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ASTHMA: PHENOTYPES AND ENDOTYPES

SUTAR J[1*] AND CHAKRABORTHY GS[2]

1: Department Of Pharmacology, Parul Institute Of Pharmacy and Research, Parul University, P.O. Limda, Waghodia, Vadodara, Gujarat, India

2: Department Of Pharmacognosy, Parul Institute Of Pharmacy and Research, Parul University, P.O. Limda, Waghodia,Vadodara, Gujarat, India

*Corresponding Author: Ms. Jangyaprava Sutar: E Mail: savita11699@gmail.com

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ABSTRACT

Among the most prevalent chronic immunological disorder among people is asthma. People of all ages, from young toddlers to the elderly, are affected. It is classified as a syndrome with heterogeneous presentation rather than a single disease and is fairly prevalent. The majority of people are successfully controlling their asthma with the aid of currently available drugs, such as salbutamol, dexamethasone, prednisolone, etc. This review outlines our knowledge of the many endotypes, phenotypes, and biomarkers associated with each form of asthma. These insights will help us in the future to create new therapies. We gained a better grasp of the clinical nature of asthma, its pathophysiology, and its indications and symptoms thanks to the work of several researchers. As a result of several research efforts, asthma has been classified into various phenotypes and endotypes. Non-atopic (intrinsic) asthma, which mostly affects women, and atopic (extrinsic) asthma, which mostly strikes during infancy or early children, are the two most prevalent forms of phenotypes. The most prevalent endotypes are "T2- High endotype" which is present in about 50% of asthmatic patients, and "Non T2-High endotype (T2- Low endotype)" which calls for urgent care. The discovery of pertinent cellular or molecular biomarkers and expanding knowledge of these mechanistically diverse groups are already shown promise as a means of forecasting clinical response to various asthma medications. A customised approach to diagnosis and treatment is becoming more common

as the number of targeted medicines for asthma increases, which should benefit patients asthma outcomes and quality of life.

Keywords: Chronic immunological illness, Asthma, Endotypes, Phenotypes

INTRODUCTION

Breathing smoothly is something you usually take for granted. Many people with asthma live with the worry of losing control over their breathing every day.

Different phenotypes and endotypes of the illness known as asthma make it varied and complicated. Based on the existence of certain effector T-cell and innate lymphoid cell (ILC) lineages, three different cellular immunological reactions (the types 1, 2 and 3) may be distinguished. The TH1, TC1, and ILC1 cells of type 1 immunity, which primarily targets intracellular microbes, secrete tumour necrosis factor and interferon; type 2 effectors (TH2, TC2, and ILC2), which have been linked to type-3 immune response , which is based on interleukin-17 producing cells and defence against microorganisms, allergies and irritants. **[1]**.

ASTHMA

When tracheobronchial smooth muscle is too sensitive to various stimuli, it narrows the airways and is frequently accompanied by increased secretion, mucosal edoema, and mucus clogging **[2]**. Asthma is characterised by :-

- bronchial hyperreactivity,
- airway inflammation, and
- reversible blockage of airways **[3]**

PATHOGENESIS OF ASTHMA

Helper T-cell typical of other atopic illnesses are T-2 immune responses. Both allergic and non-allergic stimuli, such as infection caused due to virus, smoke of tobacco, cool air, and heavy workout, can act as asthma triggers and set off a series of events that result in chronic airway inflamation. Some examples of allergic asthma triggers include house dust mites, cockroach droppings, and pollen. Release of certain cytokines such interleukin -4, 5, 9, and 13 is triggered by increase of T-2 cell populations in air which will further stimulate the formation of IgE and eosinophilic inflammation. Inflammatory mediators like histamine and cysteinyl leukotriene's release, leads to spasm formation in bronchi, which is then triggered by IgE synthesis. (contraction of airway smooth muscles), increase in secretion of mucous and edoema cause the typical signs and symptoms of asthma **[4, 5] (Figure 1)**.

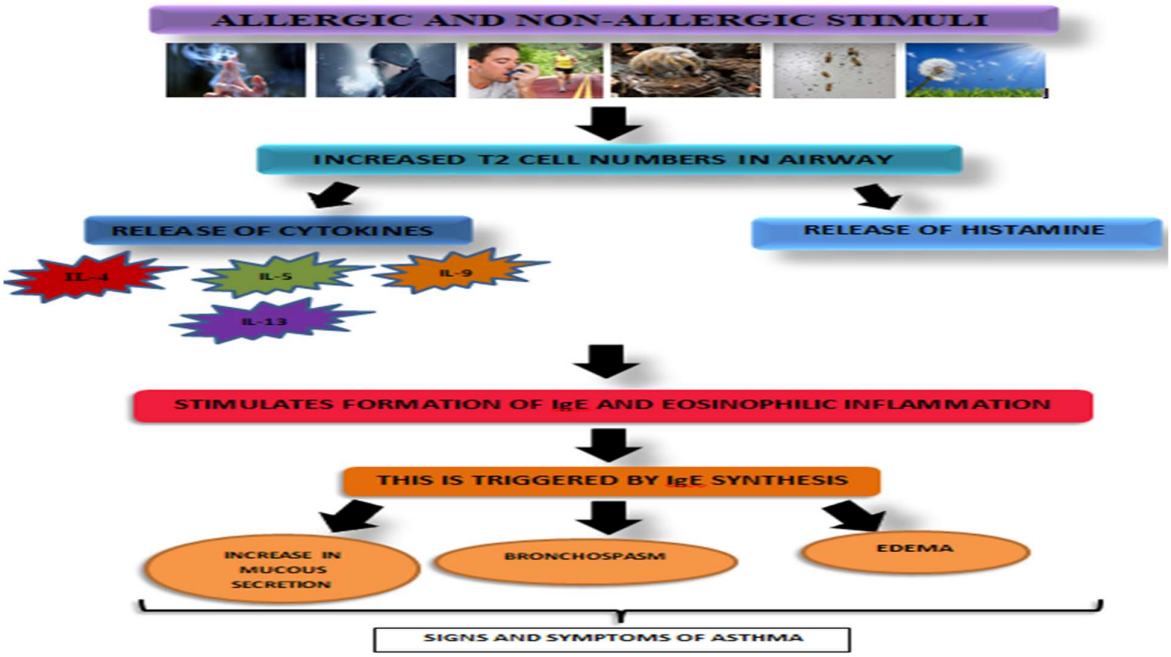

Figure 1: Pathogenesis

PHENOTYPES VERSUS ENDOTYPES:-

On the basis of seriousness, natural course, and response to therapy, asthma is varied, and this variation reflects the underlying causes. Traditionally, people with asthma have been categorised into so-called phenotypes on the basis of comibed form of their clinical, biochemical, and physiological features. Phenotype are categorised as observed features which are combination of genetic and environment related effects, to put it simply.

At the cellular and molecular level, asthma endotypes characterise these various pathophysiologic processes. Patients may react quite differently to the same therapy approaches despite sharing comparable clinical symptoms. Treatment aimed upon patient endotype is referred to as precision medicine. For instance, the design of some early targeted biologic medicines was influenced by the identified intricate severe asthma type 2 inflammatory network **[9]**. More than one endotype of asthma may contain more than one phenotype, and vice versa **[8]**.

ASTHMA PHENOTYPES :-

For a long time, it was believed that there were two main phenotypes of asthma:

A. NON-ATOPIC OR INTRINSIC ASTHMA:-

- Non-atopic form of asthma is estimated to affect ten percent to thirty three percent of people in comparison to atopic asthma, and is more common in women. In many instances, non-atopic asthma is far more

serious as compared to atopic asthma **[36, 37]**.

- The absence of seasonal or exposure-related triggers is typical, as is the absence of a personal or family history of allergies. Past of nasal polysurgeries, being girls, having a forced expiratory volume 1 below 80% of predicted, and being older were all found positive in association to atopic form, while it was discovered to be decreased risk of non-atopic form related with hay fever, seasonal exacerbations, and a longer duration of asthma was associated with decrease in risk of non-atopic asthma **[37,40]**.

-In compared to moms of children with atopic asthma, moms of children of suffering from intrinsic asthma report with nonatopic asthma report, this mucus, and a doctor diagnosed asthma **[38]**.

COMORBITIES :-

Polyps in nose, sinusitis, and GERD are among the comorbidities frequently linked to non-allergic asthma. According to a companion article in this issue, aspirin exacerbated respiratory disease (AERD), which includes serious form of asthma, chronic rhinosinusitis with nasal polyps, aspirin sensitivity and other non-steroidal anti-inflammatory drug sensitivity can all be considered of as separate phenotypes or subtypes of non-allergic asthma, respectively **[39-41]**.

Atopy (positive skin prick tests), on the other hand, has been discovered to be present in fifty two percentage of individuals with AERD and ranged from fourty seven to sixty five percentage of participants in 4 classes of these individuals identified by latent class analysis **[42]**.

BIOMARKERS :-

Nonallergic asthma has a lot of immunopathologic characteristics with allergic asthma **[37, 39, 40]**. With the probable exception of lower IL-4 levels, they share similar local IgE production, a similar or greater number of FCeR1 cells, and a similar or higher number of eosinophils in the bronchial mucosa with allergic asthma. In mucosa and bronchoalveolar lavage fluid, nonallergic asthmatics have greater levels of RANTES expression. They also have higher levels of GM-CSF receptor alpha expression **[36]**.

B. ATOPIC OR EXTRINSIC ASTHMA:-

- It happens at or just before early infancy **[6, 7]**. The majority of individuals with this kind of asthma have a hereditary propensity for allergies. Specific allergens can cause acute asthmatic attacks when inhaled. House dust, feathers, animal dander, furniture filling, fungus spores, and a variety of plant pollens are just a few examples of the airborne allergens **[43, 44]**.

- Atopic form is among the most prevalent from of phenotype of asthma and is

characterised by allergic sensitivity. Even though it frequently affects adults as well, asthma in youngsters affected by asthma is more prevalent than adults. People with such type of phenotype usually experience their first symptoms as children because gene-environment interactions alter how the innate and adaptive immune systems develop and how allergic sensitization begins.

-An atopic person's early phase of the reaction is triggered when they are exposed to an allergen. Leukotrienes, histamine, prostaglandins, and cytokines are just a few of the mediators that are released during this phase and lead to emphysema and bronchoconstriction. The presence and activation of lymphocytes and other inflammatory cells during late phase is what gives rise to a production of pro-inflammatory cytokines **[35]**.

COMORBIDITIES:-

Atopic dermatitis and allergic rhinoconjunctivitis are prevalent in person suffering from allergic asthma. Patients with allergic vs. nonallergic asthma share a comparable proportion of rhinitis symptoms; those with nonallergic asthma are likely suffering nonallergic rhinitis. When compared to non-allergic asthma, chronic rhinosinusitis and nasal polyps are less frequent in extrinsic asthma **[37]**.

BIOMARKERS :-

Regardless of their phenotype, most asthmatics are prone to airway Th2 inflammation because of intrinsic factors such IL-25, IL-33, and thymic stromal lymphopoietin **[44]**. It is necessary to have allergy sensitization (allergy specific IgE) inorder to have intrinsic asthma. Although allergic asthma typically has higher total blood IgE levels than nonallergic asthma, these 2 phenotypes cannot be distinguished merely on the basis of these levels since there is significant overlapping of two groups **[45]**.

Both intrinsic and extrinsic form of asthmatic patients may have peripheral blood eosinophilia which has been associated to airway obstruction and may be a predictor of exacerbations **[46]**.

Peripheral eosinophilia level is high in allergic asthma patients in comparison to asthma patients, according to several studies **[47]**. Increased mean interleukin-5 and 13 production and decreased ratio of interferon - gamma and interleukin-12 to 3 Th2 cytokines (Interleukin-4, 5, or 13) were reported as Th2-polarized responses in the peripheral blood of Detroit Childhood Allergy Study participants who had allergic asthma **[48]**. Additionally, eosinophils, mast cell mediators, and Th2 cytokines are present in greater concentrations in airway secretions of people with allergic asthmatics **[49]**. Positive allergy challenges are associated with an increase in exhaled

nitric oxide fraction (FENO). According to certain studies, there is no link between atopy and a significant FEV1 decline or a persistent airflow limitation **[50, 51]**. However, a different study indicates that individuals with persistent airflow limitation have less atopy than those who do not **[52]**. Comparatively to an early onset, atopic cohort, a low atopic, late-onset group showed a higher decrease in pulmonary function in a 2014 research **[53]**.

T2- HIGH ENDOTYPE :-

Inflammation of type 2 (T2) is important in aetiology of asthma. Inflammatory mediators such as interleukin-4, 5, and 13 increases the inflammation caused by cellular eosinophils.

Type 2-high inflammation is seen in about 50% of asthma patients. Frequently used biomarkers of Type 2-high asthma include sputum and blood eosinophils, exhaled nitric oxide, blood IgE levels, and airway gene expression indicators. Type 2-high patients posses distinctive clinical traits such as increased airway remodelling and modifications in mucus production. Reduced lung function and frequency of asthma exacerbations are among the signs of increased asthma severity that type 2 asthmatics frequently exhibit **[9]**.

FACTORS AFFECTING T2-HIGH ENDOTYPE :-

A. Host factors :-

1. Genetic factors
2. Comorbid factors

B. Environmental factors :-

1. Infections caused by virus
2. Smoke of cigarette
3. Polluted air **[9]**

BIOMARKERS OF T2- HIGH ENDOTYPE :-

A "biomarker" is a property that has been objectively examined and evaluated as a predictor of usual biological processes, pathogenesis processes or pharmacological responses to a therapeutic intervention.

Biomarkers offer a means of classifying people into Type 2-high or non-type 2-high categories. To improve the definitions of asthma phenotypes, further biomarker validation is required.

In order to narrow down the options for biological treatments, a panel of biomarkers, or mixture of multiple biomarkers, may be more appropriate than just one **[9]**.

These are some of the biomarkers of T2-high endotypes:-

- **Sputum eosinophils** :-

  One of the most important characteristics of asthma which affects forty –sixty percent of those with severe asthma with eosinophilic airway inflammation. Eosinophils in induced sputum are frequently analysed to identify T2 asthma. Eosinophils in sputum are

regarded as the "gold standard" type 2 biomarker **[11, 12, 13, 17, 19]**.

- **Pheripheral blood eosinophils**:-
  As peripheral blood eosinophils differ phenotypically from those in the lung, the relationship between peripheral eosinophilia and airway inflammation has been inconsistent among investigations. The patient groups examined, the experimental environment, and the pre-existing drugs might all be factors in this disparity. Since eosinophilic count in blood as mentioned in some study was not able to reflect activities of eosinophilic in airway **[18, 27]**.
- **Serum total IgE**:-
  Total IgE level in serum is a useful atopy status biomarker because of its crucial involvement in the onset of allergic asthma. Both the group of adult and young children, serum IgE levels are strongly correlated with the severity of asthma. Although serum total IgE is not effective for tracking response, it is used to predict how well a patient would respond to anti-IgE medication **[28, 30]**.
- **Allergen sensitization panel**:-
  A important biomarker for the categorization of asthma is the evaluation of aeroallergen sensitivity, according to the “NIH Asthma Outcomes Task Force” . Risk that asthma symptoms may manifest is directly correlated with the allergen level sensitivity as shown by serum-specific IgE **[28, 31]**.
- **Fractional excretion of nitric oxide** :-
  FeNO measurement has the benefit of being a useful instrument and can be done quickly and consistently in exhaled air. Airway epithelial cells, eosinophils, and macrophages create nitric oxide (NO) by conversion of L-citrulline from amino acid arginine through nitric oxide synthase (NOS). Inducible NOS (iNOS) is transcribed as a result of T2-high airway inflammation, which boosts NO production. FeNO's functions in connection to morbidity caused by asthma hence can be additive **[14, 18, 29]**.
- **Periostin**:-
  An extracellular matrix protein called periostin is expressed as a result of IL-4 and IL-13 activity in lung fibroblasts and AECs. Periostin promotes degranulation of eosinophil, superoxide anion production, and eosinophil production of TGF- and cysLTs.

It's expression in tissue present in bronchi demonstrated to be a biomarker of continuous eosinophilic airway inflammation despite corticosteroid therapy, although not being linked with the seriousness of asthma. Serum periostin level may be useful to gauge response of person suffering from asthma to non-T2 based ttreatment. **[15, 16, 18, 32]**.

- **Dipeptidyl peptidase 4 (DPP-4)** :-

  It is unknown whether DPP-4 activity contributes to asthmatic inflammatory up- or down-regulation.

  However, it has been shown that in asthma patients, bronchial epithelial cells stimulated with IL-13 produce more DPP-4 mRNA.

  Anti-IL-13 therapeutic outcomes can be predicted by serum DPP-4. DPP-4 may therefore be a crucial indicator in treatments that target IL-13 **[33]**.

- **Urinary Leukotriene 4** :-

  Higher level of urine leukotriene 4 can distinguish between aspirin-tolerant asthma and AERD with extreme sensitivity . This will be utilised for clinical testing for assessment of AERD in people with asthma who also have nasal polyps **[34]**.

NON-T2-HIGH / T2-LOW ENDOTYPE :-

When compared to severe eosinophilic asthma, non-eosinophilic illness, we found that it was associated with normal subepthelial basement membrane thickness, less CD31 cells, and macrophages it is characterized histologically by the absence of eosinophils in the mucosa **[21]**.

T2-low asthma is an issue that requires immediate attention: The cornerstone of treating severe asthma in these people is bronchodilators in combination with steroids.

T2-low inflammation treatments are ineffective, and patients with these conditions have poor disease management, reduced quality of life, and future therapeutic challenges **[22]**.

BIOMARKERS OF T2-LOW ENDOTYPE :-

There are currently no specific biomarkers, at least in a routine clinical environment, that can distinguish between Type 2-low asthma vs Type 2-high endotypes alongwith to sputum differential cell counts **[23]**. However, a number of biomarkers have been evaluated in the blood and airways of Type 2-low asthma patients, offering hope for their potential application in clinical practise in the future. Neutrophils are activated by interleukin-8 (IL-8), which causes chemotaxis, exocytosis, and the respiratory burst.

Based on currently known biomarkers, neutrophilic inflammation cannot be identified. Although most doctors are were not able to collect sufficient sample from sputum of asthmatic patients, as per some research reveals presence of increase in sputum which was capable of detecting airway inflammation caused by neutrophil **[24]**.

Blood/sputum neutrophilia is one of the proposed biomarkers, however it has some inherent drawbacks. It is unclear that whether the neutrophils are practically significant or not. Additionally, the discovery of neutrophilic inflammation may be a subsequent symptom of a number of unrelated conditions, including concurrent high-dose corticosteroid medication, exposure to smoking or environmental toxins, or recurrent bacterial infections. MMP9, a protein involved in asthmatic airway remodelling and inflammation, is a further potential indication **[25]**. The inflammation of the neutrophilic airways is accompanied by many cytokines. A variety of cell types generate the pleiotropic cytokine IL-6 as response of stimuli causing inflammation. Neutrophil is both biomarker for obese people suffering from asthma as well as sign for abnormal chemical reactions and seriousness of asthma **[26]**.

CONCLUSION :-

Asthma is a very diverse condition since it has such a broad range of endotypes and manifestations. When considering exposure to particular triggering agents like cigarette smoke, cold air, exercise, house dust mites, cockroach droppings, and pollen grains at very specific times in a person's life, asthma develops as a result of a complex interplay of structural cells, including immunological and epithelial cells. Even if study by researchers has improved our understanding of the many endotypes and phenotypes of asthma, we still need more information to rationally support it. We shall be able to apply the theory to produce new discoveries in the near future after rationally verifying the evidence.

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