



Involvement of lymphocytes in asthma and allergic diseases: a genetic point of view

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Purpose of review

The activation and regulation of lymphocytes play a central role in asthmatic inflammation. It is increasingly recognized that diverse panels of lymphocyte lineages and cytokine profiles are involved in the asthmatic phenotypes. In this review, we discuss the advances in the gene variants associated with the regulation of lymphocytes and relevant cytokines underlying asthma and allergic diseases. We also discuss the current evidence about the epigenetic regulation of lymphocyte differentiation and the interaction with environment.

Recent findings

Many genetic variants in asthma are functionally associated with lymphocytes and relevant cytokines. Interleukin (IL)-2RB is important in the homeostasis of T regulatory cells (Tregs) through effects from IL-2. IL-18R1 and ST2/IL-1RL1 drive the T helper 1 and 2 inflammation via the ligands of their encoding receptors. Novel genes, like orosomucoid 1-like 3/gasdermin-like gene and taste receptor type 2 members are being explored for their roles in T-cell activation. T-cell lineages are epigenetically regulated by de novo methyltransferases, histone methylase, CD44 and microRNA. Environmental factors such as second-hand smoke and ambient air pollution modify Tregs differentiation significantly.

Summary

Plenty of genetic loci of lymphocyte regulation provide us a deeper insight into the asthma pathogenesis. Future challenge is to define genetic drivers in asthma phenotypes to provide therapeutic targets.

Keywords

asthma, epigenetics and environment, gene expression, lymphocytes

INTRODUCTION

Asthma is classically considered as a Thelper (Th)2 inflammation related disease, but other T-cell subtypes might play a role. Given the persistent high prevalence of asthma and related allergic diseases after decades of anti-Th2 treatment [1] and resistance to the therapeutic effects of corticosteroids in 5–10% of patients with severe asthma it is likely that other mechanisms are involved in asthma pathogenesis. Studies [2–4] on asthmatic phenotypes provide new insights into lymphocyte differentiation and the role of interleukin (IL)-2, IL-9, IL-12, IL-15, IL-17, IL-18 and IL-33 in asthmatic inflammation.

Positional cloning and candidate gene studies have identified more than 100 genes that contribute to asthma susceptibility and atopy [5]. These genes could be classified functionally into several groups: innate immunity, for example, human leukocyte antigen (HLA) genes and toll-like receptor-4; T-cell receptor activation, for example, inducible T cell

costimulator, cytotoxic T-lymphocyte antigen-4, and CD28; Th2-cell activity, for example, IL-4/IL4R, IL-13, the high-affinity immunoglobulin E (IgE) Fc receptor β chain and plant homeodomain finger protein 11; epithelial biology and mucosal immunity and asthma severity, for example, tumor necrosis factor and a disintegrin and metalloprotease 33 and novel genes, for example, dipeptidyl

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KEY POINTS

- IL-18R1, ST2/IL-1RL1 and ORMDL3/GSDML play important roles in T-cell response and are important genetic loci of severe asthma.
- Accumulated effects of rare variants may drive asthmatic inflammation in different aspects of lymphocyte activation.
- Epigenetic regulation of Tregs and Th1/Th2 stability and interaction with environment imply the multidimensional cross-talking mechanism in the asthmatic pathogenesis.

peptidase 10 [6^{***}]. A lesson from these studies is that no single gene could explain the majority of asthma phenotypes [2].

Genome-wide association study (GWAS) utilizes commercial chip systems to search for common genetic risk variants (allele frequencies >5%), single-nucleotide polymorphisms (SNP) mainly, in the entire genome that influence health and disease. More than 30 GWASs have been conducted for asthma and allergic diseases including the largest one from GABRIEL (A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community) consortium [7^{*},8,9]. Candidate genes identified from GWASs can further be enriched by gene ontology analysis into two functional groups: immune system process (IL-13, IL-1RL1, IL-6R, IL-18R1, HLA genes, NOTCH4 and SMAD3) and molecular/signal transducer activity (IL-1RL1, IL-2RB, IL-6R, IL-18R1, HLA genes, Sma and Mad 3(SMAD3), Retinoic acid

receptor related orphan receptor A (RAR-related orphan receptor A)-related orphan receptor A, NOTCH4 and GRB2-associated binding protein 1) [6^{***}]. These genes indicate the importance of lymphocytes activation and several cytokines in the pathogenesis of asthma. However, the risk genes identified by GWASs can explain only a small fraction of asthma. Attention has been focused on the rare variants (allele frequency <5%), genetic structural variations, epigenetic regulation and inter-action with environment for association with asthma [7^{*},10–12].

This review discusses recent advances in our understanding about the genetic aspects of lymphocyte regulation in asthma pathogenesis, focusing on cytokines and associated receptors, novel genes associated with lymphocyte regulation, rare variants and epigenetics–environment interaction.

GENETIC LOCI OF CYTOKINES AND RELEVANT RECEPTORS INVOLVING LYMPHOCYTES DIFFERENTIATION

Signaling from cytokines and relevant receptors modulates T-cell lineages differentiation and activation. Genetic variations of these cytokines and receptors have been identified as risk factors for asthma (Table 1) [6^{***},7^{*},8,10,13^{*},14–17,18^{*}].

IL-2RB

IL-2RB is located on chromosome 22 and encodes the β receptor (IL-2R β) on naïve T cells. SNP rs2284033 of IL-2RB is reported as a risk for asthma susceptibility in the GWAS from GABRIEL consortium [9]. IL-2 is secreted by antigen-activated T cells and plays an important role in the mutual

Table 1. Genetic loci of susceptibility of asthma involving lymphocytes differentiation

Gene	Chromosome	Gene variation	Functions	References
IL-2RB	22q13.1	rs2284033	Encoding IL-2R β and mediating regulatory T cells differentiation	[6 ^{***} ,7 [*] ,8]
IL-18R1	2q12	rs3771166	Encoding IL-18 receptor and driving Th1 responses along with IL-12	[6 ^{***} ,13 [*]]
IL-1RL1	2q12	rs1420101	Encoding IL-33 receptor and driving Th2 responses	[6 ^{***} ,13 [*]]
IL-13	5q31	rs1295686	Drive Th2 responses	[6 ^{***} ,8]
IL-4	5q31.1	rs2243300	Drive Th2 responses	[6 ^{***}]
IL-9/IL-9R	5q31.1 / Xq28 and Yq12	rs31563/rs3093467	Produced from Th9 cells, proliferation of mast cells	[14]
IL-12RB1	19p13.1	Nonsynonymous rare variants	Drive Th1 responses	[6 ^{***} ,10]
ORMDL3/GSDML	17q21	rs7216389/rs230548	Drive Th17 responses with unknown mechanism	[13 [*] ,15–17]
TAS2R13, 14, 19	12p13	Upregulation	Drive Th2 responses with unknown mechanism	[18 [*]]

IL, interleukin; ORMDL, orosomucoid 1-like 3; GSDML, gasdermin-like gene; TAS2R, Taste receptor type 2 members.

balance between Th17 cells and Foxp3⁺ Treg cells. IL-2 binds to its receptors, IL-2R α , β and the common cytokine receptor γ chain, to form the quaternary complex IL-2-IL-2R α -IL-2R β - γ (c) complex and exerts its effect on transduction of mitogenic signals of T cells. Naive T cells express a low density of IL-2R β and IL-2R γ , and are therefore relatively insensitive to IL-2, but acquire sensitivity after IL-2R α expression [19]. IL-15, another cytokine secreted by mononuclear cells, shares IL-2R β to form IL-15-IL-15R α -IL-2R β - γ (c) complex. Interleukin-15 has a role in proliferation of CD8⁺ T cells and natural killer cells [20]. In the allergen-challenged mouse model, blocking IL-2R β reduced Th2 inflammation in the lung and ameliorated the airway hyperresponsiveness (AHR). It was also found the IL-15 levels in bronchoalveolar lavage fluid were decreased in asthmatics and inversely related with AHR during rhinovirus infection. Lack of IL-15 production in asthmatics may contribute to the virus-induced asthma exacerbations [21].

IL18R1 AND ST2/IL1RL1

The IL18R1 belongs to the interleukin 1 receptor family, which includes IL-1RL1 (suppression of tumorigenicity 2, the receptor of IL-33), located on chromosome 2q12. Interferon- α and IL-12 are reported to induce the expression of this receptor in natural killer and T cells. This receptor specifically binds IL-18, which drives Th1 responses along with IL-12 [3]. A study [22] in ovalbumin-challenged lung-specific IL-18 transgenic mice revealed IL-18 inducing Th1 and Th2 airway inflammation and increase AHR via CD4⁺ T cell and IL-13. Three isoforms of suppression of tumorigenicity 2 have been identified: a membrane-bound form (ST2L), a soluble form of suppression of tumorigenicity 2 (sST2) and a constitutively active variant ST2 (ST2V) [23]. ST2L is expressed on Th2 lymphocytes, eosinophils and mast cells. The IL-33/ST2L axis drives Th2 response in asthma and allergic rhinitis, and dominant Th1/Th17 systemic response has been shown in the ST2-deficient mice [24]. sST2 provides a neutralizing effect of IL-33 and attenuates ovalbumin-induced allergic asthma in mice [25]. The SNP in the IL-1RL1-IL-18R1 region has been identified as a risk for eosinophil counts in asthma and severe asthma, suggesting the importance of IL-18 and IL-33 in the pathogenesis of severe asthma [8,13[■]].

TH2 CYTOKINES

Chromosome 5q31–33 encodes Th2 cytokines and RAD50. RAD50 encodes a protein responsible for DNA repair and its 3' end contains conserved

noncoding sequences and enhancer elements, which act as a locus control region for the IL-4 and IL-13 genes nearby. These genes have been identified consistently by GWAS and are linked with asthma or allergic diseases [6[■]].

INTERLEUKIN-4 AND RAD50-IL13

IL-4 and IL-13 have many common biologic activities, which is possible because of sharing IL-4 receptor α (IL-4RA) and results in activation of signal transducer and activator of transcription factor 6 in B cells. SNP (C-589T) of IL4RA promoter region has been mentioned as a risk factor for life-threatening asthma attacks and (C + 33T) located on the 5' untranslated region of the IL-4 gene is associated with elevated IgE level in Japanese population [26]. Importantly, gene–environment interactions between the IL-4 promoter and mold exposure are related to the development of asthma in children [26]. In a recent meta-analysis of 3000 asthmatic patients, C-589T represented as a low-penetrant risk factor for atopic asthma [27]. SNP rs2244012 in intron 2 of RAD50 has been identified as risk factor for severe asthma. SNP-1112C/T on IL-13 promoter increases IL-13 transcription, and the IL-13+2044A/G SNP located on exon 4 is associated with more active IL-13 function. A recent meta-analysis also confirmed IL-13–1112C/T polymorphism exhibited increased asthma risk in whites [odds ratio (OR)=1.30] and in atopic patients (OR=1.25) [28]. The same study also found significant association between IL-13+2044A/G polymorphism and increased asthma risk in Asians (OR=1.19) and whites (OR=1.22) [28].

INTERLEUKIN-9

IL-9 is produced by activated Th2 lymphocytes, Th9 cells, Th17 cells. IL-9 can expand Th17 population by autocrine fashion and enhance Tregs function through unknown mechanism [3]. IL-9/IL-9R genetic involvement in allergic disease has been recently discovered that the rs31563 SNP (-4091G/A) in the IL-9 gene was associated with an increased risk for atopic dermatitis and the rs3093467 SNP in IL-9R gene was associated with an increased risk for nonallergic atopic dermatitis [14].

NOVEL GENES LOCI ASSOCIATED WITH LYMPHOCYTES REGULATION

Some novel genes identified by GWAS with unknown mechanism in the asthma pathogenesis and further studies are needed to explore their roles in lymphocyte regulation.

ORMDL3/GSDML

The first GWAS and then GABRIEL consortium identified orosomucoid 1-like 3, (ORMDL3) and the nearby gasdermin-like (*GSDML*) gene on chromosome 17q21 as a significant childhood-onset asthma candidate genes in Europeans. ORMDL3 is expressed abundantly in lymphocytes and encodes trans-membrane proteins anchored into the endoplasmic reticulum (ER) and are believed to be involved in multiple pathways in the ER. It is also involved in sphingolipid metabolism, which affects multiple cellular functions [8]. An interesting finding is the expression of ORMDL3/GSDML in the cord blood mononuclear cells of children that is significantly associated with IL-17 secretion [29], and association between 17q21 genetic variants and neutrophil counts has been reported in different races [30,31]. ORMDL3/GSDML is also strongly associated with severe asthma, childhood wheeze phenotypes, eosinophil-mediated AHR and allergic rhinitis [13[¶],15–17].

TASTE RECEPTOR TYPE 2 MEMBERS

Taste receptor type 2 members (TAS2Rs) are initially recognized as a group of bitter taste receptors located on the tongue. The study of pediatric asthma revealed the expression of TAS2R13, TAS2R14 and TAS2R19 is significantly associated with severe asthma [18[¶]]. Further functional examinations revealed the TAS2Rs are highly expressed in lymphocytes and stimulation of TAS2R could inhibit Th1 and Th2 inflammation, promote bronchodilation and their expression was correlated with lung function inversely.

RARE VARIANT INVOLVING THE LYMPHOCYTES REGULATION

Alleles with frequency <5% (minor allele frequency) and accumulative effects from small-effect common variants could not be detected through GWAS screening. Rescreening the current GWAS database with candidate genes of rare variants or integration with other functional gene information provides the advantages to reduce the number of association tests and thereby to increase power.

Four rare variants were identified as asthma risk loci by resequencing in the database of EVE consortium. One of them, IL-12RB1, involving lymphocyte regulation, was significantly associated with asthma in both African Americans and European Americans [10]. IL-12 plays the important role in promoting Th1 response. *IL-12RB1* gene located on chromosome 19p13.1 encodes IL-12 receptor in T cells and natural killer cells. IL-12RB1

is essential for resistance to intracellular pathogens by conferring IL-12/IL-23 signaling [32]. Reanalysis of the GABRIEL database found an asthmatic risk locus, CYP2A6, the primary enzyme responsible for the clearance of retinoic acid, in B cells with dysregulated methylation status in house dust mite-allergic asthma [7[¶]].

Cusanovich *et al.* have identified lymphocyte counts as an immunological quantitative trait associated with asthma in the Hutterites. By combining gene screen data of lymphoblastoid cell lines and GWAS data of lymphocyte counts in Hutterites, these authors associated a subset of 117 genes implicated in lymphocyte activation, and T cell receptor signaling with asthma pathogenesis. Their findings carry the message that many loci of small effects control variation in lymphocyte count and asthma susceptibility. The associated loci include genes involved in T cell receptor signaling CD3ε molecule, epsilon (CD3E) and lymphocyte cytosolic protein 2, mitochondrial adenosinetriphosphate (ATP) synthesis (ATP5H, ATP5I and ATP5L) and other novel loci [33]. Another GWAS study [30] of white blood cell phenotypes identified the rs2524079 SNP on 6p21 and rs11878602 SNP on 9p13 are associated with lymphocyte counts.

EPIGENETIC AND ENVIRONMENT REGULATION IN THE T CELL DIFFERENTIATION

Epigenetics is the heritable modification of gene expression. It is established after fertilization and is affected dynamically by environment. Three main mechanisms operate the epigenetic regulation: deoxyribonucleic acid (DNA) methylation of cytosine bases to silence gene transcription, acetylation or methylation of histone tails to regulate DNA accessibility to RNA polymerase II and noncoding RNAs. Demethylation around the DNase I hypersensitive sites within IL-4 and RAD50-IL-13 promoters have been extensively studied [34]. IL-2 is important for Treg-associated gene expression, and higher IL-2 Site1 methylation in the cord blood from the pediatric asthmatics is associated with more exacerbation and hospital admission [35].

Recent evidence of co-expression of two or more T cell subsets in asthmatic patients re-challenges our thinking about the T cell lineages in asthmatic phenotypes [2]. Higher co-expressing T-bet(+) GATA-3(+) cells in the eosinophil-high asthmatics after in-vitro stimulation implies the involvement of T cell plasticity in the pathogenesis of asthma [36[¶]]. The forkhead box transcription factor (Foxp3) is the master regulator of the development and function of Tregs. Foxp3 expression is tightly

regulated (summarized in the list below) by: the methylation status of Treg-specific demethylated region in the enhancer through complex signals from T cell receptors, transforming growth factor- β , IL-2 and IL-6 cytokines and other active mechanisms in the thymus [37,38[■]]; histone tail modification by various chromatin modifying/remodeling proteins, for example, histone deacetylases inhibit Foxp3 gene expression and Treg function, [38[■],39]; and microRNA, for example, miR-10a prevents the Tregs differentiation into Th17 subset by targeting the transcriptional repressor Bcl-6 [40]. Examples of epigenetic regulations involving the T cell stability are:

- (1) Epigenetic regulation of regulatory T cells (Tregs) stability
 - (a) Regulation the methylation status of Treg-specific demethylated region by active mechanism in thymus and signals from T cell receptors and cytokines [37,38[■]]
 - (b) Histone/protein deacetylases: inhibitory effect on Tregs expression [38[■]]
 - (c) MicroRNA. e.g. miR-10a, inhibitory effect on Tregs expression [40]
- (2) Epigenetic regulation of Th1/Th2 stability
 - (a) De-novo methyltransferases 3a: methylation at IFN- γ and IL13 promoter site [41,42]
 - (b) Histone methylase SUV39H1-H3K9me3-HP1alpha pathway: methylation at IFN- γ promoter site [43]
 - (c) CD44: demethylation at the interferon (IFN)- γ /IL-17a promoter site and hypermethylation at the IL-4/foxp3 gene promoter [44,45]

Lower Treg-specific miR-10a expression has been found in mice with a genetic susceptibility for autoimmune diabetes [46].

Growing evidence shows that de-novo methylation and histone regulation in the IFN- γ promoter site maintain the stability of T cell lineage. In the T cell-specific deletion of de-novo methyltransferases 3a (DNMT3a) mice, failure of the methylation at IFN- γ promoter site results in production of INF- γ from Th2, Th17 and tire cells following reticulation with IL-12. Adding DNMT inhibitor could reverse the inflammation and AHR [41]. It has also been shown that DNMT3a deficiency was also accompanied by decreases in DNA methylation at the IL-13 locus suggesting DNMT3a is involved in IL-13 gene expression [42]. Other studies revealed different regulatory mechanisms. One study reported the involvement of histone methylase SUV39H1, which participates in the trimethylation of histone H3 on lysine 9 (H3K9me3), in Th2 lineage

stability. H3K9me3 provides binding sites for heterochromatin protein 1a (HP1a) and enables transcriptional silencing. In Th2 cells deficient in SUV39H1, expression of Th1 gene increased followed by an impairment of effective H3K9 and reduced binding of HP1 α to the promoters of the silenced IFN- γ [43]. Another study found CD44 expression on the T cells regulates the Th1/Th17 and Th2 differentiation. Activation of the CD44 by the CD44 legend, osteopontin, led to demethylation at the IFN- γ /IL17a promoter region and hypermethylation at the il4/foxp3 gene promoter. Blocking CD44 remethylated the IFN- γ /IL-17a promoter region and promoted Th2 differentiation [44]. It was found previously that polymorphism in osteopontin gene is associated with asthma in a Puerto Rican population [45].

A study of a cohort of monozygotic twins discordant for asthma provides the evidence of epigenetic and environment regulation of Tregs in the pathogenesis of asthma. It was found that Tregs from asthmatic discordant twins expressed lower level of Foxp3 protein and impaired Tregs function that was associated with increased levels of CpG methylation within the Foxp3 locus when compared with their nonasthmatic twin partner. Meanwhile, Tregs from asthmatic discordant twins exposed to second hand smoke (SHS) expressed less Foxp3 protein when compared with the asthmatics without exposure to SHS [47]. It was also found the exposure to SHS and ambient air pollution are associated with hypermethylation and decreased expression of Foxp3 in Tregs [48]. Gene-gene interaction between the IL-4RA (gene encoded IL-4 receptor alpha chain) and insulin-induced gene 2 (INSIG2) (obesity-related gene) and gene-environment interaction between IL-13 and indoor dampness on the risk of childhood asthma have been recognized [49].

FUTURE DIRECTIONS

The introduction GWAS provides the capacity for analyzing hundreds of targets, but only a small fraction of phenotypes could be explained by gene signatures, implying the diverse gene-epigenetics-environment cross-talking in asthma pathogenesis [4,50]. The next-generation sequencing (NGS) techniques now can screen the whole genome including the noncoding variants and structural variants [11]. Meanwhile, more delicate approaches targeting the phenotypes are warranted to facilitate data harmonization and improve power. Sophisticated phenotype definition by clinical features, inflammatory and signaling profiles can be approached via systems biology. Systems biology provides a strategy

to integrate large-scale multidimensional information into a comprehensive map by mathematical models [51]. An approach by 'Bayesian networks' for mapping the lung expression quantitative trait loci has revealed six key-driver genes in asthma and inflammation, including IL-1B and suppressor of cytokine signaling 3 (SOCS3) [52]. SOCS3 is known as positive regulator of Th2-mediated allergy and promotes IL-17 production [53].

CONCLUSION

Genes, epigenetics and environment affect the lymphocyte regulation in allergic diseases. Plenty of novel loci of lymphocyte regulation in asthma and allergic diseases provide us with a deeper insight into the pathogenesis. Efforts to define genetic drivers in proper phenotypes through NGS and systems biology are important to provide better monitoring, prediction and development of targeted therapy for asthma.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

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- of special interest
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