Review Article

An update on the diagnostic biomarkers for asthma

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Abstract

Asthma is a respiratory disorder accounts for ~339 million cases per annum. The initial diagnosis of asthma relies on the symptomatic identification of characters, such as wheeze, shortness of breath, chest tightness, and cough. The presence of two or more of these symptoms may be considered as indicative of asthma. The asthma-diagnostic also involves spirometry test before and after inhaling a bronchodilator like albuterol. Because asthma pathophysiology involves participation of immune system, the cytokines play an important role. The review discusses various molecules that are or may be used as biomarkers for the asthma diagnosis.

Keywords: Asthma, chronic, interleukins, IL-17, respiratory

Asthma Overview

Asthma is a prolonged disorder of the lungs. It excites airway routes and leads to morphological changes to narrow down the passage. This narrowing creates difficulty in breathing leading to uneasiness. Extreme asthma manifests as ruckus talking or being dynamic. The condition is termed as interminable respiratory sickness. Global initiative for asthma[1] defined Asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as, wheeze, shortness of breath, chest tightness, and cough that vary over time and intensity together with variable expiratory airflow limitation. The airflow limitation may later become persistent".

The asthma condition is manifested as episodes of breathlessness, wheezing, etc., In response to exposure to certain allergens and the symptoms may subside with time. However, repeated episodes of asthma may also prove fatal, if not managed properly. The symptoms of the diseases are curable with medication.[2] Asthma is believed to be a multifactorial disorder affected not only by genetic predisposition but also by environmental factors.

Asthma Epidemiology

Asthma is a serious ailment. Asthma causes ~339 million cases throughout the world in a year and nearly 1000 deaths in a day.[3] Almost 18% of the world population is at risk of the disease. As per GINA estimates,[1] 100 million more cases would be added by the year 2025. Nearly, 25 million Americans are at risk of the disease. ~2 million clinical visits in America are attributed to the disease. The countries categorized as a low-and-middle-income group by the World Health Organization are the worst in the case of asthma-related deaths.[4]

Nearly, 6% of Indian children and 2% of adults are presented with asthma symptoms per year in a population of 1.31 billion.[4] Underreporting and misdiagnosis of asthma are important contributors to variations in the number of

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asthma cases reported by various workers.[5] "Indian Study on Epidemiology of Asthma, Respiratory Symptoms, and Chronic Bronchitis" (INSEARCH) reported a prevalence rate of was carried out in the adult population and to be 2.05% during 2007-09, with an estimated burden of about 17.23 million in 2011.[6] The National Family Health Survey had predicted asthma at ~2% during 2005-06.[6]

The year-wise asthma cases curve is exponential.[4] The rise in the asthma cases each year was related to decreased exposure to microbes in early life. However, the hypotheses failed to explain the high number of cases in New York that have a higher microbial burden.[7] Another hypothesis held the deteriorating quality of air responsible for the exponentiality of the asthma curve.[8] Exposure to smoke, dust, pollen, or any other allergen, or high humid weather trigger asthmatic reactions and the condition may be delayed by preventing the exposure.[5] Asthma is widely penetrated in rural areas.[9] The asthma cases are largely under-reported. Further, misdiagnosis of the disease further complicated the assessment of the true cases.[5]

Asthma Diagnosis

The initial diagnosis of asthma relies on the symptomatic identification of characters, such as wheeze, shortness of breath, chest tightness, and cough. The presence of two or more of these symptoms may be considered as indicative of asthma. The intensity of these symptoms may vary with time and may worsen with viral infections, cold, exposure to allergens, and at night. The symptom-based diagnosis of asthma warrants confirmation by other tests.

The asthma-diagnostic spirometry test involves observing and subsequent recording of the forced vital capacity (FVC) and forced expiratory volume (FEV) of lungs. The measurement is carried out before and after inhaling a bronchodilator like albuterol. The FEV1/FVC ratio less than 0.75 in adults, whereas less than 0.85 may be used as diagnostic for asthma. Further, bronchodilator reversibility verifies the results. The diagnostic tool for asthma includes peak flow tests, methacholine challenge, imaging tests, allergy testing, nitric oxide test, sputum eosinophils, provocative testing for exercise, and cold-induced asthma.

Asthma Pathophysiology

Asthma is an exaggerated immune response. Its development involves complex pathophysiology comprising of various immunological and morphological changes. Several allergens, such as cockroach residues, spores, and pollens or non-allergic causes like tobacco smoke, cold air, and viral infection induce the onset of inflammatory reactions of asthma. These inflammatory reactions are mediated by type-2 helper T cells eventually causing breathlessness due to temporary narrowing of airways.[10]

T-helper cells, upon induction, secrete interleukins (IL-4, IL-5, and IL-13), and other cytokines such as interferon (IFN-g), thereby, promote immunoglobulin E (IgE) synthesis. Besides IgE, histamines and cysteinyl leukotriene are also involved in mediating allergic reactions.

The prime focus of asthma research is always adaptive immunity, though innate immunity is also being explored for its role in asthma.[11] Unlike adaptive immune responses, innate immunity has been reported in invertebrates[12,13] and plants[14] as well. Innate immunity lacks specificity and memory. The non-self-recognition mechanisms rely on pathogen-associated molecular patterns (PAMPs) on the microbe surface.[15] The innate immunity is also involved in the regulation of the adaptive immune response.[16]

Toll-like receptors

Toll-like receptors (TLRs) are important innate immune receptors that recognize specific PAMP ligands on the surface of the invading microbe, such as lipopolysaccharides (LPS), peptidoglycans, etc.[17] TLR-4, for example, specifically binds Gram-negative bacteria surface molecule, LPS.

Protective action of lipopolysaccharides

Exposure to LPS in an early stage of life confers a certain degree of tolerance to asthma.[18] LPS exposure to adults including as an occupational hazard makes them prone to asthma.[18] Inhalation of LPS causes asthma in mice.[19] Even low concentrations of LPS can induce or aggravate asthma symptoms in sensitive adults.[20] However, when LPS was administered as an adjuvant along with an allergen induces a weak allergic reaction in animals compared with the allergen alone.[21] LPS stimulates the secretion of TLR-4. TLR-2, and TLR-4 were found to downregulate the intensity of an allergic reaction.[22] The response seems to be affected by the genetic makeup and environment. The TLR-2, however, was found to be associated with the onset of allergic inflammation as well as airway hyper-responsiveness in a murine model.[23]

NOD Proteins and asthma

Nucleotide-binding oligomerization domain (NOD) proteins are the receptor proteins located in the cytoplasm of a cell.[24] Human beings have two NOD proteins namely NOD-1 and NOD-2. Of these, the NOD1 gene is physically located in a chromosome region that is strongly linked with asthma.[25] Moreover, the mutation at this locus compromises the ability of the host to have protection from asthma which is otherwise natural in the subjects raised in a farm.[18] A study on German adults, the mutation in this gene was found correlated with highly frequent atopy and asthma.[26]

Tumor necrosis factor-alpha

Tumor necrosis factor (TNF) exists majorly as TNF-α and TNF-β with 35% sequence homology and similar receptors. TNF-α, a type II membrane protein, is attached by a signal anchor transmembrane domain.[27] TNF-α is secreted by macrophages, T cell, mast cell, and epithelial cells.[28] The release of TNF-α involves the activity of TNF-α converting enzyme

that cleaves the transmembrane signal anchor (TACE).[27] The cytokines such as IL-1, GMCSF, and IFN-γ boosts the TNF-α secretion in monocytes/macrophages. The eosinophils are also known to secrete TNF-α.[29]

Role of antigen-presenting cells in asthma

Dendritic cells mediate the regulation of the acquired immune response via the presentation of the antigen to the T cells.[30] The dendritic cells have their origin in CD34+ bone marrow progenitor cells or CD14+ monocytes. Upon differentiation three types of immature dendritic cells viz., Langerhan's cells, myeloid cells, and plasmacytoid cells arise. These immature cells are capable of antigen presentation that in turn acts as a deciding factor for their maturation. The maturation of the dendritic cells is mediated by cytokines, activated T cells expressing CD40 and other PAMPs on the surface. The event is accompanied by reduced endocytosis with increased expression of co-stimulatory molecules, such as CD40, CD80, and CD86 on the surface of the dendritic cells along with the proteins that are part of major histocompatibility complex-II. In the case, if these co-stimulatory molecules are not over-expressed and the allergen binds to the immature dendritic cells, the tolerance to the allergen takes place.[31]

The tolerance to the ovalbumin in the lungs during its nasal injection is mediated via interleukin 10 (IL10) and led to the production of CD4+T regulatory cells. The regulatory T cells further secrete IL10.[32] The action of T-regulatory cells, leading to a decrease in airway hyperresponsiveness, requires APCs displaying CD80, and CD86 ligands.[33] The number of dendritic cells in the airways is known to increase in numbers in case of asthma. Moreover, the decrease in the number can reverse the symptoms up to a large extent.[20]

Cytokines

Structural cells such as epithelial and endothelial cells as well as the myocytes of airways secrete various mediators of the pathophysiology of asthma.[34] The numbers of mediators identified have exceeded 50. Of the 50 inflammatory mediators identified, the cytokines organize, perpetuate, and strengthen the inflammatory reaction in asthma.[35]

The cytokines are small secretory proteins usually with their molecular weight smaller than 80kDa and are usually modified by glycosylation. The cytokines are involved in the signaling during inflammation of the airways in the case of asthma.[36] Cytokines regulate cell-mediated immunity.[37] The activity of cytokine is concentration-dependent[38] and is effective in picomoles.[39] The cytokines include lymphokines, pro-inflammatory and inhibitory cytokines, chemokines, and growth factors.

In the case of allergen-induced asthma, the activated CD4+ T cells led to a higher concentration of Th2 cytokines, such as interleukin-4, IL-5, IL-13 than that of the Th1 cytokines. However, the role of Th-1 cytokines in promoting asthma cannot be ruled out completely.[26] Type-2 immunity plays an important role in the pathophysiology of asthma. Among the three type-2 cytokines (i.e., IL-4, IL-5, and IL-13), IL-13 plays an important role. In experimental mice model, the interleukin alone is capable of manifesting asthma-like symptoms, moreover, its silencing reverses the inflammation.[40] The IL-13 acts on goblet cells and is also involved in the upregulation of the hyperresponsiveness of the airways.[41]

The Th17 has also been implicated in the airway inflammation in the case of a rodent model.[42,43] The Th1 suppresses the Th2 cells by secreting interferon-gamma, whereas Th2 secretes IL-4 to suppress Th1. The Th17 secretes IL-10 to suppress both the Th1 and Th2.[44]

Interleukin-17

Interleukin-17 is a 155-residue long homodimer protein of nearly 35kDa molecular weight. The two monomers of the interleukin are bonded by a disulfide bridge.IL-17 is produced and is secreted by CD4+ T cells. The role of the Th17 subset of T-helper cells in asthma has been investigated.[43] The IL-17 is not directly involved in the pathophysiology of Asthma, though it stimulates the production of other cytokines involved in asthma pathophysiology. The IL-17 of CD4+ T cell origin induces IL-6 secretion by fibroblasts,[45] and IL-6, IL-8, GM-CSF, and PGE2 secretion by epithelial, endothelial, and fibroblastic cells.[46] Besides, the IL-17 also target NF-kB cells[45] that leads to nitric oxide secretion in the cartilage of osteoarthritis patients.[47] IL-17 is involved in T cell proliferation[45] and of CD34+ hematopoietic progenitors.[47]

The IL-17 exhibit polymorphism in various region of IL-17A and IL17F.[48] IL-17 interacts with dimer IL-17RA/IL-17F receptors that trigger a cascade of signaling reactions ultimately leading to the secretion of inflammatory mediators and other cytokines.[49] The polymorphisms in various regions of IL-17A and IL-17F have been associated with the adult, children or infant asthma in various parts of the globe.[50-52] Recently, the polymorphism in the IL-17 is associated with atopic asthma and the IgE levels in the serum.[53]

Phenotypic Inflammations in Asthma

The inflammation in asthma may be categorized into four types based upon the phenotype of inflammation, viz., eosinophilic, neutrophilic, paucigranulocytic, and mixed granulocytic phenotype.[54] An asthma inflammation is categorized as eosinophilic asthma when sputum of the patient has higher than 3% of eosinophils; neutrophilic asthma, when the sputum cells are predominantly neutrophils (i.e., more than 76%); mixed granulocytic, when an increase in the proportion of both types of the inflammatory cells are observed in the sputum sample; and paucigranulocytic asthma, when none of the two inflammatory cells increase beyond a threshold level. The increase in the eosinophils levels is related to adaptive immune response involving mainly interleukin-4, IL-5, IL-9, and IL-13. Whereas,

neutrophil cell elevation is related to an innate immune response in response to immunogens or allergen such as air pollutants.[55] In the case of the paucigranulocytic asthma methacholine triggers hyperresponsiveness.

Corticoid steroid administration via inhalation is therapeutic for eosinophilic asthma and reduces the percentage of eosinophils in sputum to a greater degree,[56] downregulate the secretion of type 2 cytokines from lymphocytes[57] and eotaxin from epithelial cells.[58] The therapy, however, is not that effective for combating the neutrophilic asthma.

Diagnostic Biomarkers

Biomarkers Definitions Working Group (2001) defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention." The diagnosis of the respiratory diseases involves an analysis of sputum or blood samples and the biomolecules are usually molecules or chemicals involved in the immune/allergic reactions.

The biological molecules/chemicals that act as a putative diagnostic of asthma are either type-2 inflammation-related or type-2 inflammation-independent markers.[59] The type-2 inflammation-related markers are cytokine secreted by type-2 T helper cells such as interleukin-4, IL-5, and IL-13. In addition, eosinophil count in blood and sputum, fraction of elevated NO levels of breath and periostin levels in blood serum, and Dipeptidyl peptidase-4 in lung epithelia are also type-2 inflammation-related biomarkers for asthma.[59] The type-2 inflammation-independent markers includes interleukin-6, IL-17, C-reactive proteins, and neutrophil count in sputum.

Type-2 inflammation-related diagnostic marker

Eosinophil count

The eosinophil cells, being responsive to corticoid treatment, were considered potential diagnostic markers for COPD (Chronic Obstructive Pulmonary Disease).[60] The sputum sample from a patient exhibiting two or more symptoms of asthma is checked for eosinophil count as a diagnosis of asthma. 1—2% of eosinophil per total inflammatory cells are considered normal.[61] Asthma induces the sputum eosinophil count.[62] Sputum eosinophil levels of more than 2% are correlated with decreased lung function as well.[63] The percent eosinophil count is also sensitive to corticosteroids, which may directly or indirectly influence its levels in sputum.[64,65] The corticosteroids were found to subside allergen-induced sputum eosinophils.[64,65] The lowering of allergen-induced sputum eosinophil levels upon inhalation of corticosteroids is being used for the diagnosis of asthma.[66,67]

Serum eosinophil count elevates in COPDs and blood eosinophil count more than 150 cells per microliter is used as markers in clinical trials by several authors.[68] The serum eosinophil level, however, shows no correlation with the asthma-induced sputum eosinophil levels.[63] Antibodies raised against IL-5 receptors counter elevated sputum as well as serum eosinophil count.[69]

Fractional exhaled nitric oxide (FENO) concentration

Nitric oxide synthase exists as a constitutive enzyme in two isoforms, viz., nNOS, and eNOS in a healthy individual. Both the constitutive isoforms are induced in case of inflammatory reactions of asthma.[70] Nitric oxide synthesized from NOS has a mixed role in asthma.[71] NO may act as a bronchodilator, vasodilator, and may play some role in plasma extravasation.[34] NO plays diverse roles in the pathophysiology of asthma that includes recruitment of the cells involved in inflammation,[72] hyperresponsiveness of airways,[73] and airways remodeling.[74]

Nitric oxide is a part of the expiratory mixture of gases of a healthy human being.[75] The proportion of NO in exhaled gases increases in the case of asthma.[76] Moreover, corticoid treatment reverses the upregulation of NO in the expiratory gases in asthmatic patients, whereas, the corticoids have no effect on the expiratory NO of healthy subjects.[77]

The level of nasal nitric oxide (nNO) can be used using Chemiluminescence based analyzer. Higher than 50 parts per billion of FENO in adults and more than 35 ppb in children is indicative of airway eosinophilia and steroid-responsive inflammation.[78] The increased proportion of the exhaled NO is directly proportional to the inflammation reaction, the method thus can be used to detect most-reactive and worst asthma phenotype.[79] However, no correlation is found between exhaled NO and the number of sputum eosinophils.[80] FENO less than 25 ppb in adults and less than 20 ppb in children indicate symptomatic asthma without eosinophilic inflammation.[78]

Periostin

Periostin is a FAS1 domain-containing protein located in the extracellular matrix that plays an important role in the allergic inflammation including asthma.[81] The periostin is inducible by IL-13 and mediates hyperresponsiveness of the airways.[82] The IL-13 induced expression of periostin is countered by corticosteroid treatment, upon which the level of the periostin decreases.[83] The exact role of periostin in asthma pathogenesis is still controversial yet it was proposed as a strong biomarker for sputum and tissue eosinophilia.[84]

Dipeptidyl peptidase-4

Dipeptidyl peptidase-4 is another asthma inducible protein secretion of which is triggered by IL-13.[85] Inhibition of the protein deter the transport of CD4+ cells in the CD26 deficient rat model of asthma[86] and the deficiency of the protein is also linked with the reduction in eosinophilic airways inflammation.[87] The expression of the gene encoding DPP4 in the airways was reported to be positively correlated with the production of nitric oxide/nitric oxide synthase in the asthma patients.[88]

Other biomarkers of Type-2 related inflammation

Immunoglobin E

For atopic asthma, IgE level in serum acts as an important biomarker of an allergic reaction. Serum IgE levels elevate upon interaction with an allergen and the immunoglobin was associated with the eosinophilic inflammation esp., Th-2 high inflammation.[89] Immunoglobin E synthesis is mediated by Th2 cytokines.[90] The estimation of serum IgE levels is mandatory to be estimated in case of severe asthma. In addition, the IgE levels, along with IL-5 and IL-13 are also reported to elevate in the sputum of an asthmatic patient with type-2 eosinophilic inflammation.[91]

Soluble mediators of sputum

The proteins derived out of eosinophil cells are important markers of inflammation that includes cationic proteins,[92] neurotoxin,[62] and peroxidase.[93] The eosinophilic inflammation of asthma is associated with increased levels of eotaxin-2,[94] cytokines IL-5 and GM-CSF.[92] Another important cytokine that is upregulated in the sputum of type 2 inflammation-related asthma is IL-13. The upregulation of IL-13 in sputum in the case of type-2 related inflammation is negatively correlated with methacholine. The ratio of IL-4: TNF-alpha can also serve as a marker to diagnose eosinophilic asthma.[95] In addition, the nitric oxide metabolites also respond by accumulating in sputum in case of eosinophilic inflammation, moreover, the level reverses upon treatment.[96] In the case of severe refractory asthma, sputum osteopontin was found to be induced strongly,[97] while the level of sputum angiopoietins-1 was weakly affected.[98]

Volatile profile

Gases like ethane have been reported to be associated with severe asthma.[99] The volatile profile of asthmatic patients as a diagnostic tool has been proposed,[100] however, it still needs validation, before being implemented.[101]

Type-2 inflammation-independent diagnostic markers

Neutrophil in sputum samples

The neutrophil count in the sputum sample of a healthy individual remains at a median 37% per inflammatory cells. The sputum neutrophil count increases upon smoking and exposure to pollutants and toxins.[61] The neutrophils in the sputum of asthmatic patients when increases beyond 76%, it is classified as neutrophilic inflammation.[54] Neutrophilic inflammation is related to severe exacerbations.[102] The sputum neutrophil count is an antagonist to the FEV1/FVC ratio,[54] pre- and post-bronchodilator FEV1.[103] Sputum neutrophil count is associated either with impaired lung function or inhalation therapy of corticosteroids.[104]

Interleukin-8

IL-8 is responsive to severe asthma[105] and it mediates the activation of neutrophils.[106] The upregulation of the interleukin has been reported at the transcript level in the sputum[107] and at the protein level in the soluble fraction of sputum.[108] The upregulation of the IL-8 is correlated with the neutrophil level in sputum samples.[109] Moreover, the expression of two receptors of IL-8 viz., CXCR1, and CXCR2 was also upregulated.[108] The antagonist to the CXCR2 receptor provides relief to LPS-induced inflammation in healthy adults.[110]

Tumor necrosis factor-alpha

The TNF-alpha seems to play an important role in severe refractory asthma.[111,112] The transcript levels of the gene encoding TNF-α are induced in the case of neutrophilic inflammation which was not true in the case of paucigranulocytic inflammation.[107] The action of TNF-α is a result of the transcription of several genes including IL-1β, IL-6, IL-8, and TNF-α.[111] The inhalation of TNF-α even in case of mild asthma triggers airway hyperresponsiveness associated with increase neutrophils and eosinophils.[113]

Other markers of type-2 inflammation-independent asthma

The level of myeloperoxidase and neutrophil elastase are reported to be induced in the sputum upon the activation of neutrophil cells in the patients of asthma.[105,106,114] Neutrophilic asthma also induces the transcript of TLR-2 and TLR-4 and the receptor may be used to distinguish neutrophilic asthma from other types.[114,115] Similarly, the levels of C-reactive protein and IL-6 in plasma also elevates vis-a-vis that of other types of asthma.[108]

Th-17 Cytokines

Th17 cells are important cells participating in the pathophysiology of asthma via mediating airway hyperresponsiveness involving both eosinophils and neutrophils.[116,117] The Th-17 cytokines include interleukin-17A through IL-17F. The number of Th17 cells increases in the case of allergic inflammation, thereby increase the production of Th17 cytokines.[118]

The cytokine family IL17 was related to various diseases. Increased rates of IL17 have been documented in chronic inflammatory disorders, inflamed bacterial infection tissue,[119] arthritis patient synovial fluid,[120] and asthmatic patient bronchoalveolar lavage fluid.[121] The IL-17 high phenotype was shown to induce genes that resemble those that appears in response to psoriasis[122,123] a disease closely associated with the asthma.

These interleukins have been demonstrated to mediate the synthesis of IL-6 and IL-8 in vitro.[42] Moreover, the transcript formation for gene encoding IL-17 was found to be associated with the IL-8 transcript and also the neutrophil count in the sputum samples.[124] The IL-17 immunity is proposed as an alternative immunity in case of the suppression of type 2 immunity.[122] However, their coexistence in the blood T cells is possible.[122,125]

Studies on severe asthma revealed that the interleukin-17 is responsive to the disease and induction in its expression has been reported from the sputum, BAL samples, and bronchial biopsies upon induction.[124,126] Even in laboratory animal models of asthma, IL-17

cytokine is reported to be inducible upon allergen challenge and is involved in recruiting neutrophils using its receptor, IL-17RA.[127]

The interleukin-17A and IL-17F were reported to upregulate in airway tissues at the protein of an asthma patient[128] and recruit neutrophils.[42] Similarly, the level of IL-17A was also found to upregulate in the serum[129,130] lungs, and BAL fluid of asthma patients.[131] Moreover, the comparative levels of the IL-17A in the blood serum of the smoker asthma patients were higher than that of the serum of the non-smoker asthmatic patients.[129] The level of both the smoker and non-smoker asthma patients was higher than the healthy control samples. Smoking is known to alter the epithelium barrier, the function that is regulated by the interleukin IL-17.[122] The transcript of both IL-17A was reported to be induced in the asthma patients as compared with the corresponding healthy control subjects.[132]

Upregulated levels of both the IL-17A and IL-17F in airways showed a strong association with neutrophilic inflammation and the severity of the condition.[128,133] Besides these two important cytokines, IL-25 (IL-17E) is an important component of a cascade of events ultimately leading to the secretion of cytokines IL-4, IL-5, and IL-13.[134] More importantly, the gene expression signature related to IL-17 has been reported in the case of severe asthma. This signature was orthogonal to the type-2 related inflammation.[135] Though, the two pathways can be associated with the blood T cells.[122]

Inhibiting the interleukin Il-17 adversely affects the inflammation of the airways, hyperresponsiveness of the lungs, and the secrete of Th2 cytokines.[127] Antithetically, the role of IL-17 in the pathophysiology of asthma became dubious when anti-IL17RA monoclonal antibody, Brodalumab is administered to the patients manifesting moderate to severe asthma symptoms in a randomized, double-blind, placebo-controlled study and the asthma symptoms did not subside.[136]

Immunoglobin E synthesis is accompanied by an increase in the Th17 cells.[118] Interleukin-17 is an important cytokine secreted by Th17 cells. Both IL-17A and IgE were found to have elevated levels in patients with severe asthma.[137] The cytokine, IL-17A level was found to have a positive correlation with immunoglobin E.[129]

IL-17A may be useful as a diagnostic marker for patients with symptomatic asthma to identify the role of these biomarkers in patients.[129,137] The genes encoding the IL-17 proteins exhibit polymorphism in populations. These different populations exhibit changes in the gene sequence based on SNPs in between. These gene populations exhibit differing tendencies for the development of asthma after bronchiolitis in infants.[52] An allele with residue 'A' in the region, rs2275913 of IL-17A,[138] and T alleles of region rs1974226 and rs279548 of IL17A[53] were reported to confer susceptibility to asthma in individuals.

IL17 levels above 20 pg/mL were considered to be a risk factor for serious asthma.[139] IL-17 may serve as an important biomarker to distinguish atopic and nonatopic asthma.[2] The IL-17 assays may be incorporated in the routine practice of the primary care physicians while dealing with the severe asthma especially in the case of infant asthma.

Transcription Factors, GATA-3 and FOX-P3 during the Progression of Asthma

The transcription factor, GATA-3 is found to elevate in the blood serum in case of asthma.[129] However, the reverse was true for FOX-P3, the serum levels of which was found lower in the asthma patients than in the corresponding controls. The GATA-3 was positively correlated with the IgE levels in the serum while the FOX-P3 was negatively correlated. Moreover, the serum levels of the transcription factor GATA-3 were found to be higher in the smoker asthma patients than in the non-smoker patients.[129] These two transcription factors may act as mediators/protectors of the asthmatic reaction and their use as biomarker candidates for detecting asthma needs further study.[140]

Conclusion

Asthma is a serious problem. The seriousness of asthma disorder is compounded by underreporting and misdiagnosis. The diagnosis of the disorder relies upon symptomatic manifestation and serum and sputum analysis of biomarkers. Interleukin-17 seems to be an important biomarker of asthma. Serum IL-17 levels are already in use for the diagnosis of the disorder. Development of the molecular tools enabled us to devise more sensitive diagnostic tools. The expression of IL-17A at transcript level can be used to devise a suitable RT-PCR based test for the diagnosis of asthma.

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Conflicts of interest

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