

## BIOMARKER TARGETED THERAPY IN ASTHMA

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The prevalence of Asthma is increasing throughout the world. The cause for this upsurge is still not conclusively determined, though a lot of speculations are put forward. Advances in the understanding of potential immune, cellular, biological mechanism contributing to asthma pathobiology, knowledge about genetic contributors and elucidation of environmental factors is leading to the establishment of biomarker-targeted asthma treatment replacing the guideline based therapy because of variability in response [1]. Current guideline suggests use of both short and long acting agonists, inhaled and systemic corticosteroids, anticholinergics, methylxanthines, LT inhibitors and anti-IgE agents.

Besides TH2 cells, many other cells and cytokines are involved in airway inflammation in asthma. These biomolecules are the area of research for therapy targeting the specific biomolecule initiating the inflammatory response in each individual patient with asthma.

Widely used long acting  $\beta$  agonists(LABA) is now questioned for its safety because of increase in the asthma related hospitalizations or deaths when used singly or concomitantly with inhaled corticosteroids (ICS) [2]. Intermittent ICS use was as good as regular ICS use in terms of asthma control in mild asthma and was preferred over regular ICS in children because of resultant decrease in linear growth with regular ICS use [3]. Symptom-initiated high dose budesonide inhalation for shorter period was as effective as daily lower dose budesonide therapy and resulted in 70% reduction in ICS use [4]. ICS therapy in pregnant women did neither suppress glucocorticoid-regulated pathways in the placenta and fetus nor increase the risk of pneumonia [5]. Clinical effectiveness of leukotriene receptor antagonist was as effective as ICS alone and LABA with add-on ICS for short period [6]. It was observed that anti IgE therapy improved days without symptoms for some seasons of the year [7]. Asthma education comprising of provision of written action plan increased the adherence to medication & thereby improved asthma control [8].

Identification of polymorphism in the glucocorticoid-induced transcript gene (GLCC11) explains variability in improvement in FEV<sub>1</sub> after ICS therapy indicating the potential individualization of the therapy [9].

Mepolizumab, an IL-5 inhibitor is an effective and well tolerated agent that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma [10].

Lebrikizumab, a monoclonal antibody that binds to interleukin(IL)-13 was shown to improve the FEV<sub>1</sub> in individuals with poorly controlled asthma on moderate to high doses of ICS as it was observed that IL-13 has effect on airway caliber [11]. The patients having elevated levels of periostin are more likely to experience improvement with Lebrikizumab. The efficacy of Reslizumab, an anti-IL-5 antibody in asthma control with persistent eosinophil in sputum & patient with nasal polyposis needs further validation [12].

Five clusters of phenotypically heterogeneous group of patients with difficult to control asthma, related to diverse underlying etiologies & differing complicating factors with probable alternate biological processes have been identified on the basis of increasing severity & atopy which includes presence of lower exhaled nitric oxide, reversibility of lung function & health care utilization [13].

Vocal cord dysfunction is present in small number of difficult to treat asthma patients [14]. Gastroesophageal reflux disease(GERD) is thought to be related to poor control in a subset of adult patients showing improvement in lung function with the use of esomeprazole in asthma with symptomatic GERD [15]. Race, socioeconomic status, education & ethnicity have clear relationship with lung function probably related to access to care or controller medications, dietary differences and genetic variation [16].

A panel of four biomarkers associated with iron metabolism pathways and acute phase response showed the ability to identify individuals with asthma from healthy controls and chronic obstructive lung disease [17]. Metabolic derangement in obesity with acanthosis nigricans and elevated triglycerides were associated with increased prevalence of asthma [18]. Bronchoalveolar lavage fluid from individuals with asthma revealed increased concentrations of group specific component protein (Gc) a protein which induces inflammation by its ability to bind vitamin D metabolites, and neutralization of this protein leads to significant improvements in airway hyperresponsiveness and inflammatory cell recruitment [19].

Decreased foetal size is a determinant of lung function and risk of asthma in childhood [20]. Persistent slow growth in the second trimester was also associated with asthma risk. Cord-blood vitamin D levels were inversely associated with risk of developing respiratory infection and wheeze in childhood [21]. An inverse relationship was found between serum vitamin D level and severe asthma and their smooth muscle mass in young children [22]. Menarche at an early age is associated with lower lung function and more airway symptoms [23]. The biology of asthma exacerbation may not be identical to processes that play an etiological role in asthma. Human Rhinovirus infection is associated with asthma exacerbation [24]. Patients possessing histoblood group O secretor mucin glycan phenotype are more likely to have exacerbations [25]. Eosinophils are strongly associated with asthma and a subset of severe asthma, though long term effect on the airway anatomy is controversial. Both tryptase and chymase positive mast cells are more abundant in the airway walls of patients with more severe asthma and is associated with increased bronchoalveolar lavage levels of PGD<sub>2</sub> [26]. Dendritic cells may play a role in the reported relationship between an increase in diversity of microbial exposure and decreased risk of development of asthma [27]. Commensal flora are important in dendritic cell development and maintenance of immunologic tolerance [28]. Anti – IL-13 antibody in humans targeting patients with elevated periostin levels showed greater improvement in FEV<sub>1</sub> [11]. Th-17 cell induced inflammation occur in the non-steroid responsive asthma patient [29]. TGF- $\beta$  stimulates the development of Th-17 cells explaining a possible role for this biomolecule in asthma. Subset of CD4+ memory effector cells cause elevated levels of IL-17 present in the circulation of patient's with asthma [30]. Nuclear factor E2-related factor 2 up-regulates antioxidant genes and reduces airway smooth muscle proliferation. Control of these genes was altered in severe asthma[31]. Exposure to chlorine in swimming pool and association of asthma symptoms in children was reported by many authors [32]. Use of paracetamol more than once a month was found to be associated with increase in asthma risk probably through depletion of antioxidant glutathione S-transferase [33]. Substantial increase in endothelial progenitor cells were found in patients with asthma having late-phase allergen responses [34]. Increased number and diameter of blood vessel were observed in endobronchial biopsies after allergen challenge.

Repeated bronchoconstriction via methacholine produced structural changes in the airways similar to allergen challenge, suggesting that repeated epithelial stress is an independent contributor to airway remodeling [35]. Disruption of the structure of surfactant protein D after allergen challenge was associated with an increased inflammatory response to allergen [36].

NO(Nitric oxide)production is altered by Arginase through competing with NO synthase(NOS). DNA methylation of the Arginase2 gene was inversely correlated with exhaled NO in children[37]. Common regulatory haplotypes of arginase1 were associated with altered bronchodilator response[38]. NOS inhibition might lead to increased airway reactivity. Asymmetric dimethylarginine, a NOS inhibitor was increased in asthma [39]. Endogenous cortisol induced by stress might modulate NO production [40].

A variant in the IL-6 receptor(IL6R) increased the odds ratio for asthma [41]. The association with variant in the IL6R gene raises the possibility of examining the effectiveness of tocilizumab in the treatment of asthma in a genotype-dependent manner [1].

All individuals with asthma do not share the same biological underpinning. Identification of particular endotypes along with the development of therapies targeting very specific pathway will lead to development of targeted and biomarker driven therapy.

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