucosa and stimulated macrophages recruited in the lung. The proteolytic–antiproteolytic activity of these proteins is regulated by several cytokines and thought to be significant for various physiological processes like healing and development. In the contrary, the dysfunction of this proteolytic system provoked by deregulation of their expression or change of their biological activity is involved in a wide range of lung diseases including chronic obstructive pulmonary disease, lung fibrosis, lung cancer and asthma (96, 97).

Additionally to MMPs causing airway wall remodeling (see above), several sophisticated pathophysiological mechanisms are also proposed as a linkage between atypical infection and asthma. An emerging body of molecular studies has shown that *C. pneumoniae* has the ability to inhibit affected cells apoptosis in order to assure the longevity of the host which is a precondition for its own viability as an obligate intracellular pathogen. The impairment of apoptotic mechanisms enhances chronic inflammation by favouring persistent *C. pneumoniae* infection and creates a link with chronic asthma inflammatory manifestations (98, 99). On the other hand, chronically affected cells appear to have an increased susceptibility to respiratory viruses due to impaired apoptosis which may provide evidence that atypical infections can also indirectly contribute to acute exacerbations of asthma (100).

The viral–bacterial co-infection consists a representative example of coexisting causative factors, while further interactions are parallel under discussion even between infectious and non-infectious agents like pollution, allergens, nutrition elements and stressful conditions (101). The most discussed theory in this context is the induction of airway sensitisation against allergens on the ground of chronic *C. pneumoniae* infection. Cellular and molecular studies have partly elucidated the potential role of the immune system in such bacterial–allergens interactions, but more comprehensive analysis remains to be done in order to evaluate all the involving mechanisms (102, 103).

In the contrary *M. pneumoniae*, being an extracellular microorganism, destroys the ciliated epithelium after attached to the bronchial mucosa and is so far associated with a wide spectrum of acute respiratory infections such as pneumonia, exacerbations of bronchitis and bronchiolitis, sinusitis and median otitis (104–106). *M. pneumoniae* infection is also accompanied, as similarly observed by *C. pneumoniae*, with increased production of IgA antibodies and greater mast cell tissue infiltration in the airways and may subsequently play a role in the chronic course of asthma (107).

Do atypical bacteria promote asthma?

All the previous described biological mechanisms, although many of them still under discussion, indicate that atypical respiratory infection may contribute to inflammation and remodeling of the airways of asthmatic patients. Regardless of this, the causative relationship between atypical bacteria and asthma remains unclear, as not all infected patients develop asthma and not all of the people with asthma are found to become infected. The main question to be answered is, whether the atypical infection makes the development of asthma more likely, or pre-existed alterations of the airways favour the colonisation and persistence of these pathogens, leading to their increased detection in asthma as an epiphenomenon with any etiological correlation (87, 108).

However, despite the absence of definite causative direction, many controlled observational clinical studies have demonstrated the association between chronic stable asthma and atypical bacteria as infected subjects were found to have elevated markers of inflammation, increased severity of obstruction identified by FEV1, higher daytime symptom score and required high dose of inhaled corticosteroids in comparison with non-infected controls (46, 100). A strong connection between acute exacerbations of asthma and infection with *C. pneumoniae* and/or *M. pneumoniae* was also identified in the majority of research protocols conducted for this purpose, while insufficient data allow any reliable conclusion about the role of atypical bacteria in late-onset asthma (109, 110). It is important to note that inadequate laboratory methods used for the detection of these pathogens may influence the results of clinical studies, where no

correlation was confirmed, underling the need of more standardised diagnostic techniques in this setting.

Other bacteria involved in asthma

Additionally to atypical bacteria, other respiratory and most recently non-respiratory bacterial species have drawn attention concerning their role in asthma. *Helicobacter pylori* for example is one of the non-respiratory pathogens assumed to have, except of its local complications, systemic immunomodulatory effects that may prevent the development of asthma (111, 112). An inverse prevalence between *H. pylori* infection and asthma is consistently confirmed in many different populations and geographical areas. It still remains unclear if this is an etiological association or an observation triggered by other lifestyle trends or even an incidentally occurred phenomenon (113). Up to now, eradication therapy is no recommended treatment strategy for asthma, as prospective studies are lacking in this field and much more research is required.

Communal bacteria of the human gut are also thought to have an immunomodulatory effect on the innate and adaptive immunity of the host by interacting with immune cells of intestinal mucosa. These interactions lead (i) to the activation of tolerogenic dendritic cells, and through these (ii) to a balanced Th1/Th2 differentiation important for the lifetime maintenance of immune tolerance of the host. If the establishment of intestinal microbiota is disrupted by early-life events like antibiotic use, the tolerogenic immunomodulatory effects are minimised, resulting in overproduction of Th2 cytokines which is a risk factor for autoimmune and allergic diseases (114). Interventional methods with potentially probiotics (*Bifidobacterium* and *Lactobacillus* strains) aiming to create healthy microflora have been intensively tested as treatment or prevention in many allergic diseases like atopic dermatitis, allergic rhinitis and asthma, but so far available studies provide contradictory results, and the generalisation of a positive effect in all allergic conditions should be carefully considered (115, 116).

Sufficient evidence is available suggesting that exposure to *Staphylococcus aureus* and/or its enterotoxins function as an environmental risk factor for the development and severity of asthma. The local or systemic released enterotoxins show superantigen activity and may provoke Th2 and eosinophilic stimulation with multi-clonal IgE production leading to deterioration of upper and lower respiratory tract atopic diseases (117). Specific IgE antibodies against *S. aureus* enterotoxins are more likely to be found in patients with nasal polyps, allergic rhinitis, chronic rhinosinusitis and asthma, and may indicate a future therapeutic target (118).

The role of other respiratory bacteria like *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* was mainly discussed in the framework of hygiene hypothesis (see above) where infections in early years was claimed to have a protective effect against asthma and atopy development. In contrast of being protective, these pathogens more often cause severe persistent wheeze in preschool children, and this group may significantly benefit from long-term antibiotic treatment (119). It was also found that neonates colonised in hypopharyngeal region are under increased risk for recurrent wheeze and asthma within the first 5 years of life (120). Particularly evident is the association of these pathogens with a subset of stable asthma, known as neutrophilic asthma, where inflammation is primarily mediated by neutrophils and less by eosinophils. *H. influenzae* was isolated from the airways of neutrophilic people with asthma, and infection-induced inflammation was mediated by IL-17 expression (121).

The role of antibacterial therapy in the control of asthma

Asthma is a complex disease with a great heterogeneity in its clinical features and even greater heterogeneity in treatment responses as a result of individual environmental and genetic pressures. Therapeutic measurements cannot always adequately cover all different subtypes of the disease and even patients having the same clinical phenotype may not benefit equally. The complexity increases as more than one pathogen is involved in the pathogenesis. An accumulating number of new therapies are emerging as highly efficient, especially for patients with persistent asthma. This benefits optimised health care but it is also a challenge for the selection of the right target group for each compound. The opportunity of phenotype-driven treatment options may open the way for personalised health care in asthma (122, 123).

Antibiotics and especially macrolides (erythromycin, clarithromycin, roxithromycin, azithromycin) were tested in this context aiming against persistent atypical infection in chronic asthma or in acute exacerbations caused by atypical bacteria. Their effects were recognised as time as well as dose dependent, but the underlying mechanisms of their action is not completely clarified. Macrolides, except of their obvious antimicrobial properties, are shown to exert anti-inflammatory and immunomodulatory activity by

suppressing the production of cytokines in inflamed tissue (124, 125). They have been reported to reduce airway hyperresponsiveness, improve pulmonary function and sometimes soften the symptoms, but it still remains a matter of debate if this is an antimicrobial effect resulting to the limitation of the bacterial load or just an anti-inflammatory action of the macrolide, or both as the reduction of bacteria is subsequently followed by decreased cytokine expression (126). Much additional research is required to define the right agents for the right patient, the optimum dosage and duration of therapy and the adequate treatment until macrolide treatment can be recommended as a long-term treatment option for asthma patients (127).

In the contrary, the antibiotic exposure during pregnancy or within the first years of life is thought to be associated with increased risk of childhood asthma through incomplete establishment of microflora or modified natural exposure in pathogens described by the hygiene hypothesis. Studies conducted to clarify this matter confirmed an increased risk of developing asthma in later years, but many factors confound this relationship (128, 129).

The role of parasitic infections

Epidemiologic data suggest that helminth infections may be protective against asthma, as allergic diseases are rarely observed in populations where prevalence of intestinal parasites is high. It is thought, that the immunomodulatory effect of the parasites which is supposed to influence atopic responses is mediated by regulation of Th2 differentiation and IgE production (130). However, a meta-analysis of epidemiologic studies did not confirm this general conclusion, as only infection with *hookworm* was found to be protective, while *Ascaris lumbricoides* was associated with increased risk of asthma, and no significant effect was found with other species. *Trichuris trichiura* in early life are associated with less positive prick tests in childhood, while *Toxocara* infection increases the risk of wheeze in some populations (47). Apparently, the positive or negative effect of helminths in allergy and asthma differ between different species, and it is now suggested that many more factors can also be causative for this interaction as the chronicity, the timing and the parasitic burden of the disease (113, 131).

What can we learn from this?

The relationship between inflammation and remodeling and the pathogenic role of viral and bacterial infection in the airways of asthmatic patients is still highly debatable and incompletely understood. The presence of airway inflammation does not always translate into irreversible changes in many cases, and there is not always a clear-cut relationship between the degree of inflammation and the level of remodeling (Fig. 1). Remodeling processes in paediatric population raises further questions about the meaning of chronic inflammation and the genetic susceptibility that needs to be explored. This area is certainly challenging in regard to the development of new therapeutic compounds aiming at the inhibition of specific inflammatory pathways including those triggered by viruses and bacteria. Finally, identification of biomarkers identifying remodeling is essential to study these processes in detail: (i) to identify patients being particularly at risk to

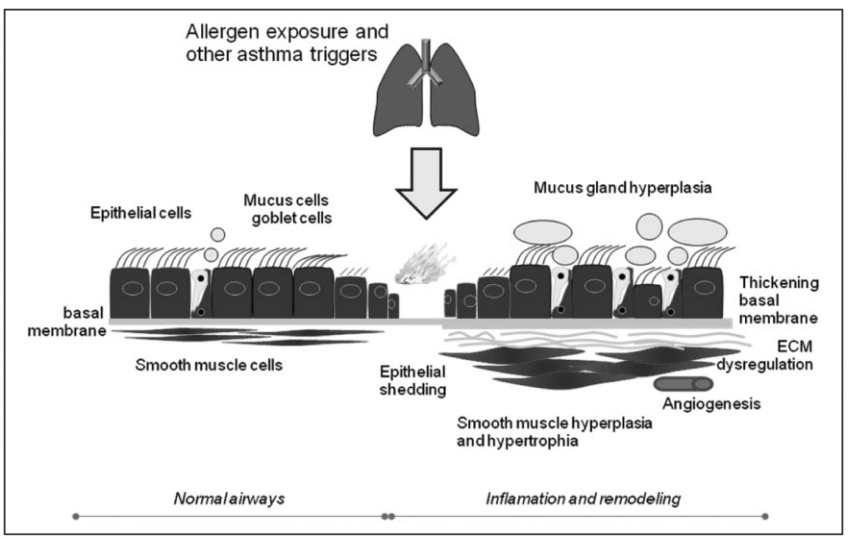

Figure 1. Chronic inflammation in the airways leads to remodeling in the airways (right side). ECM, extracellular matrix.

develop those irreversible changes, and (ii) to clarify the effect of anti-inflammatory treatment regimes.

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