Paediatrica Indonesiana
Paediatr Indones 2001; 41:125-131

Review article

Airway remodeling in asthma

Roni Naning, MTS Darmawan

Department of Child Health, Medical School, University of Gadjah Mada/Sardjito General Hospital, Yogyakarta

ABSTRACT Airway remodeling is the term given to a series of structural changes characterized by chronic, irreversible airway obstruction. Structural changes in the airway wall caused by chronic inflammation of asthma. Evidence for asthma airway remodeling demonstrating an accelerated decline of lung function that cannot be completely reversed with therapy. Combination therapy produced at least as much protection against inflammation as the use of the higher dose of the inhaled corticosteroid. **[Paediatr Indones 2001; 41:125-131]**

Keywords*: childhood asthma, airway remodelling, pathophysiology*

ASTHMA IS THE MOST COMMON CHRONIC DISEASE OF childhood[1;] Its prevalence in this age group is increase.[2,3,4] While the reasons for this reported increase, and indeed the true magnitude of the increase, remain unclear, there can be no doubt that asthma is now a major health problem in children worldwide.[1,3]

In the US, incidence of acute asthma, defined as the number of persons who develop asthma within a specific time period, is approximately 0.2-0.4% annually. Childhood asthma persists into adulthood in 30% of cases. Those with symptoms persisting into the second decade of life usually have asthma throughout adulthood. Asthma prevalence is 4-8% (ie, 10-20 million persons); one half of these cases are children (ie, 7-19% of all children).[4]

Correspondence: Dr. Roni Naning, Department of Child Health, Medical School, Gadjah Mada University, Jalan Kesehatan No. 1. Yogyakarta, Indonesia.

About one third of the US adult population experiences symptoms of gastroesophageal reflux on a monthly basis. Asthma is present in about 5% of the same population,[5] that accounts for 1.5-2 million ED (?) visits each year. In urban centers, cases of acute asthma may comprise 2.5-10% of all ED(?) visits.[4] It runs in families, with atopy associated with chromosomes 5 & 11. Mortality from status asthmaticus has been increased since 1980, with 1 to 2 % of patients with severe asthma dying during an exascerbation.[2] Unfortunately, there is no identified means to prevent asthma and consensus to prevent the natural progression of the disease.[1]

The clinical course and natural history of asthma may vary significantly from one individual to another. The majority of asthma has its onset early in life, usually before age 6. Although some children may experience remission, others have symptoms that persist into adulthood. In addition, some individuals continue to have progressive, irreversible airway obstruction.[6]

Definition

There is no single definition of airway remodeling in asthma. Remodeling has been described as persistent structural changes in the airways that are thought to occur as part of the disease process. These may include increases in the thickness of the airway wall, alterations in the extracellular connective tissue components of the wall including the sub-basement membrane, and increased number (hyperplasia) and/or increased size (hypertrophy) of resident cells, including airway smooth muscle cells and glandular epithelium. However, that the direct link of airway inflammation to the pathogenesis of airway remodeling remains unclear.[6]

The term "airway remodeling" in asthma refers to structural changes that occur in conjunction with, or because of, chronic airway inflammation. Airway remodeling results in alterations of the airway epithelium, lamina propria, and submucosa, leading to thickening of the airway wall. The consequences of airway remodeling in asthma include incompletely reversible airway narrowing, bronchial hyperresponsivenesss, airway edema, and mucus hypersecretion.[7]

Working definition of airway remodeling: the noninflammatory alterations in structural cells and tissues of the asthmatic airway. These changes appear as airway wall thickening, subepithelial fibrosis, and mucus cell hyperplasia and metaplasia. Conceptually, airway remodeling may, in turn, contribute to changes in airway hyperreactivity, disease severity, and incomplete resolution of asthma.[8]

Childhood asthma

Asthma often begins in childhood, and when it does, it is frequently found in association with atopy, which is the genetic susceptibility to produce IgE directed toward common environmental allergens, including house-dust mites, animal proteins, and fungi.[9]

Asthma appears to be a biphasic disease, with its greatest impact in early childhood and older adults. Risk factors for adult asthma include early-onset childhood asthma, airway hyperresponsiveness, abnormal lung function at ages 15-35 years (the low prevalence time for asthma), personal or family history of atopy, female gender, and history of cigarette smoking. Having an FEV_1 at 80% of predicted levels at age 20 is below the 95% confidence level for normal lung function. Patients with more symptomatic disease are likely to experience greater airway dysfunction in the future.[1, 10] The highest prevalence of the disease occurs in childhood and then again in middle age and older adults.[1]

With the production of IgE antibodies, mast cells and possibly other airway cells (e.g., lymphocytes) are sensitized and become activated when they encounter specific antigens. Although atopy has been found in 30 to 50 percent of the general population, it is frequently found in the absence of asthma. Nevertheless, atopy is one of the strongest predisposing factors in the development of asthma. Furthermore, among infants and young children who have wheezing with viral infections, allergy or family history of allergy are most strongly associated factor with continuing asthma through childhood.[9]

Airway remodeling

Central to this variability in disease progression is the concept of "airway remodeling," the term given to a series of structural changes characterized by chronic, irreversible airway obstruction.[6] Structural changes in the airway wall caused by chronic inflammation of asthma -called airway remodeling- can lead to irreversible decline in lung function. Evidence for asthma airway remodeling comes from clinical studies, and demonstrated an accelerated decline of lung function which cannot be completely reversed with therapy. The permanent destructive changes, which can be seen through electron microscopy, include thickening of the sub-basement membrane and the destruction of elastic tissue, he said (?) . This elastic tissue acts as an opposing force to smooth muscle contraction and therefore tends to keep the airway open. Without it, contraction force produced by smooth muscle is unopposed.[11]

Airway remodeling in asthma thus may predispose persons with asthma to asthma exacerbations and even death from airway obstruction caused by smooth muscle contraction, airway edema, and mucus plugging. Although it has been learned in the past 25 years about the pathophysiology of airway inflammation and airway remodeling in asthma, important questions remain about the relationship between airway inflammation and remodeling, the natural history of airway

remodeling, and the effects of current asthma treatments on remodeled airways.[7] The best documentation of remodeling comes from patients who died from asthma; evidence from transbronchial biopsy specimens from patients with less severe asthma is less definitive due to the small size of the sample (usually less than 2 mm in diameter). Epithelial shedding may occur in association with exposure to the toxic granule proteins released from activated and degranulated eosinophils.

Until recently, information on airway pathology in asthma has come largely from post-mortem examination, which shows that both large and small airways often contain plugs composed of mucus, serum proteins, inflammatory cells, and cellular debris. Viewed microscopically, airways are infiltrated with eosinophils and mononuclear cells, and there is vasodilation and evidence of microvascular leakage and epithelial disruption. The airway smooth muscle is often hypertrophy, which is characterized by new vessel formation, increased numbers of epithelial goblet cells, and deposition of interstitial collagens beneath the epithelium.

These features of airway wall remodeling further underscore the importance of chronic, recurrent inflammation in asthma and its effects on the airway. Moreover, these morphologic changes may not be completely reversible. Consequently, research is currently focused on determining whether these changes can be prevented or modified by early diagnosis, avoidance of factors that contribute to asthma severity, and pharmacologic therapy directed at suppressing airway inflammation.[9] The submucosa may be infiltrated with inflammatory cells, including eosinophils and lymphocytes, fibrotic changes in connective tissue between the cells, increased smooth muscle mass, mucous gland hypertrophy, and increased vascularity. Irreversible airway obstruction, especially in older asthmatic patients, may also be caused by smoking, resulting in emphysema or chronic bronchitis. A number of factors are important to consider in approaching the debate over airway remodeling.[6]

In some patients with asthma, airflow limitation may be only partially reversible. The etiology of this component is not as well studied as other features of asthma but may relate to structural changes in the airway matrix that may accompany longstanding and severe airway inflammation. There is evidence that a histological feature of asthma in some patients is an alteration in the amount and composition of the extracellular matrix in the airway wall. As a consequence of these changes, airway obstruction may be persistent and not responsive to treatment. Regulation of this repair and remodeling process is not well established, but both the process of repair and its regulation are likely to be key events in explaining the persistent nature of the disease and limitations to a therapeutic response. Although yet to be fully explored, the importance of airway remodeling and the development of persistent airflow limitation suggest a rationale for early intervention with anti-inflammatory therapy.[9]

Structural changes in the airway wall caused by chronic inflammation of asthma - called airway remodeling - can lead to irreversible decline in lung function. Evidence for asthma airway remodeling comes from clinical studies demonstrating an accelerated decline of lung function that cannot be completely reversed with therapy. The permanent destructive changes, which can be seen through electron microscopy, include thickening of the sub-basement membrane and the destruction of elastic tissue. This elastic tissue acts as an opposing force to smooth muscle contraction and therefore tends to keep the airway open. Without it, contraction force produced by smooth muscle is unopposed.[11]

It was generally believed that these structural changes in the airways of asthmatics required years to develop and was seen only in patients with severe asthma. Many experts date the change in thinking to several studies published in the early 1990s.[12] An important advance in our understanding of the pathophysiology of asthma has been found that airway inflammation was not confined to severe asthma but also characterizes mild and moderate asthma.[7]

Trophic changes include smooth muscle hypertrophy, new vessel formation, increased numbers of epithelial goblet cells, and the deposition of interstitial collagens beneath the epithelium (basement membrane thickening) as well as airway wall remodeling. Thus there is evidence of both acute and chronic inflammation that is irregularly distributed throughout the airways. There is accumulating evidence that other trophic changes, including hypertrophy and hyperplasia of airway smooth muscle, increase in goblet cell

number, enlargement of submucous glands, and remodeling of the airway connective tissue, are important but neglected components of the disease. Although many of the mediators responsible for these changed, the airway architecture have yet to be defined, cytokines and growth factors seem to be particularly important.[13]

What are the cellular events associated with the development of airway remodeling ? Using a mouse animal model that over-expresses interleukin-11 (IL-11), Dr. Elias was able to demonstrate that this cytokine was associated with an increase in the number of mononuclear cells, enlarged alveoli, fibrotic remodeling, fibrosis, and collagen deposition. These changes are consistent with the physiologic alterations that are associated with an increase in airway hyperreactivity and a doubling of airway resistance. In a group of parallel studies, further he demonstrated that IL-13 could cause hypertrophy of epithelia cells, increased subepithelial fibrosis, and increase in mucus production. In humans, IL-13 is known to be elevated in patients with asthma. Although IL-11 appears to be normal in patients with mild asthma, IL-11 expression is increased in those with severe asthma. These data support the multiple cytokine hypothesis of airway remodeling. [8]

Mechanical stress as a cause of remodeling

An intriguing hypothesis of remodeling — that mechanical stress, rather than inflammation, leads to remodeling. Numerous studies have demonstrated an increase in subepithelial collagen thickness in patients with asthma. Fibrosis is thought to derive from the products of inflammatory cells and or airway constriction. Can the airway remodeling that produces buckling of the airway produce further change? Is airway bronchoconstriction further involved in the process of airway remodeling? Preliminary evidence suggests that this may be the case.[8]

Although asthma is mostly considered an airway inflammatory disease, it is possible that some of the airway function changes observed, particularly persistent airway hyperresponsiveness are, largely due to airway remodeling. Indeed, the bronchial structure of asthmatic subjects is quite altered, the most evident features being damaged epithelium, subepithelial collagen deposition, increased goblet cell numbers, enlarged bronchial smooth muscle layer area, and changes in various extracellular matrix components such as glycoproteins. These changes are probably part of an abnormal repair process secondary to intense and/or repeated inflammatory insults in subjects predisposed to develop those alterations. This abnormal repair process may be initiated or modulated by mediators and cytokines released by lymphocytes, eosinophils, macrophages, mast cells or other resident cells. Epithelial damage may also be involved in the initiation of the fibrotic process, since epithelial cells are able to release different mediators and cytokines.[9,14] A key-cell in extracelular matrix changes is the fibroblast. Activated macrophages and eosinophils produce TGF-ß1, which induces transformation of fibroblasts into myofibroblasts, with actin expression. Furthermore, according to some of our recent observations, asthmatic bronchial fibroblasts synthesis of collagen seems to be increased.[14]

Mast cells and fibrosis

Mast cells are frequently found in sites of chronic inflammation throughout the body and have been associated with pulmonary fibrosis. A major product of the mast cell is tryptase, a serine protease that is stored preformed in the mast cell granule. Tryptase stimulates the synthesis of type I collagen by human lung fibroblasts. Because the number of mast cells in the airway tissues is typically increased, even in subjects with mild asthma, and because mast cell activation by allergen results in the release of tryptase into the airway, the mast cell is believed to contribute to remodeling.

It has been reviewed evidence from studies in which human mast cells (HMC-1) were cocultured with fibroblasts. Mast cell–derived histamine and tryptase had direct effects on fibroblast proliferation and on collagen synthesis. In addition, HMC-1 sonicates augmented the ability of cultured fibroblasts to contract the collagen lattice on which they were cultured, presumably by inducing alpha–smooth muscle actin, the actin isoform found typically in vascular smooth muscle.[14]

The role of eosinophils and its effects

The exact role of eosinophils in airway remodeling is unclear. Typically, asthma is characterized by increased

numbers of eosinophils in the airway, even under stable conditions, and eosinophils are recruited into the airway following allergen exposure. The ubiquity of eosinophilic inflammation has lead some to suggest that asthma be renamed "chronic eosinophilic bronchitis." Eosinophils produce a variety of mediators that contribute to airway inflammation: leukotrienes, granule proteins, toxic oxygen products, and cytokines. In addition, metalloproteinases, collagenase, and growth factors from eosinophils may be important in regulating matrix tissues. It has also been reported on studies of the effects on fibroblasts of sonicates obtained from purified human eosinophils. These solutions, containing all of the preformed mediators produced by eosinophils, enhanced fibroblast proliferation, and enhanced fibroblast contraction, and studies with neutralizing antibodies suggest that most of the eosinophil-induced enhancement was attributable to transforming growth factor (TGF)-beta.[14]

Mast cells and eosinophils: summary

The effects of mast cells and eosinophils as follows: Both have the capacity to act as direct modulators of fibroblast proliferation, collagen synthesis, and lattice contraction, although they act through different mediators. Because they both have similar effects on lung fibroblasts, they were "collaborators" in tissue repair and possibly fibrosis. [11,14]

The role of myofibroblasts

The myofibroblast is a distinct fibroblast phenotype that is believed to play a critical role in pulmonary fibrosis. Myofibroblasts are characterized by the expression of alpha–smooth muscle actin. Various cytokines can induce the transformation of fibroblasts to myofibroblasts, but TGF-beta is the most important inducer of alpha–smooth muscle actin. Myofibroblasts produce a variety of cytokines whose functions appear to be important in inflammation and repair. These include MIP-1–alpha, MCP-1, and TGF-beta — agents that recruit inflammatory cells and stimulate extracellular matrix production.[14]

Airway remodeling: functional consequences

Certainly, there is great potential for histologic changes in the airway to affect its function, but controversy remains regarding physiologic impact of airway remodeling. Modest amounts of airway wall thickening may have little effect on airflow when airway smooth muscle is relaxed. However, when bronchoconstriction occurs, exaggerated airway narrowing may develop because of this increase in wall thickness. Both hypertrophy and hyperplasia of airway smooth muscle have been reported in asthma**,** and these changes, along with airway wall thickening, may be important causes of airway hyperresponsiveness.[9,14]

The summary of potential mechanisms by which structural changes in the airway might change airway function. Increased intraluminal secretions may amplify airway narrowing. Increased thickening of the inner wall of the airways may amplify narrowing, and stiffening of the airway wall may increase the elastic load. Increases in thickness of the muscle layer may increase force and shortening against the elastic load. Finally, increased outer wall thickness may decrease the parenchymal load transmitted to airway smooth muscle and result in increased smooth muscle shortening. It is concluded that evidence for remodeling is definite; evidence that it matters remains theoretical.[14]

Therapy and prevention

Over the past decade, the thinking about the pathophysiology of asthma has shifted away from abnormalities of airway smooth muscle and toward a focus on the role of airway inflammation. It is now generally well accepted that airway inflammation is a critical feature in the pathogenesis of asthma. It is less clear, however, what the long-term consequences of this inflammation are.[14] Airflow limitation sometimes fails to reverse with corticosteroid treatment. The cellular and molecular basis of this "steroid resistance" may be at the steroid receptor transduction level or may be associated with structural changes to the airway matrix accompanying longstanding and severe airway inflammation.[13]

Newer approaches to therapy

A number of investigators are examining primary treatment of persistent asthma. Some patients respond to single agents, but those with more resistant symptoms require combination therapy to achieve the

goals of care.

Monotherapy Comparisons

Can lower doses be effective ? A comparison of flunisolide 2000 mcg/day and fluticasone 800 mcg/day. This study demonstrated that a lower dose of fluticasone was associated with statistically greater improvement in lung function as well as patient-oriented outcomes such as nighttime awakening. Dose of fluticasone also produced greater improvement in methacholine-induced bronchial hyperreactivity.[8]

The use of once-daily inhaled corticosteroids was the topic of 2 other studies. Bensch and colleagues studied the use of mometasone at nighttime for the control of asthma. The patients selected for this study had previously been maintained on short-acting bronchodilators. When switched to 1 evening dose of this inhaled corticosteroid, there was clinically significant improvement in lung function compared with placebo controls.[8]

In a pediatric open continuation study of fluticasone once daily, Clements and coworkers also demonstrated safety and efficacy of this inhaled corticosteroid. This 3-armed study consisted of once-daily, twice-daily, and placebo groups. The previous closed-label portion of the study, demonstrated the efficacy of this once-daily dosing.

These 2 studies demonstrate the potential use of these products in a once-daily dose. This dosage regimen is more convenient for patients and may promote better compliance.[8]

Combination Therapy

During the past several years, many studies have demonstrated superior clinical improvement of lung function in patients who treated with a combination of a long-acting bronchodilator and fixed dose of an inhaled corticosteroid versus a double dose of the inhaled corticosteroid. One of the questions has remained unanswered is whether the equal reduction in airway inflammation between these regimens. In a study by Wilson and colleagues, 56 patients with symptomatic asthma were randomized to 1 of 3 regimens: fluticasone 200 mcg/day, fluticasone 500 mcg/day, or fluticasone 200 mcg/day plus salmeterol 50 mcg. Bronchoscopy with biopsy was conducted before and then 12 weeks after treatment. The patients treated with the combination of fluticasone and salmeterol had greater reductions in mast cells and activated T lymphocytes. Both the combination regimen and the higher dosage of fluticasone protected against increases in CD3+ and CD4+ T lymphocytes that were seen with the lower dose of the inhaled corticosteroid. The combination also produced reductions in the expression of IL-4 and VCAM-1. The investigators concluded that combination therapy produced at least as much protection against inflammation as the use of the higher dose of the inhaled corticosteroid.[8]

This report is consistent with previous data demonstrating that inhaled corticosteroids combined with long-acting bronchodilators produce decreases in exacerbation in patients with asthma. The Formoterol and Corticosteroids Establishing Therapy (FACET) study showed decreased exacerbation with the combination of budesonide and formoterol. A report by Matz at the annual meeting of the American Academy of Allergy showed a similar decrease in exacerbation rates with the combination of fluticasone and salmeterol. These decreases in exacerbations are consistent with the changes noted in inflammation.

Continuing the examination of combination regimens, comparison budesonide 800 mcg and formoterol with the combination of fluticasone 250 mcg and salmeterol, the latter in a single inhaler. Both regimens produced equivalent improvement in lung function, but fluticasone-treated patients had greater improvement in symptom-free nights.[8]

Prevention of asthma airway remodeling also includes standard therapeutic approaches of allergen avoidance, environmental control and allergy vaccination (immunotherapy).[11]

References

1. **Stempel DS.** Asthma: A Disease of the Young and Old. Asthma and Immunology Annual Meeting. American College of Allergy; 1999 November 14
2. **Shreve M.** Asthma: Epidemiology & Pathophysiology. From: http://www.picuBOOK.net/1999/03-03(el)
3. **Valacer DJ.** Childhood asthma: causes, epidemiological factors and complications. Drugs 2000;(59 Suppl 1:1-8): 43-5
4. **Brenner B, Bessman E, Talavera F, Blackburn P,**

Halamka J, Adler J. Asthma, Author Information. Topic Last Updated: 2001 March ;10, pg ??

5. **Alexander JA, Hunt LW, Patel AM.** Prevalence, pathophysiology, and treatment of patients with asthma and gastroesophageal reflux disease. Mayo Clin Proc 2000;75(10):pg 1055-63
6. **O'Hollaren MT.** Airway Remodeling: Where's the Evidence?. American College of Allergy, Asthma and Immunology Annual Meeting. Day 4 – 1999 November 15
7. **Fahy JV, Corry DB, Boushey HA.** Airway inflammation and remodeling in asthma. Curr Opin Pulm Med 2000;6(1):15-20
8. **Stempel DA.** Airway Remodeling and Asthma: A Confederacy of Factors. 96th International Conference of the American Thoracic Society. Day 1 - 2000 May 5
9. **Peterson MW.** Asthma Education: Interactive Guidelines Pathogenesis and Definition. Last Revision Date: December 1998, pg ??
10. **Stempel DA**. Is Asthma an Irreversible Lung Disease? American College of Allergy, Asthma & Immunology Annual Meeting. Day 2 – 1999 November 13,
11. **Faber JA**. Airway remodeling in asthma can result in irreversible decline in lung function. News Release: 1998 November 6, pg ???
12. **Lazarus SC**. Airway Remodeling in Asthma. American Academy of Allergy, Asthma and Immunology 56th Annual Meeting Day 4 – 2000 March 7
13. **Lenfant C, Khaltaev N**. Global Initiative for Asthma (GINA). National Institutes of Health, National Heart, Lung and Blood Institute, Workshop Report Publication 1995 #95-3659