CURRENT DEVELOPMENTS IN THE PHYSIOLOGY AND MANAGEMENT OF ASTHMA

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Introduction

Asthma is one of the classic diseases recognized by Hippocrates over 2000 years ago, yet it remains a serious global health problem because it is still not yet well understood. Asthma prevalence is reported to be on the increase worldwide especially among children (Kemp, 2003). Fortunately, recent advances in science have improved our understanding of asthma and the ability to manage it effectively (GINA, 2004) although deaths from asthma far from disappearing, have become more frequent in some countries (Jackson *et al,* 1982).

Previously, most information on the pathology of asthma was obtained from postmortem tissue. Macroscopically, in patients that died of asthma the lungs are over – inflated, with both large and small airways filled with plugs comprised of a mixture of mucus, serum proteins, inflammatory cells, and cell debris. Microscopically, the findings are usually of extensive infiltration of the airway lumen and wall with eosinophils and lymphocytes, vasodilatation, evidence of micro vascular leakage and epithelial disruption (Dunnil, 1960; Krait *et al,* 1996).

More recently, studies of living subjects with asthma have involved endobronchial biopsies of patients with mild disease, which have generally reflected the findings at autopsy. However studies in patients with more severe asthma suggest that in addition to eosinophils and lymphocytes, neutrophils are also present and may play a role in more severe disease (Wenzel *et al,* 1997).

Currently, the application of immunological and molecular biological techniques to asthma has greatly improved understanding of the disease. This has placed T – lymphocytes as pivotal cells in orchestrating the inflammatory response through the release of multifunctional cytokines (Robinson *et al*, 1992). In addition to potent mediators that contract airway smooth muscle, increase micro vascular leakage, activate different neurons and stimulate mucus secreting cells, a number of factors are released that have the capacity to produce structural changes in the airways or attract inflammatory cells to cause injury to the bronchial tissue. Chemokines have also been shown to play a crucial role in the recruitment of inflammatory cells to the airways (Bousquet *et al,* 2000).

Airway Remodeling

Asthma is currently recognized as a chronic inflammatory disorder of the airways that leads to tissue injury and subsequent structural changes collectively called airway remodeling (Homer and Elias, 2005). The inflammatory process in asthma is dominated by so – called Th2 inflammation, characterized by T cells that make interleukin (IL) – 4, - 5, and – 13 along with the classically described eosinophil - , mast cell - , basophil - , and macrophage – rich inflammation (Cohn *et al,* 2004). This is in contrast to Th1 T cells, which make interferon - γ, lymphotoxin, and IL – 2. Th1 and Th2 cells differentiate into polarized populations from a common precursor on the basis of signals from the local microenvironment. After they have developed, Th1 and Th2 cells are commonly thought to inhibit the development of the other cell type. In addition, there are regulatory cells that also appear to regulate the appearance of each cell type. Th1 cells play a dominant role in controlling intracellular pathogens like tuberculosis, whereas Th2 cells play a dominant role in controlling extracellular pathogens like parasites and mites, and allergens like dusts and pollens (Alakija *et al,* 1990). However, the absence of either population leads to enhanced immunopathology, even in conditions classically thought to depend on the other cell type.

It is thought that inflammation alone may lead to some features of asthma, including reversible bronchospasm. However, as with many chronic inflammatory disorders, asthmatic airway inflammation is also believed to cause tissue injury and subsequent structural changes. These changes are referred to collectively as *airway remodeling* and include

1) an increase in overall wall thickness, 2) an increase in airway fibrosis and 3) smooth muscle mass, 4) abnormalities in composition of the extracellular matrix, and 5) an increase in vascularity (Homer and Elias, 2000). These changes have attracted interest due to the increased realization that these changes may account for aspects of asthmatic physiology that are poorly addressed with current anti – inflammatory strategies (Busse *at al,* 2004).

Analysis and Studies on Airway Remodeling
        In fatal asthma, pathological analysis has shown that most elements of the airway wall (smooth muscle, non – smooth muscle connective tissue, mucus glands) are increased (Carroll *et al*, 1993; Huber and Koessler, 1922; James *et al*, 1989; Kuwano *et al,* 1993). The changes (except for the increase in mucus glands) are found in airways of all sizes (Saetta *et al,* 1991). The pathological changes in airways of patients with nonfatal asthma are much less pronounced, with changes seen predominantly in small airways (2 – 4 mm in diameter) (Carroll *et al,* 1997; Kuwano *et al,* 1993). Airway wall thickness as measured radiologically also correlates with disease severity and length of time with disease, with small airways again being the predominant abnormality in milder disease (Awadh *et al,* 1998; Boulet *et al*, 1995; Goldin *et al,* 1998; Harmanci *et al*, 2002; Kasahara *et al*, 2002; Little *et al,* 2002; Okazawa *et al*, 1996 and Paganin *et al*, 1996).

        An increase in airway smooth muscle mass is one of the best – known features of asthmatic remodeling (Huber and Koessler, 1922). Like total wall thickness, smooth muscle thickness correlates with fatal or nonfatal asthma (Carroll *et al,* 1993; James *et al,* 1989 and Kuwano *et al*, 1993). The degree to which hyperplasia compared with hypertrophy contributes to this response continues to be controversial, but both probably contribute in different patient populations (Benayoun *et al,* 2003; Ebina *et al,* 1993, and Woodruff *et al*, 2004). The degree to which this increased smooth muscle is abnormal is also controversial (Benayoun *et al*, 2003 and Woodruff *et al*, 2004).

        An increase in fibrosis just below the large airway epithelium occurs as a prominent feature in asthma. This layer has been extensively studied due to its accessibility on endobronchial biopsy. The normal layer of collagen under the airway is ~ 5 μm thick, which increases to 7 – 23 μm in patients with asthma. Initially described as basement membrane thickening, it is now apparent that the true basement membrane (the lamina rara

and densa as seen on electron microscopy, which contain laminin and collagen IV) is not grossly altered (Roche *et al,* 1989). There is, rather, thickening of the area just below the true basement membrane, the lamina reticularis, with deposition of interstitial collagens I, III, and V. Studies have reported correlations of subepithelial fibrosis as measured in larger cartilaginous airways with overall wall thickness in the same airways but not in small airways elsewhere in the same lung (James *et al,* 2002 and Kasahara *et al,* 2002). There are inconsistent results with respect to enhanced collagen deposition in the submucosa (area between the layer of dense subepithelial fibrosis and smooth muscle) (Benayoun *et al,* 2003; Chu *et al*, 1998 and Wilson and Li, 1997). Abnormalities have also been noted in noncollagenous matrix, including elastin, proteoglycans, and cartilage (Lazaar and Panettieri, 2003).

        The significance of this specific feature of asthmatic airway remodeling is unclear. Although measurements of airway distensibility correlate well with subepithelial fibrosis (Ward *et al*, 2001), other functional measurements (clinical illness scores, measures of pulmonary function and airway hyperresponsiveness) show variable correlations (Benayoun *et al*, 2003; Boulet *et al*, 1997; Chetta *et al*, 1997; Cho *et al,* 1996 and Hoshina *et al,* 1998). Other groups have identified severe asthmatics with no increase in subepithelial fibrosis (Chakir *et al*, 2003; Chu *et al,* 1998 and Wenzel *et al,* 1999). Subepithelial fibrosis is actually a very early marker for the asthmatic phenotype in children and does not correlate with length of time with the disease nor necessarily with the severity of inflammation (Boulet *et al,* 2000; Chu *et al*, 1998; Cokugras *et al*, 2001; Laitinen *et al*, 1996 and Payne *et al*, 2003). It has therefore been suggested that subepithelial fibrosis represents disordered epithelial – mesenchymal signaling rather than a direct response to inflammatory injury (Holgate *et al*, 2004). A tracheal explant model has shown that cigarette smoke can induce remodeling in the absence of inflammation, indicating that other pathways to fibrosis need to be considered (Wang *et al,* 2003 and Iyawe *et al*, 2005).

        Myofibroblasts are specialized cells with features of both fibroblasts and myocytes. They have the synthetic machinery of fibroblasts used for synthesis of extracellular matrix but also have at least some components of the contractile apparatus of myocytes. They are well known to be increased in tissues undergoing repair, such as in wounds or in

pulmonary interstitial fibrosis. In human asthma, the submucosa shows an increase in myofibroblasts that correlates with the thickness of the lamina reticularis but not with severity of disease (Benayoun *et al*, 2003; Brewster *et al*, 1990 and Hoshino *et al*, 1998). Since myofibroblasts are well known sources of interstitial collagens, it is plausible to suggest that the myofibroblasts are the source of the subepithelial fibrosis. The origin and fate of these cells is somewhat obscure. Cells with this phenotype appear very quickly after antigen challenge, possibly implying a quiescent precursor cell that acquires myofibroblastic markers without necessarily dividing (Gizycki *et al*, 1997). Other data suggest that these cells may arise from circulating precursors (Schmidt *et al,* 2003).

Increased vascularity is a common feature of chronic inflammation. In addition, increased vascular congestion, leading to wall thickening, has been suggested as the basis of exercise – induced asthma, the airway hyperresponsiveness seen in congestive heart failure and in normal subjects after a rapid infusion of intravenous fluids (Cabanes *et al,* 1989 and Rolla *et al,* 1986). More severe asthmatics have a greater number of vessels than milder asthmatics (Salvato, 2001 and Vrugt *et al,* 2000). Increased vascularity is noted in both newly diagnosed patients and in patients with long – standing asthma. There is a correlation of vascularity with airway hyperresponsiveness and change in lung function after bronchodilator treatment (Hoshino *et al*, 2001 and Orsida *et al,* 1999). The vessels that are increased appear to be capillaries and venules and are concentrated just under the airway epithelium (Orsida *et al*, 2001 and Salvato, 2001). Abnormalities of various types of vessels in the airway mucosa have also been described. (Salvato, 2001). Paradoxically, but consistent with results measuring other aspects of airway remodeling, there is no correlation of degree of abnormality with length of time with disease. As in animal models, in patients, vascularity is denser in intercartilagenous areas than over cartilage (McDonald, 2001).

Mechanisms of Airway Remodeling

A large number of mediators have been described in airways of asthmatics that could theoretically be relevant to airway remodeling. In many cases, the presence of these mediators correlates with the severity of airway remodeling or some clinical feature. However, it is difficult to know the significance of these findings in the absence of a specific inhibitor of that mediator. So far, only one specific mediator, IL–5, has been targeted in humans. IL-5 was well established as potentially relevant to asthma on account of its powerful influence on eosinophil development and priming. Treatment of asthmatics with a humanized anti – IL-5 antibody confirmed this suspicion, because it caused a marked reduction in circulating and airway lumen eosinophils and a lesser reduction in airway tissue eosinophils. Furthermore, treatment with this antibody was able to reduce matrix proteins present beneath the epithelial basement such as tenascin C and lumican (Flood-Page *et al*, 2003). Whether this effect of anti – IL-5 on matrix turnover is eosinophil dependent is not known because airway fibroblasts and epithelial cells also possess IL-5 receptors. Unfortunately, despite these impressive biological effects, the antibody failed to produce any clinically significant effect on asthmatic physiology.

IL-13 has been shown to be critically important in acute models of allergic inflammation (Wills-Karp et al, 1998). It was originally discovered as an IL-4 like molecule with which it shares some receptor subunits. It has since become clear that IL-13 is more important in the effector phase and that IL-4 is more important in the initiation phase of Th2 inflammation. With the use of both conventional and inducible transgenic modeling, IL-13 was shown to be a potent inducer of an eosinophils -, macrophage -, and lymphocyte – rich inflammatory response, airway fibrosis, mucus metaplasia, and airway hyperresponsiveness (Zhu et al, 1999). IL-13 mediates many of its effects through a signal transducer and activator of transcription (STAT)-6 signaling pathway, and human asthmatics have elevated levels of STAT-6 in airway epithelium (Mullings *et al,* 2000).

Collagen deposition in tissues is controlled by the balance of the collagen – degrading matrix metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). In addition to their role in matrix remodeling, it has also become apparent that MMPs have important roles in inflammation, angiogenesis, and cell – cell signaling (Kelly and Jarjour, 2003). In asthma, the potentially most important members of this family are MMP-9 and TIMP-1. MMP-9 is produced in an exaggerated fashion by asthmatic alveolar macrophages and is found in exaggerated quantities in sputum, bronchoalveolar lavage (BAL) fluid, and biopsies from patients with asthma. The ratio of MMP-9 and TIMP-1 in asthmatics is lower than in control subjects and correlates with the

degree of airway obstruction (Kelly and Jarjour, 2003).

Other Th2 cytokines, such as IL-9 and IL-10, appear to function at least partly via inducing IL-13 (Lee *et al*, 2002 and Whittaker *et al*, 2002). IL-10 has been considered in some cases a Th2 cytokine but has also been implicated in immunoregulation. Mice that overexpress IL-10 in the airway show a reduction in aspects of innate immunity, including endotoxin – induced tumor necrosis factor production and neutrophil accumulation. However, IL-10 also causes mucus metaplasia, B cell - and T cell – rich inflammation, and airway fibrosis and augments the levels of mRNA encoding Gob-5, mucins, and IL-13. These responses are mediated by multiple mechanisms, with mucus metaplasia being dependent on an IL-13-IL-4Rα-STAT-6 pathway, whereas the inflammation and fibrosis were independent of that pathway (Lee *et al*, 2002).

The most heavily studied mediator of tissue fibrosis is transforming growth factor (TGF)-β1. TGF-β1 is made by many cells within the lungs, such as epithelial cells, macrophages, eosinophils, lymphocytes, and fibroblasts. TGF-β1 can induce fibroblast and smooth muscle proliferation and enhances matrix production. TGF-β1 mRNA appears to be increased in moderate and severe asthmatics compared with normal subjects, and the expression of this cytokine is directly related to the degree of subepithelial fibrosis (Minshall *et al,* 2000 and Ohno *et al,* 1996). As determined by using in situ hybridization, eosinophils and fibroblasts are the principal cells synthesizing TGF-β1 in the airway, whereas alveolar macrophages release more TGF-β1 from asthmatics than from controls (Hoshino *et al,* 1998; Vignola *et al*, 1997 and Vignola *et al*, 1996). Expression of downstream signaling molecules from TGF-β also shows an increase in asthma and a correlation with subepithelial fibrosis (Nakao *et al,* 2000 and Sagara *et al*, 2002). Macrophages were the major site of TGFβ-1 production as assessed by immunohistochemistry and in situ hybridization. IL-13-induced fibrosis was significantly ameliorated by treatment with the TGF-β antagonist soluble TGFβR-Fc (Lee *et al,* 2001).. It is possible, therefore, that the main significance of MMP-9 overexpression in human asthma may be to activate TGF-β1 (Lee *et al,* 2001).

A large number of factors are known that control airway smooth muscle cell proliferation in vitro (Panettieri, 2003). However, little is certain about their role in vivo. IL-11, a member of the IL-6 – type cytokine family, shares a common receptor – signaling subunit with IL-6 and has been shown to induce airway hyperresponsiveness in mice when administered intratracheally (Einarsson *et al,* 1996). It is produced by a variety of lung stromal cells, including epithelial cells, smooth muscle cells, and fibroblasts, in response to a variety of stimuli, including asthma – related viruses, histamine, and eosinophils major basic protein (Einarsson *et al,* 1996 and Elias *et al,* 1994). Overexpression of IL-11 in the lungs caused an increase in peribronchial fibrosis and an increase in true airway smooth muscle mass and myofibroblasts (Tang *et al,* 1996). There is an increase in baseline airway resistance and marked airway hyperresponsiveness. The studies with the IL-11 mice led to analysis of human airways that showed that IL-11 is overexpressed in chronic human asthma but only in the most severely remodeled airways (Minshall *et al,* 1999).

Increased vascularity may be due to any number of proangiogenic factors, especially vascular endothelial growth factor (VEGF). VEGF was originally described as vascular permeability factor on the basis of its ability to generate tissue edema. It has subsequently been appreciated to be a multi – functional angiogenic regulator that stimulates epithelial cell proliferation, blood vessel formation, and endothelial cell survival (Clauss, 2000 and Gerber *et al*, 1998). VEGF levels are increased in asthmatics, and levels correlate directly with disease activity and inversely with airway caliber and airway responsiveness (Asai *et al,* 2002; Hoshino *et al,* 2001 and Lee and Lee, 2001). VEGF has been postulated to contribute to asthmatic tissue edema via its vascular permeability factor effect (Anthony *et al*, 2002 and Thurston *et al,* 2000). IL-13 is known to cause an increase in VEGF production (Corne *et al*, 2000). In mice that over - express VEGF, there is a dramatic endothelial sprouting under the airway epithelium (Lee *et al,* 2004), potent induction of angiogenesis and edema in the airway and lung. There is evidence for remodeling, with an increase in smooth muscle mass around airways. Later there is an increase in collagen around airways. TGF-β1 was also increased at this latter time point. These airway and lung changes were accompanied by an increase in airway hyperresponsiveness.

VEGF also caused a marked increase in inflammation, with an increase in mononuclear cells, T and B cells, and eosinophils. There was an increase in the number and activation state of dendritic cells that correlated with ability to prime the mice via the airways, a feature not found in wild – type mice.

As expected from the IL-13 – over expressing mice, after allergen challenge, VEGF was found to be markedly increased in BAL fluids. In the lung, VEGF is localized to airway epithelial cells, mononuclear cells, and T cells. In vitro, polarized Th2 cells are much more potent producers of VEGF than Th1 cells. When a VEGF receptor antagonist was used in vivo, there was a dramatic decrease in BAL and tissue inflammation as well as airway hyper responsiveness. There was also a decrease in IL-13 and IL-4 production (Lee *et al*, 2004).

These results suggest a positive feed – forward circuit in which allergen challenge increases VEGF while VEGF also increases allergic inflammation, dendritic cell activation and airway remodeling. It is thought that viral infection early in life can predispose one to the development of asthma (Schwarze and Gelfand, 2002 and Sigurs *et al*, 2000). Because viral infection can also lead to increased VEGF (Einarsson et al, 1996), these results suggest a mechanism whereby this may occur. Finally, given the ability of VEGF to promote both inflammation and airway remodeling, this data supports a possible role for VEGF antagonists in therapy of asthma, especially in severe asthma, which is resistant to conventional therapy.

Physiological Significance of Airway Remodeling

Airway remodeling has been invoked to explain various aspects of asthma severity, including airway hyper responsiveness and fixed airway obstruction (Busse *et al*, 2004). The cross – sectional studies comparing fatal and nonfatal asthma certainly support the general concept of a relationship between airway remodeling and asthma severity. Although experimental studies of allergic models show that airway hyper responsiveness can be induced without airway remodeling (Hoshino *et al,* 1998) and individual cytokines are known that can increase airway smooth muscle responsiveness both in vitro and in vivo (Amrani and Panettieri, 1998 and Einarsson *et al*, 1996) a murine model of airway remodeling suggests that airway dysfunction persists after resolution of inflammation, implicating the airway remodeling itself in airway dysfunction (Leigh *et al*, 2002). Extensive mathematical modeling also suggests effects of airway remodeling on airway function similar to those seen clinically (Okazawa *et al,* 1996).

Fixed airway obstruction associated with progressive loss of lung function has now been demonstrated in several cohort studies of both adults and children (Covar *et al,* 2004; Lang *et al,* 1998; Peat *et al,* 1987 and Ulrik *et al,* 1992). Although the pathological basis for this phenomenon is not completely known, studies have shown a remarkable correlation of asthma severity with measures of smooth muscle area, smooth muscle hypertrophy, and density of fibroblasts in the airway wall (Benayoun *et al,* 2003). Interestingly, another group had not only not seen this effect, they also saw a correlation of subepithelial fibrosis with disease severity, which was specifically not seen by the first group (Cho *et al,* 1996). It is possible that this represents disease heterogeneity.

A number of papers have addressed the issue of reversibility of airway remodeling. Early studies showed no effect of steroids on subepithelial fibrosis (Jeffrey *et al*, 1992; Lundgren *et al,* 1988 and Roche *et al,* 1989). More recent randomized studies have shown a significant reduction in subepithelial fibrosis after short – term or long – term therapy or after withdrawal from exposure to antigen (Chetta *et al,* 1997; Hoshino *et al,* 1998; Saetta *et al*, 1995 and Ward *et al*, 2002). It has been suggested that prior treatment with steroids, delayed treatment, or low doses and short courses of steroids prevented an effect from being noted in the earlier studies. Steroids also decrease the number of (myo)fibroblasts in the submucosa and reduce airway vascularity (Chetta *et al*, 2003; Hoshino *et al*, 1998; Hoshino *et al,* 2001 and Orsida *et al,* 1999). The decrease in vessel number correlates with the decrease in airway hyper responsiveness, reduction in inflammation, and change in subepithelial collagen (Chetta *et al,* 2003 and Hoshino *et al,* 2001). One study suggests that addition of a $\beta2$ – agonist to inhaled steroids may reduce vascularity further (Orsida *et al,* 2001). These pathological studies have been used to support the suggestion from clinical trials that early treatment with inhaled steroids is required to prevent irreversible loss of lung function, at least in adults (Haahtela *et al*, 1994; Overbeek *et al*, 1996 and Selroos *et al*, 1995).

Recent advances in the treatment and management of asthma have shown that leukotriene (LT) receptor antagonists or LT modifiers are very beneficial as a second generation therapy with steroid – sparing properties and negligible side effects (Moqbel, 1999, and Mission *et al*, 1999).

A few studies have addressed the issue of response of putative remodeling mediators to therapy. TGF-β appears resistant to steroid therapy, whether there is a reduction in

measures of airway remodeling or not (Chakir *et al,* 2003 and Hoshino *et al*, 1998). However, since remodeling presumably requires more than one mediator and because alternative pathways are likely, it is hard to interpret this kind of data.

There remain many areas of uncertainty in this field. Despite the suggestion that airway remodeling explains the lack of response to therapy of some patients, no study has specifically shown that those patients who either fail to respond to therapy or progress despite therapy do in fact show airway remodeling (or excess expression of some mediator of remodeling) that fails to respond or progresses despite a reduction in inflammation. No prospective study has examined the effects of therapy on smooth muscle. Finally, one explanation for the disparate results discussed here is that of clinical heterogeneity, i.e., different subpopulations of patients have different aspects of airway remodeling related to their particular physiology. If this hypothesis was true, it would ultimately be necessary to characterize the pathological basis of each patient's physiology before determining which therapy would be most beneficial in reversing or preventing airway remodeling in that individual patient. This field remains open for research, especially in relation to treatment.

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