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REVIEW ARTICLE

Airway Remodeling: A Key Event in Asthma

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ABSTRACT

Morbidity and mortality due to asthma are increasing dramatically which necessitates the development of treatment targeting the key mediators in pathogenesis of the disease. Mainly it is characterized by airway hyper responsiveness, inflammation, remodeling. Mast cells and cytokines are the major mediators in the process. Mast cell degranulation gives out many substances responsible for smooth muscle hyper responsiveness resulting in bronchoconstriction. Key event in the progression of asthma is the airway remodeling. This event encloses epithelial cell damage, subepithelial fibrosis, goblet cell hyperplasia, angiogenesis. There are also many assessment techniques like imaging, invasive, non-invasive techniques. Treatment targeting the events in airway remodeling presents the promising way for eradication of asthma.

KEYWORDS

Asthma, Airway remodeling events, Assessment of airway remodelling, inflammatory cells

INTRODUCTION

Growing urbanization, air pollution, and environmental tobacco smoke are the major contributing factors for increased prevalence of asthma and its genetic predisposition. Since 1919, the prevalence is increasing from 9% to 30% according to the statistical studies carried out by hospital in city of Bangalore.[1] Inflated morbidity due to asthma is mainly contributed by exposure of environmental tobacco smoke during childhood, as well as adulthood. Also, local aeroallergen triggers the hyper responsiveness in asthmatic condition[2]. According to World Health Organization, 300 million people suffer from asthma from which 180,000 people die due to it.

Asthma is characterized by the airway inflammation manifested by cough, wheezing chest tightness, acute exacerbations, dyspnea, and bronchoconstriction[3]. Triggers which take part for initiation of asthmatic symptoms are allergens, irritants, exercise, emotional stress, viral or sinus infections. Other substances which aggravate the condition of asthma are cigarette smoke, pollen, molds, chalk dust, talcum powder, paints, varnishes, animal dander. Whatever may be the cause for trigger, the end result is nothing but smooth muscle contraction and airway inflammation[3].

Asthma is reversible disease sometimes showing permanent or irreversible structural changes in airway during remodeling. These changes include smooth muscle hyperplasia, neoangiogenesis, and glandular hyperplasia. Key feature in pathology of asthma, is being characterized by release of pro-inflammatory substances like chemokines, cytokines and other peptides. Infiltration of eosinophils, leukocytes, fibroblasts is another source of precipitating mediators for the same[4].

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Airway narrowing also seen in asthmatic conditions along with altered levels of cytokines lymphocytes, mast cells etc. and their subsequent products necessary for inflammation mediation[5]. Mast cells populate in upper as well as lower respiratory tract which is then accompanied by mast cell hyperplasia. Non-invasive techniques such as sputum induction, exhaled breath condensate are the investigatory ways for asthmatics and also give the evidence for the contribution of pathological factors causing to it[3]. Inhibition of these mediators along with the enzymes such as lipoxygenase, cyclooxygenase, which synthesize the cytokines offer way for resolution of asthma[6]. Increased morbidity necessitates the understanding of pathophysiology and also available targets for growing asthma.

Pathogenesis of Asthma

Many immune cells, their cytokines enzymes are responsible for the pathogenesis of asthma. Allergy is the major predisposing factor for initiation of disease. It starts with antigen exposure to antigen presenting cell which is further then digested and presented to T cells. T cells further get differentiated into many Th2 cells and produce the cytokines like interleukin-4, interleukin-5, and interleukin-13.

B cells are stimulated by Interleukin 4.They play an important role in acute and chronic path biology and development of antibodies like IgE. These antibodies interact with antigen on the surface of mast cells resulting in degranulation and the subsequent release of histamine. Histamine is the major factor which mediates the bronchoconstriction. Leukotrienes and thromboxanes are also reduced taking part in that process. Interleukin 5 mainly orchestrates for eosinophilic inflammation and further inflammatory response. Mucus hypersecretion is mediated by Interleukin 13 resulting into narrowing of airway and ultimately leading to restlessness and breathlessness. Atopic asthmatics show increased level of lymphocytes in their bronchoalveolar lavage (BAL).

Upregulation of inflammatory response is mediated by resident cells like macrophages also. They perform defense functions like phagocytosis, generation of enzymes, reactive oxygen species, Transforming growth factor-β, GM-CSF, Interleukin-1, Interleukin-6, LTB-4, thromboxane A2. Matrix metalloproteinase is also generated in response to activity of macrophages.

Goblet cells underlying the respiratory tract play a very functional role in bronchocongestion. Mechanical insult, chemical irritation also certain bacterial toxins augment the mucus release[7]. Mucus blanket helps for prevention of dehydration, also, to trap inhaled particles and also to protect against physical or chemical injury to epithelial cells. Mucus comprises of glycoproteins covalently linked to proteins[8].

Induction of Th2 response is the basic mechanism for initiation of inflammatory response. Mast cells, IgE, eosiniphils, basophils also have role in pathogenesis of the disease.[8, 9]

Histopathological changes in airway remodeling are smooth muscle hypertrophy, mucus gland hyperplasia, shedding and metaplasia of epithelium, Angiogenesis, Nerve proliferation

Mast cells and T lymphocytes are recruited and activated which ultimately leads to bronchial inflammation. Smooth muscle mass is also increased as a result of increased cell size and cell number both.

Pathological markers[9, 10]

1. Cushman's spirals – It is characterized by mucus plugs containing epithelial debris form.
2. Charcot Leyden crystals – it is characterized by crystals of eosinophils proteins. These crystals are observed in sputum.

Asthma is chronic inflammatory disorder characterized by bronchial hyper responsiveness. From last 2-3 decades asthma became a major cause of death. Airway remodeling is one of the central features of asthma. Remodeling is defined as tissue injury followed by structural changes seen in airways. This ultimately leads to loss of lung function. Airway thickening is observable as much as 50

to 300% in severe asthmatic patients and 10 to 100 % in the cases with mild asthmatic conditions[11]. Inflammatory cells such as T cells, neutrophils, mast cells, eosinophils, macrophages, airway smooth muscles play a major role in inflammatory reactions and airway remodeling. Mediators like TGF-β, vascular endothelial growth factor (VEGF), matrix metalloproteinase-9, Th2 cytokines (interleukin [IL]-5, IL-13, IL-4, and IL-9) are linked to remodeling play an important role in progression of airway remodeling[12].

Events in Airway remodeling

1. Epithelial layer damage
2. Subepithelial fibrosis
3. Goblet cell hyperplasia

Airway remodeling is basically a repair mechanism[13]. It includes changes in epithelium, lamina propria, submucosa of the airway. This review presents the mechanism, diagnosis and treatment of airway remodeling which is one of the culprits of asthma. Persistent inflammation and epithelial damage ultimately leads to severe condition in asthma.

The process involves changes in cellular, biochemical, and molecular components of bronchial wall. Changes involve apoptotic activity of epithelial cells, goblet cells hyperplasia, and hypertrophy. Lamina reticularis layer become thickened. This leads to deposition of collagenous and non-collagenous mater beneath the epithelial basement membrane[14]. Smooth muscle mass is also increased. Pathological analysis of bronchial biopsy and autopsy reveal that deposition o extracellular matrix in subepithelial layer, submucosal glands hypertrophy, hyperplasia, increase in submucosal vessels collectively orchestrates the event of airway remodeling.

Epithelial Layer Damage

It includes shedding of epithelial cells, Upregulation of cytokines, several growth factors and chemokines. Injury is associated with changes in integrity of tight junctions in between epithelial cells[13]. Bronchial biopsy results showed epithelial detachment from base. More apoptosis is seen in asthmatic airways than in normal ones. It can be a consequence of ongoing inflammation[11]. Eosinophil basic proteins and oxygen-derived free radicals contribute for the damage process. In bronchio alveolar fluid, epithelial cells are found in clumps suggests the detachment of cells from basement membrane. Consequences of epithelial layer damage are enhancement of entry of allergen due to loss of barrier function, less degradation of inflammatory mediators[15]. STAT-1 has a key role in remodeling process; its increased level is associated with T cell accumulation in tissue[16].

Subepithelial Fibrosis

Thickening of reticular basement membrane is the characteristic feature of airway remodeling. Just below basement membrane, subepithelial fibrosis occurs in lamina reticularis. Decreased degradation and increased deposition of extracellular matrix proteins by fibroblasts mainly contribute for this situation. This is basically due to higher ration of tissue inhibitor metalloproteinase 2(TIMP) to matrix metalloproteinase (MMP). This results in less degradation of ECM[17]. Deposition of ECM is due to imbalance between its synthesis and degradation. Lamina reticularis is found to be 4-5 µm in normal individual, whereas, in asthmatic patient, its thickness become 23µm. Extracellular matrix deposition, primarily collagens I, III, and V are mainly responsible for such thickening[18]. Myofibroblast play an important role in subepithelial fibrosis. These are the phenotypic intermediate between smooth muscles and fibroblasts[19]. They secrete ECM protein and produce smooth muscle actin also. TGF β is the cytokine which is produced by fibroblast, eosinophils, lymphocytes, macrophages. TGF β induces the expression of smooth muscle actin[20]. It also inhibits the degradation of matrix metalloproteinase. Level of TGF β is increased in asthmatic airways and broncho alveolar lavage in asthmatic patients than normal individuals. Matrix metalloproteinase degrade extracellular matrix

molecules[21]. TIMP 1 over expression causes to ECM to deposit.

Goblet Cell Hyperplasia

This is one of the important features in asthma which shows histological changes in peripheral airways. Proliferation of epithelial cells and hyperplasia of goblet cells are the characteristic ones. Mucus is mainly secreted by goblet cells and submucosal glands. Hypersecretion of mucus is the result of enlargement of goblet cells and submucosal glands[22]. This may be due to desquamation of epithelial cells. This results in airway narrowing and obstruction[23]. Thus, goblet cell hyperplasia results in mild, moderate and severe asthma. Interleukin 9 and interleukin 13 play an important role in induction of hypersecretion of mucus. IL – 4, IL-13 also contributes for the same. Mucus occupies higher percentage of space in airway lumen. Obstruction results from overproduction of mucus, mucus plugging. This can be due to interaction between environmental factors or genetic susceptibility. Hyperplasia in peripheral airways may be one of the risk factors in deaths due to asthma[24].

Angiogenesis

Increased angiogenesis is one more characteristic of airway remodeling. Smooth muscle cells produce vascular endothelial growth factor (VEGF), which results in increased vascular permeability and angiogenesis. Airway edema and recruitment of inflammatory cells are the consequences of this[25]. This change is associated with related functional alterations. Changes in airway microvascularization results from these alterations. This results in airway edema[26]. Overexpression of VEGF contributes mainly for increased angiogenesis. Clinical consequences include excess delivery of inflammatory and remodeling mediators in airways[27]. Congested and enlarged mucosal blood vessels result in thicker airway walls[28].

Assessment Techniques

The number of immunological cells like eosinophils, mast cells, T cells, and fibroblasts take part in progression of airway remodeling can be measured by many techniques like bronchial biopsy, bronchoalveolar lavage analysis, sputum analysis. Many invasive techniques are used for assessing the levels of pro-inflammatory and other inflammatory mediators[29]. Centrifugation of BAL fluid and subsequent procedures give the number of inflammatory cells.

Non-invasive techniques	Invasive techniques	Imaging techniques	Lung function measur-ements
Sputum induction Nitric oxide exhalation Exhaled breath condensate Biological fluids	Bronchoal veolar lavage Bronchial biopsy	HRCT Endobron-chial ultrasonog-raphy	LFT

A. Non Invasive Techniques

These methods are based on the analysis of inflammatory cells in biological fluids, exhaled breath, and sputum. The information obtained from non-invasive techniques gives useful clinical features and investigational data which may be useful in analysis of progression of asthma.

Sputum Induction

It encloses the inhalation of hypertonic saline solution. Solid sputum is separated from saliva. After the treatment with dithiothreitol, centrifuge is done to separate solid and liquid phase. This allows the analysis of inflammatory cells, cytokines and other mediators[30].

Nitric Oxide Exhalation

Exhalation of nitric oxide is associated with presence of inflammation in airways; therefore, this can be the efficient technique for knowing

the degree of inflammation. This can be done with the help of chemiluminescence analyser[31].

Exhaled Breath Condensate

Use of exhaled breath condensate is one of the non invasive techniques of analysis. For obtaining the exhaled breath condensate, refrigerating exhaled breath circuit is used. Cysteinyl lukorienes level can measure by this technique[32].

Biological Fluids

It is one of the economical and easy way for determination of airway remodeling. Blood, urine, plasma and other biological fluids are employed in murine model for evaluation of remodeling markers[33].

B. Invasive Techniques

Invasive methods like bronchoalveolar lavage and bronchial biopsy are the techniques by which structural modifications and infiltration of inflammatory cells in bronchial wall can be traced. The methods involve evaluation of inflammatory and epithelial cells, pro-inflammatory mediators, and cytokines levels measurements.

Bronchoalveolar Lavage

This method involves instillation of saline solution through a channel of bronchoscope. The solution is then aspirated into sterile container. The samples then centrifuged and solid and liquid phase is separated[34].

Bronchial Biopsy

This is most accurate method for determination of airway remodeling.

By this method, thickness of reticular basement membrane can be checked. Timing and natural history of thickening can be evaluated. Therefore, changes over time and improvement due to treatment can be traced[35].

C. Imaging Techniques

HRCT

High resolution computed tomography assesses structural changes in airways. This provides morphological features of lungs. Several abnormalities of airway wall can be scanned by HRCT. Many airway diseases like bronchectasis, thickness of peripheral bronchial emphysema (centrolobular and bullous), peripheral linear hyperdensities can be scanned with this. Three dimensional evaluation of lung is possible due to this[36]. Presence and Relationship between inflammation and remodeling can be detected by HRCT.

Endobronchial Ultrasonography

Presence of different tumors and lymph node infiltration in bronchial wall can be evaluated by Endobronchial ultrasonography. A probe is surrounded by saline filled balloon, which is introduced in the bronchi through bronchoscope[37]. Due to penetration of ultrasound in the bronchi, evaluation of the whole bronchial wall by optimal resolution[38].

D. Lung Function Measurements

Lung Function Test

Bronchial function test assesses Forced expiration volume (FEV). For exploration of the airway remodeling, lung function test is an important tool. Thickening of reticular basement membrane is related with decline in bronchial function, which can be detected with the help of lung function test[39].

CONCLUSION

Inhalation of the corticosteroids may responsible for many side effects. Also, some patients reflect a poor response for such therapy. Development of new therapies like cell targeting therapy is necessary. The possible targets in such therapy are TGFβ, Inteleukins, endothelins, TNFα, IGF etc. this development of therapy will be the important perspective as it will target the direct root cause of the asthma rather than relieving it symptomatically. Improved Imaging technique will be of important value in future for the diagnosis. In future, improved knowledge of the pathophysiology of asthma and the event enclosed in it provides a promise for

development for a better anti-asthmatic treatment.

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