Role of Airway Smooth Muscle Cells in Asthma

Essay

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in **Internal Medicine**

By

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Introduction

Asthma affects people of all races and ethnic groups worldwide, from infancy to old age, with slightly more boys than girls affected and, after puberty, more women than men. Dramatic increases in the prevalence of atopy and asthma have occurred over the past few decades in Westernized countries and more recently in less-developed nations. Estimates suggest that as many as 300 million persons are affected worldwide **(Fanta, 2009).**

Severe asthmatic exacerbations and asthma-related mortality rose steeply in the United States. Yet despite the persistently high prevalence of disease, the most recently available data indicate improved outcomes, with fewer annual hospitalizations for asthmatic attacks and fewer asthma-related deaths. Among the possible explanations for these favorable trends are the more widespread preventive use of inhaled corticosteroids and the introduction over the past 10 to 15 years of new, highly effective medications and improved medication formulations for the treatment of asthma (**American Lung Association, 2004).**

Airway obstruction in asthma and the consequent symptoms of cough, shortness of breath, chest tightness, and wheezing are caused by some combination of airway smooth-muscle constriction and inflammation of the bronchi. The former can be severe, leading to life-threatening narrowing and closure of airways, even in the absence of mucous plugging.

Both abnormal smooth-muscle contractility and excess smooth-muscle mass may contribute (**Shore, 2004).** Airway inflammation in asthma consists of mucosal, submucosal, and adventitial edema; cellular infiltration, particularly by eosinophils (and in some cases, neutrophils) and activated helper T lymphocytes as well as mast cells that (unlike mast cells in other eosinophilic airway diseases) infiltrate smooth-muscle bundles; increased airway secretions, including secreted mucus, desquamated lining cells, and intraluminal eosinophils; capillary engorgement; hyperplasia of smooth muscle; and deposition of excess collagen, particularly immediately beneath the basement membrane of the epithelium **(James et al., 2007).**

Moreover, ASM may secret cytokines and express cell adhesion molecules that are important in modulating the submucosal airway inflammation and remodeling; thus becoming a proinflammatory cell itself.

As such, the cellular and molecular mechanisms that regulate both the mechanical and the proinflammatory functions of ASM may offer new and important therapeutic targets in the treatment of asthma **(Brown, 2007).**

Aim of the Study

The aim of this study is to elucidate the role of airway smooth muscle cells in asthma.

Chapter (1)
Bronchial asthma

"Asthma" is derived from Greek word meaning" to pant heavily" or "gasp for breath" **(McFadden, 2004).**

The word "asthma" is everyday use in both general and technical discussion. In the past asthma has been used to refer to almost any sort by difficulty in breathing, especially if it occurred in episodes, no matter what its cause. Both colloquially and medically, it is now generally applied to patients in whom changes in the respiratory system underlie this symptom. Colloquially, an individual who has episodes of difficulty breathing associated with wheezing would be described as suffering from asthma. Medically 'asthma' without qualification would now generally be taken to refer to a disease of the respiratory system. The adjective "bronchial" may be used in context where confusion with paroxysmal dyspnea of cardiac origin is possible **(Scadding, 1981).**

Definition of asthma:

The Egyptian guidelines for asthma management (2000) defined asthma as an inflammatory disorder of the airways in which many cells, including mast cells and eosinophils, play a prominent role leading to damage of the respiratory epithelium, widespread but variable airways obstruction over a short period of time which is usually reversible spontaneously or with treatment, and an increase in airway responsiveness to a variety of stimuli, the condition is usually intermittent and is subjected

to spontaneous prolonged remission **(Egyptian society of chest diseases and tuberculosis, 2000).** A more recent definition of asthma is that, Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in 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 that often reversible either spontaneously or with treatment **(GINA, 2007).**

Epidemiology:

Asthma has been described as a plague of the twentieth century and although there is description of the condition in antiquity, the disorder has clearly increased in prevalence with the last 30 ys. There is a strong familial component to asthma, eczema and rhino-conjunctivitis, that is called atopic cluster. While this argues for a genetic component to asthma, the rapid increase in prevalence of asthma makes it clear that there must be a substantial environmental component. The current consensus is that environmental factors must act on a genetically susceptible subpopulation, stimulating the production of specific immunoglobulin (Ig) E antibodies that mediate both the initiation of asthma and its subsequent triggering. While there is good support for most of this proposition, some elements are based more on dogma than on evidence (**Frew, 2003**).

Asthma is excessively common among the individuals (up to 10% in adults and 35% in children). Asthma is differently distributed in the world. Children are at greater risk of asthma than adults, which could be due to a cohort effect. Severe asthma is reported by 1-3% of the general population (children and adults respectively). Recent population-based data show that the asthma prevalence increase observed worldwide in the past 30 years has now stopped in industrialized countries. Such phenomenon has been paralleled by an increase in the use of asthma medications (**Annesi- Maesano, 2005).**

Prevalence in Egypt:

The prevalence of asthma among Egyptian children range from 3.25% in some studies (**Massoud et al., 2000**) to 8% of Egyptian children in others (**Basilli et al., 1998**). A study conducted by **Georgy et al. (2006)**, using a sample of 2,645 11-15 yr- old in state and fee- paying schools in Cairo, concluded that prevalence of physician diagnosed asthma in Cairo was 9.4%. They found a higher prevalence and increased severity of asthma symptoms in children of low socioeconomic group as defined by state school attendance in Cairo.

Sex:

Sex affects the development of asthma in a time-dependent manner. Until age 13–14 years, the incidence and prevalence of asthma are greater among boys than among girls. Studies through puberty have shown a greater incidence of asthma among adolescent and young adult females and a greater proportion of males with remission of asthma. Before age 12, boys have more severe asthma than girls, with higher

rates of admission to hospital. In contrast, adult females have more severe asthma than males, with more hospital admissions, slower improvement, longer hospital stays and higher rates of readmission (**Subbarao et al., 2009**). **Chen et al.** have attributed these changes in prevalence and severity to events of puberty, although mechanisms for differences between the sexes have not been established (**Chen et al., 2003)**.

Similar findings have been reported from studies of atopy, which is more common in males before age 13; during adolescence, the rate of new-onset atopy is higher among females, so that by young adulthood the prevalence of atopy is almost equal (**Sears et al., 1993 and Subbarao et al., 2009**).

The influence of some environmental risk factors such as allergens may be modified by sex. In one study of adults, 18% of women with asthma, but only 2.3% of men with asthma, had normal results on common tests related to atopy (negative skin prick tests, immunoglobulin E < 100 IU/mL and eosinophilia < 5%), which suggested different disease mechanisms between the sexes (**Weiss, 2005**). Interactions have been found between maternal and paternal history of atopy, breastfeeding and sex of the child in terms of the risk of asthma and atopy (**Oryszczyn et al., 2007)**. Finally, the influence of obesity on the development of asthma is greater among women than among men and has not been shown to be influenced by caloric intake or physical between obesity and asthma may be causal, given the consistency, temporal association and dose–response relationships reported in the epidemiologic literature, but the mechanisms remain to be elucidated (**Weiss, 2005**).

Mortality:

In a study, it was found that the overall risk of death from asthma exacerbations in patients 5 yr or older is 0.5%, and was estimated that there were 1,499 hospital deaths in the United States only in 2000 due to asthma **(Krishnan et al., 2006).**

Risk factors for asthma:

Asthma comprises a range of heterogeneous phenotypes that differ in presentation, etiology and pathophysiology. The risk factors for each recognized phenotype of asthma include genetic, environmental and host factors. Although a family history of asthma is common, it is neither sufficient nor necessary for the development of asthma **(Burke, 2003).**

Genetic factors:

Multiple studies have shown that the likelihood of developing asthma is inherited. However, those genetic studies have shown that asthma does not follow classical patterns of Mendelian inheritance; instead, asthma is inherited as a complex trait and results from the interaction of multiple genes. Problems with accurate phenotyping have hampered identification of the genes responsible for the development of asthma. Recent attempts to decipher the genetic basis of this complex trait have relied on specific intermediate phenotypes such as BHR, serum immunoglobulin E (IgE) levels, and atopy. These traits are thought to identify subsets of patients with distinct types of asthma or a predisposition to develop asthma and have been used to facilitate the identification of the many genes involved in this complex disease. Although a large number of studies have identified possible genetic loci and

chromosomal mutations that may be involved in the development of asthma or these related phenotypes, additional research is needed to clarify the interactions between these genes and the multiple environmental exposures that lead to the asthmatic phenotype **(Schwartz, 2009).**

Extensive research with different study designs and different study populations has identified a coherent pattern of familial influences on the phenotypes that represent components of asthma and allergy **(Steinke et al., 2008).**

1) Familial aggregation and twin studies:

Because the definitions of asthma and the populations studied have varied, estimates of the relative risk attributable to a family history of asthma cover a wide range. Most studies have demonstrated that there is a major inherited component to both asthma and its intermediate phenotypes. Familial clustering has been demonstrated for BHR, eosinophil levels, atopy, and serum IgE levels. Although each of these subtypes has been shown to aggregate among families, they seem to segregate independently, which suggests that these intermediate phenotypes represent distinct pathophysiologic processes. The familial inheritance of asthma and these intermediate phenotypes has led to attempts to identify the specific genes involved in this complex disease **(Niu et al., 2000).**

The inheritance of asthma demonstrated in the studies of familial aggregation was confirmed in twin studies. Studies on mono- and dizygotic twins along with the association of asthma phenotype within first degree relatives suggest a genetic basis

to asthma. More recently, genome wide screens followed by positional cloning and candidate gene association studies have identified genetic loci related to increased risk of asthma in certain populations. The effect of genetic variance on asthma and asthma-related phenotypes shows a great deal of heterogeneity, and may be strongly influenced by environmental factors. Accordingly, many children who develop asthma do not have parents with asthma, and many parents with asthma have children who do not develop asthma **(Illi et al., 2006).**

2) Segregation analysis:

The application of segregation analysis has furthered the assessment of the genetics of asthma in families. This method is used to analyze the pattern of inheritance of a disorder by observing how it is distributed within families. This analysis compares the number of affected individuals with the expected number using different analytical models. Segregation analysis can provide insight into the genetics of a trait, e.g. the number of genes involved and the genetic model: dominant or recessive, polygenic, such as mixed models, and those with environmental effects. The model which fits the data best is the model which gives the best description of the segregation of the trait in the families. Using this type of analysis, the heritability, mode of inheritance, penetrance and frequency of a trait can be estimated and indications of major genes found **(Los et al., 1999).**

3) Candidate gene study:

In candidate gene studies, genes are selected from the pathways shown or expected to play role in asthma

pathogenesis. Candidate gene studies could be based on allele frequency differences between affected (cases) and non-affected (control) individuals known as case-control studies or based on transmission distortion or disequilibrium of allele(s) as in family based association studies **(Ghosh et al., 2006).** Candidate gene studies are supposed to have high sensitivity to detect alleles or variants playing minor role in disease pathogenesis **(Kumar et al., 2009).**

Most of the candidate gene studies have focused on various cytokines, growth factors, and receptors that are thought to play a role in the development of asthma and therefore may influence its inheritance **(Schwartz et al., 2009).**

Marker D11S97 on chromosome 11q13 was first linked to atopy in 1989 and this association subsequently was demonstrated multiple times. Chromosome 11q13 contains candidate genes such as the high-affinity IgE receptor and Clara cell secretory protein. Other areas of linkage include chromosome 6p21-22, which contains some of the genes for the major histocompatibility complex along with the tumor necrosis factor-α gene. Chromosome 12q14-24 contains the genes for interferon-γ, insulin-like growth factor-1, glutathione-S-transferase, nitric oxide synthase-1, leukotriene-A4 hydrolase, and mast cell growth factor. Finally, chromosome 14q11-13 contains the genes for the subunits of the T-cell receptor **(Schwartz et al., 2009).**

4) Linkage study:

Multiple genome-wide linkage studies for asthma and allergy have been performed to date. Linkages have been found in specific ethnic groups, using different phenotypes and with various levels of statistical significance. Most of these regions have been replicated in more than one study. In particular, human chromosomes 2q33, 5q23-31, 6p24-21, 11q21-13, 12q24-12, and 13q14-12 have received the greatest attention, because these regions contain a large number of genes **(Hoffjan et al., 2002)** like IL-3, IL-4, IL-5, IL-9, IL-12b, IL-13, IFNγ, iNOS, FCεRIβ etc. Most of these influence the T cell development/polarization towards Th1 or Th2 besides modulating other features like recruitment of eosinophils, mast cells, neutrophils etc. to the site of inflammation **(Vercelli, 2008).**

However, most of these identified chromosomal regions are large, spanning 10–30 Mb, and contain several plausible candidate genes, fine mapping can be performed in these linked regions and positional candidate cloning can be performed using high-throughput sequencing, single nucleotide polymorphism (SNP) genotyping and linkage disequilibrium (LD) mapping. This has enabled researchers to identify susceptibility genes without prior knowledge of the function of those genes e.g. a disintegrin and metalloproteinase-33 (ADAM 33), dipeptidyl dipeptidase-10, plant homeodomain finger protein-11 and G protein-coupled receptor-154 **(Kere et al., 2004).**

Genes influencing the inflammatory pathways:

It was around late 1980's and early 1990s, when human chromosomal regions were first found to be linked with allergy

or asthma **(Cookson et al., 1989and Daniels et al., 1996).** Several genome-wide screens have found linkage to chromosomal regions, such as, 5q23-31, 5p15, 6p21.3-23, 11p13, 11p15, 12q14-24.2, 13q21.3, 14q11.2-13, 17p11.1-q11.2, 19q13, 21q21 etc. The most consistently replicated among them are 5q23-31, 5p15 and 12q14-24.2 containing genes like IL-3, IL-4, IL-5, IL-9, IL-12b, IL-13, IFNγ, iNOS, FCεRIβ etc. Most of these influence the T cell development/polarization towards Th1 or Th2 besides modulating other features like recruitment of eosinophils, mast cells, neutrophils etc. to the site of inflammation **(Bossé et al., 2007).** These genes have also been validated using candidate gene approaches in different studies and a number of functional polymorphisms have been identified. It was found that the polymorphisms in the intronic region of IFNγ gene may be critical for IFNγ gene regulation and atopic asthma. Similarly inducible nitric oxide synthase or iNOS which is expressed predominantly by immune cells and epithelial cells harbor a number of promoter and intronic polymorphic repeats that could be regulating its expression and asthma related traits **(Batra et al., 2007).**

Recently another T helper subset, namely Th17, has been discovered that it might be playing very significant role in inflammatory pathways critical of asthma pathogenesis. IL-17 is the effector cytokine produced by Th17 cells, and has increased concentration in asthmatic sputum **(Bullens et al., 2006).** Th17 cell also secret IL-21 which helps in its differentiation and mediates its effectors' functions. IL-21 has

been shown to regulate IgE synthesis and it has been shown that one exonic variant C5250T in exon 3 of this gene is associated with asthma and serum total IgE. This polymorphism might be affecting mRNA structure **(Chatterjee et al., 2008)**. The role of Th17 in asthma pathogenesis, however, needs further investigations, as extrapolations from inflammatory event involved in autoimmune diseases suggest that it could be playing vital role in its pathogenesis, since it suppresses the development of regulatory T cells and their action **(Barnes, 2008).**

PI3K plays critical role in the inflammatory events and shown to modulate multiple features of asthma such as mast cell development, migration and degranulation, eosinophil migration and activation, T cell differentiation, B cell activation, IgE synthesis and production etc. In immune cells PI3K mediates its action through phosphoinositol 3, 4, 5 tri-phosphate, which acts as messenger and recruits various downstream molecules constituting a signallosome. Several phosphatases have been identified that dephosphorylate this lipid messenger and downregulates PI3K signaling in immune cells **(Kumar et al., 2009).**

SHIP (src homology 2-containing inositol phosphatase) is 5' phosphatase and it downregulates mast cell degranution upon IgE cross linking, therefore it could regulate asthma pathogenesis **(Kumar et al., 2009).**

PTEN (phosphatase and tensin homologue) which is 3' phosphatase has been shown to downregulate IL-4, IL-5 and