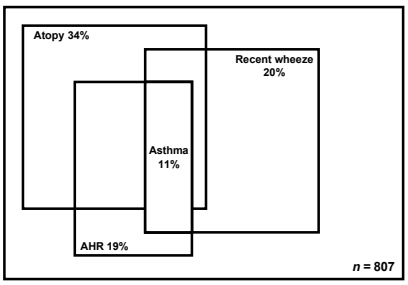
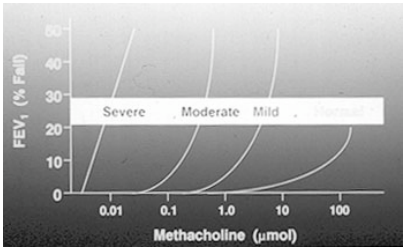
Defining Asthma: Clinical Criteria

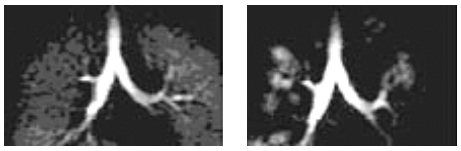


From: Woolcock, AJ. "Asthma" in *Textbook of Respiratory Medicine, 2nd ed.* Murray, Nadel, eds.(Saunders:Philadelphia) pp. 1288-1330, 1994

Defining Asthma: Bronchial Hyperresponsiveness



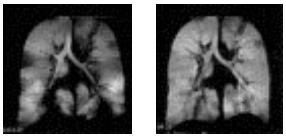
Impaired Ventilation in Asthma



Normal Asthmatic

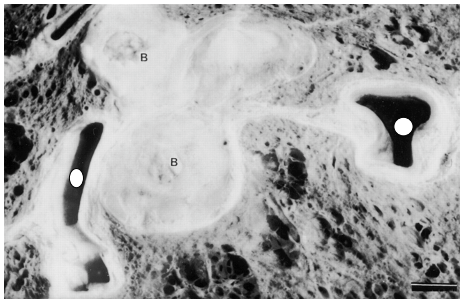
From: Klarreich, *Nature* 424:873, 2003

Dynamic Imaging of Asthma



Pre-treatment Post-treatment

Mucus Plugging is a Prominent Feature of Moderate to Severe Asthma



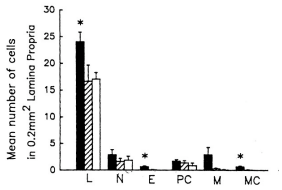
From: Bousquet et al., *Am. J. Respir. Crit. Care Med*., 161:1720, 2000

Some Landmarks in the History of the Immunology of Asthma*

1989: Early genetic mapping assigns chromosome 5q to the "cytokine gene cluster."
Early 1990s: Asthma is an inflammatory disease.
1990: Upregulation of ICAM-1 and LFA-1, adhesion molecules, in a primate model of asthma
1992: T_H2 bias of lymphocytes in asthma
1997: Experimental support grows for the "Hygiene hypothesis," first proposed in 1989.
2000: Role of Tregs in regulation of asthma

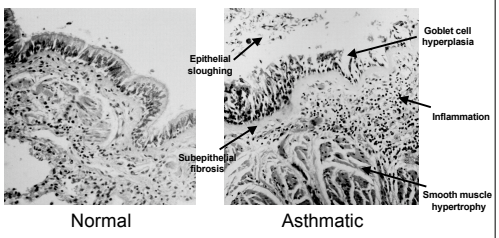
*Highly biased view

Nature of Inflammatory Cells in Biopsies From Airways of Asthmatics



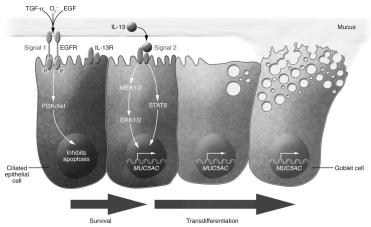
From: Ollerenshaw and Woolcock., *Am. Rev. Resp. Dis.* 145:922, 1992

Defining Asthma: Pathological Features



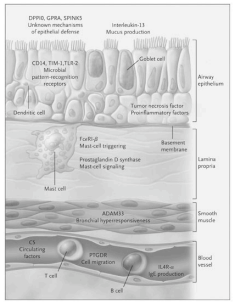
From: Bousquet et al., *Am. J. Respir. Crit. Care Med*., 161:1720, 2000

Pro-survival and Metaplatic Pathways to Goblet Cell Production

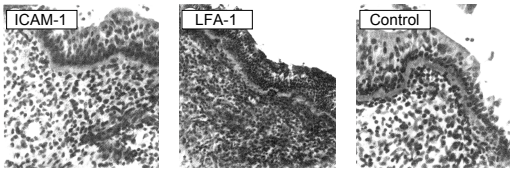


From: Cohn, *Am. J. Clin. Invest*, 116:306, 2006

Tissue "Compartments" in Asthma



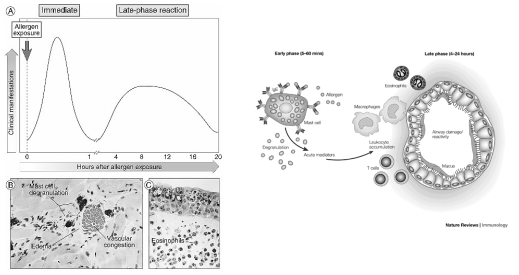
Adhesion Molecules ICAM-1 and LFA-1 in Experimental Asthma



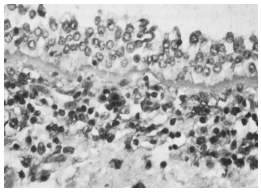
From: Wegner et al., *Science* 247:456, 1990

Asthma and the Immune Response

Early- and Late-phase Allergic Reactions



Presence of Degranulated Eosinophils in Asthmatic Airways



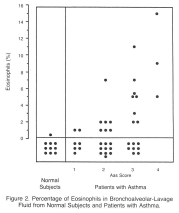
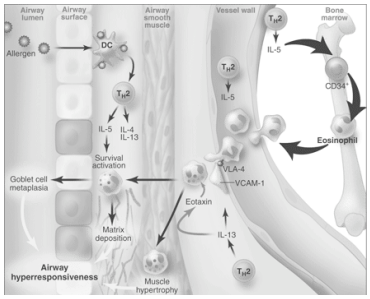


Figure 2. Percentage of Eosinophils in Bronchoalveolar-Lavage Fluid from Normal Subjects and Patients with Asthma.

From: Bousquet et al., *N. Engl. J. Med.* 323:1033, 1990

Eosinophils and Asthma



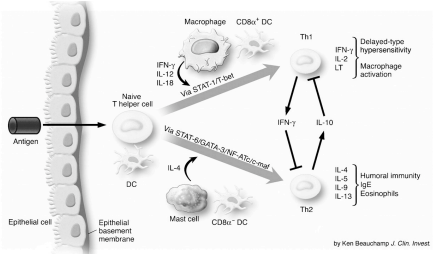
From: Wills-Karp and Karp, Science 305:1726-1729, 2004

Asthma as a T_H2-dominated Disease

First Recognition of a T_H2 Bias in Lymphocytes Obtained by BAL in Asthmatics

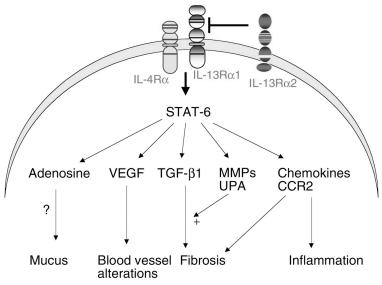
From: Robinson et al., *New Engl. J. Med.* 326:298,1992

Emergence of T_H1 and T_H2 Cells from Naïve Precursors



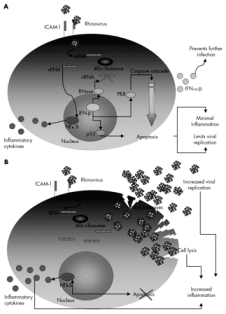
From: Elias et al., *J. Clin. Invest.* 111:291, 2003

STAT-6 Signaling Pathways Leading to the Asthmatic Phenotype



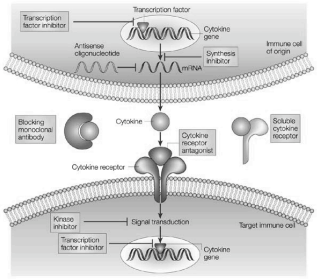
From: Elias et al., *J. Clin. Invest.* 111:291, 2003

Defective Innate Immunity to Rhinovirus Infection in Asthmatics



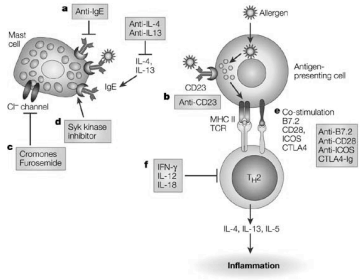
From: Wark and Gibson, *Thorax* 61:909, 2006

Potential Drug Targets in Asthma



From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Understanding the Immunology of Asthma Leads to Insights Into Novel Therapeutics



From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

Who Gets Asthma?

The Inverse Association Between Tuberculin Responses and Atopic Disorder

Taro Shirakawa, Tadao Enomoto, Shin-ichiro Shimazu, Julian M. Hopkin*

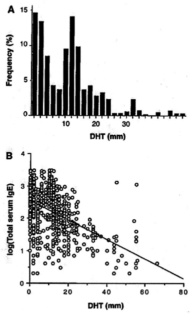


Fig. 1. Delayed hypersensitivity to tuberculin (DHT, in millimeters) and relation to serum IgE. **(A)** Histogram showing bimodal distribution of responses to tuberculin, assayed as DHT at 12 years of age in 867 Japanese schoolchildren. **(B)** Plot of log(total serum IgE) versus DHT in the same children ($r = -0.492$, $P < 0.001$).

From: Shirakawa et al., *Science* 275:77, 1997

Table 1. History of infectious diseases, atopic symptoms, IgE levels, and cytokine profiles in subjects grouped by tuberculin reactivity. ASE, allergen-specific IgE; UD, undetectable.

Measurement	Group 1 (n = 290)	Group 2 (n = 289)	Group 3 (n = 213)	Group 4 (n = 75)	Total (n = 867)
Tuberculin response					
At 6 years	−	−	+	+	
At 12 years	−	+	+	−	
Positive antiviral immunity (%)					
Measles (history + vaccine)	83.4	87.2	84.5	81.3	84.3
Chicken pox (history + vaccine)	86.9	82.3	82.2	82.7	83.9
Mumps (history + vaccine)	62.8	60.9	60.1	57.3	61.0
Number with IgE to *Ascaris*	2	2	2	1	7
Symptoms (%)					
Atopy (past + present)	46.8	33.9‡‡	25.8‡‡	38.7	36.6
Atopy (present)	32.1	7.9‡‡‡	9.8‡‡‡	30.7	18.5
Asthma (past + present)	13.4	4.1‡‡	3.7‡‡	6.8	7.4
Rhinitis (past + present)	16.2	4.8‡‡	8.6‡	14.6	10.4
Eczema (past + present)	22.7	12.8‡‡	12.2‡‡	16.0	16.2
Geometric mean IgE (IU/ml)	208	149**	98***	178	154
Positive ASE (%)	55.8	43.9‡‡	41.8‡‡	53.3	48.2
Atopic (high IgE or positive ASE) (%)	65.5	54.0‡‡	49.2‡‡	61.3	57.3
Median cytokine level (pg/ml)					
IL-4	1.88	0.96†	0.92†	1.66	1.22 (10.2-UD)§
IL-13	18.3	10.2†††	7.8†††	19.1	14.2 (45.6-UD)
IL-10	5.9	3.1††	2.9††	5.9	3.9 (10.2-UD)
IL-12	UD	UD	UD	UD	UD
IFN-γ	7.8	11.0††	13.2††	6.4	10.5 (23.2-UD)
Positive family history within three generations (%)	54.1	49.8	49.8	48.0	51.0
Mean BMI	21.1	22.0	21.9	21.2	21.6

**$P < 0.01$, ***$P < 0.001$ on the basis of Student's test. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ on the basis of a median test. ‡$P < 0.05$, ‡‡$P < 0.01$, ‡‡‡$P < 0.001$ on the basis of χ^2 against group 1, respectively. §Maximum-minimum values.

From: Shirakawa et al., *Science* 275:77, 1997

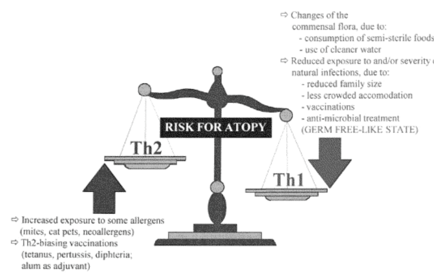
Table 2. Odds ratios for atopy and for occurrence and remission of atopic symptoms in positive versus negative tuberculin responders by age. Multiple logistic analysis was conducted with the SPSSX package, version 2.2. In all models, allowance was made for dichotomized variables including sex, life-style, nutritional status, environmental factors, and family history. Only significant values are shown.

Tuberculin response	Odds ratio		
	Atopy	Atopic symptoms	
		Occurrence	Remission
Conversion to positive up to 6 years of age	0.50 (0.29 to 0.83)*	Asthma: 0.31 (0.22 to 0.45)* Eczema: 0.50 (0.33 to 0.91)*	Asthma: 8.2 (6.0 to 9.8)** Eczema: 1.6 (1.0 to 2.2)*
Conversion to positive between 6 and 12 years of age	0.43 (0.25 to 0.83)**	Asthma: 0.42 (0.24 to 0.56)*	Asthma: 6.0 (2.8 to 10.3)*** Eczema: 6.7 (4.8 to 11.4)*** Rhinitis: 9.0 (6.2 to 14.2)***

*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$.

From: Shirakawa et al., *Science* 275:77, 1997

Environmental Influences and Asthma: The Hygiene Hypothesis



Asthma, rhinitis, other respiratory diseases

Hay fever and asthma in relation to markers of infection in the United States

Paolo Maria Matricardi, MD,[a] Francesco Rosmini, DSc,[b] Valentina Panetta, DSc,[a] Luigina Ferrigno, BSc,[b] and Sergio Bonini, MD[a] *Rome, Italy*

Asthma, rhinitis, other respiratory diseases

Background: The hygiene hypothesis proposes that declining exposure to infections is implicated in the rising trend of allergy and asthma.
Objective: We sought to test this hypothesis by examining the relationship of hay fever, asthma, and atopic sensitization with markers of infection in a large general population sample of the United States.
Methods: We analyzed the data of 33,994 US residents recorded in a public database of a nationally representative cross-sectional survey (Third National Health and Nutrition Examination Survey, 1988-1994). The variables examined were sociodemographic information, lifetime diagnosis and age at first diagnosis of hay fever or asthma, current skin sensitization to 9 airborne allergens and peanut, and current serology for *Toxoplasma gondii*, herpes simplex viruses type 1 and 2, and hepatitis A, B, and C viruses.
Results: Hay fever (adjusted odds ratio, 0.27; 95% CI, 0.18-0.41; $P < .001$) and asthma (adjusted odds ratio, 0.45; 95% CI, 0.31-0.66; $P < .001$) were less frequent in subjects seropositive for hepatitis A virus (HAV), *T gondii*, and herpes simplex virus 1 versus seronegative subjects after adjusting for age, sex, race, urban residence, census region, family size, income, and education. Skin sensitization to peanut and to all the airborne allergens examined, except for cockroach, was less frequent among HAV-seropositive versus HAV-seronegative subjects younger than 40 years of age. The prevalence of hay fever and asthma diagnosed at or before 18 years of age in HAV-seronegative subjects increased progressively from 2.7% (95% CI, 0.7%-4.7%) and 0.4% (95% CI, 0.1%-1.6%), respectively, in cohorts born before 1920 to 8.5% (95% CI, 7.3%-9.7%) and 5.8% (95% CI, 4.8%-6.8%), respectively, in cohorts born in the 1960s, whereas they remained constant at around 2% in all cohorts of HAV-seropositive subjects.
Conclusion: In the United States serologic evidence of acquisition of certain infections, mainly food-borne and orofecal infection, is associated with a lower probability of having hay fever and asthma. Third National Health and Nutrition Examination Survey data support the hypothesis that hygiene is a major factor contributing to the increase in hay fever, asthma, and atopic sensitization in westernized countries. (J Allergy Clin Immunol 2002;110:381-7.)

Key words: *Asthma, hay fever, hepatitis A virus, hygiene, infection, epidemiology, National Health and Nutrition Examination Survey III*

Allergic diseases are spreading among populations living a Western lifestyle.[1] This epidemic has been variously attributed to pollution,[2] changes of diet,[3] and allergen exposure.[4] Another theory assumes that hygiene, by reducing exposure to infections, facilitates atopic responses and their inflammatory consequences at mucosa and skin surfaces, namely allergic asthma, rhinitis, and atopic eczema (the hygiene hypothesis).[5-7]

In Europe atopy was found to be less frequent in children raised in large[5,8,9] and poor families,[5,9] on farms,[10] or in communities living a traditional-type lifestyle[11] and in children attending daycare centers.[12] Moreover, allergic rhinitis and asthma were inversely associated to positive serology for hepatitis A virus (HAV)[13,14] and for *Toxoplasma gondii*,[15] suggesting that the level of exposure to orofecal and food-borne infections might influence the inception of respiratory allergic diseases.

The emergence of allergic asthma in unsanitary inner-city areas in the United States seems irreconcilable with the hygiene hypothesis.[16,17] However, longitudinal studies in Tucson, Ariz, provided the formal demonstration that early exposure to other children in the family or at a daycare center protects children from asthma and atopy, and this was attributed to an earlier and more frequent acquisition of infections.[18] Should this interpretation be correct, markers of exposure to a higher microbial burden, such as positive serology to HAV and *T gondii*, should be independently associated with less allergy and asthma in the United States, as they are in Europe.

The Third National Health and Nutrition Examination Survey, 1988-1994 (NHANES III), examined a large national sample of Americans who responded to questionnaires on allergic and respiratory diseases and who underwent allergy skin testing and blood testing for markers of infections.[19] This public database provided a unique opportunity to investigate whether hay fever and asthma are indeed correlated with serology for HAV, *T gondii*, and other markers of infection in the US general population.

METHODS

Study design

We examined a public registry of 33,994 US residents aged 1 to 90 years or older that includes clinical and laboratory data from NHANES III and analyzed the following variables: age, sex, race,

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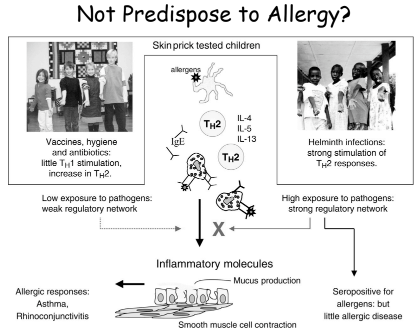
0091-6749/2002 $35.00 + 0 1/81/126658
doi:10.1067/mai.2002.126658

381

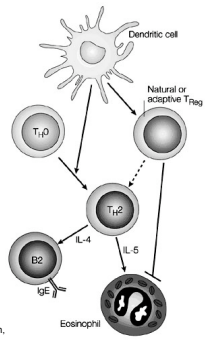
Paradox: Why Does Chronic Infection with Helminths Not Predispose to Allergy?



From: Yazdanbakhsh et al., *Science* 296:490, 2002

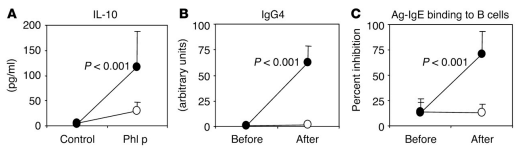
An Alternative to the Hygiene Hypothesis: Regulatory T-cells

The Role of Regulatory T-cells in Modifying T_H2 Immunity



Modified from: Maizels & Yazdanbakhsh, *Nature Rev. Immunol.* 3:733, 2003

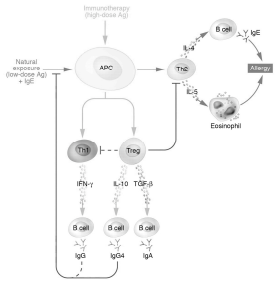
Immunotherapy of Atopic Diseases: a Role for Tregs?



Following 2-year grass pollen immunotherapy (closed circles), there were significant increases in (**A**) allergen-stimulated PBMC production of IL-10; (**B**) serum concentrations of grass pollen allergen-specific IgG4; and (**C**) serum inhibitory activity for allergen-IgE binding to B cells compared with controls (open circles). These changes were accompanied by a reduction in symptoms and inhibition allergen-induced late cutaneous response.

From: Robinson et al., *J. Clin. Invest* 114:1389, 2004

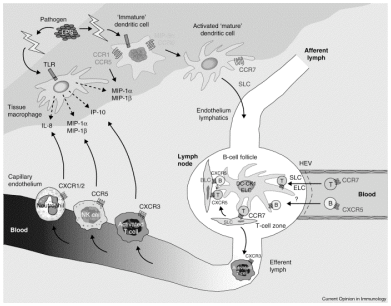
Regulatory T-cells (Tregs) in Asthma



From: Robinson et al., *J. Clin. Invest* 114:1389, 2004

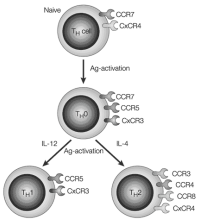
Chemokines: the Gatekeepers of Inflammation

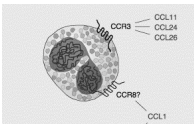
Chemokines Direct Traffic



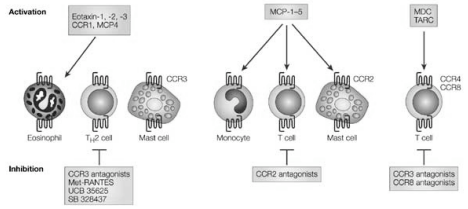
From: Luster, *Curr. Opin. Immunol.* 14:129, 2002

Chemokine Receptor Specificity in T_h2 Cells and Eosinophils





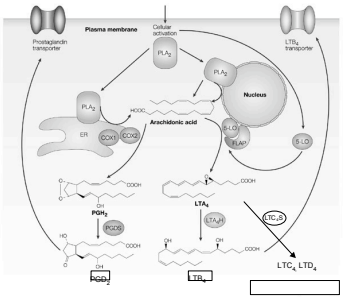
Potential Drug Targets in Asthma: Chemokines and their Receptors



From: Barnes, *Nature Reviews Drug Discovery* **3**:831,2004

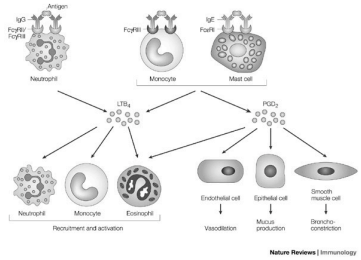
Inflammatory Mediators as Novel Drug Targets

Lipid Mediators in Asthma: LTB_4, PGD_2, LTC_4



From: Luster and Tager Nature Reviews Immunol. 4:711, 2004

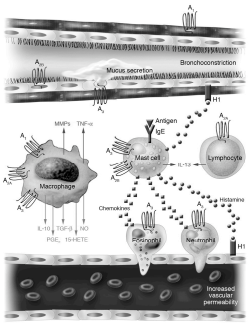
Biological Activities of LTB_4 and PGD_2



From: Tilley and Boucher J. Clin. Invest. **115**:13-16 (2005)

Adenosine Receptors as Drug Targets in Asthma

Pro- and Anti-inflammatory Activities of Adenosine in Asthma



From: Tilley and Boucher
J. Clin. Invest. **115**:13-16 (2005)

Pharmacogenetics: The Future of Asthma Therapeutics?

Summary of Genes Associated With Atopy

Gene	Chromosome	Phenotype	Genetic variation	Association	Reference
IL10	1q31	Total IgE, eosinophils	Haplotypes	Yes	[29]
CHRM3	1p41	Atopy (cockroach)	Haplotype	Yes	[34]
IL1A	2q14	Atopy	4845G/T	Yes	[35]
CTLA4	2q33	Asthma severity	−318C/T	Yes	[36]
		BHR, asthma	−1147C/T	Yes	[37]
IL-4	5q31	AD	−590C/T	Yes	[38]
IL13	5q31	Atopy	Haplotype	Yes	[39]
IL13		Atopy	Arg130Gln	Yes	[30]
		AD	Arg130Gln	Yes	[31]
CD14	5q31	Atopy, asthma, BHR, IgE, AD, Allergic rhinitis	−159C/T	No	[32]
ADRB1	5q31-34	Asthma	−1165A	Yes	[33]
B2AR	5q32-34		Arg164Ja	Yes	[34]
LTC4	5q35	Asthma	−444 (A/C)	Yes	[35]
		PEV,%		Yes	
IL13B	5q33-34	Asthma severity	−4478ins	Yes	[36]
		AD	1188A/C	Yes	[37]
MHC	6p21	Asthma, total IgE	DRB1	Yes	[38]
		Atopy	DRB1, DQ	Yes	[39]
		Atopy, specific IgE	DRB1	Yes	[41]
		Atopy, specific IgE	DRB1	Yes	[41]
		Allergic asthma	DRB1	Yes	[42]
		Asthma	DRB1	Yes	[43]
TNF	6p21	Allergic asthma	−308G/A	No	[43]
		Allergic asthma	−308G/A	Yes	[43]
		Allergic asthma	−308G/A	No	[44]
		Childhood asthma	−308G/A	No	[45]
		Asthma	−857C/T	Yes	[45]
TCRG	7p14	Asthma, IgE		No	[47]
Eotaxin 2	7q11.23	Asthma	1305A/G	Yes	[48]
NOS3	7q36	Asthma	STR(intron 4)	Yes	[49]
		Total IgE			
NAT2	8p22	Allergic asthma	Slow acetylating allele	Yes	[50]
CC16	11q12	BHR	38A/G	Yes	[51]
		Asthma	38A/G	No	[52]
		BHR			
FCER1B	11q13	Asthma	Ruaire7	Yes	[53]
		Atopy			
GSTP1	11q13	FVC, FEV,	Ile105Val	Yes	[54]
SART1	11q13-13	Atopy	Ala24Thr	Yes	[55]
			Gly40Ala		
STAT6	12q13	Allergy	3364C/A	No	[56]
			(CA)n intron 1	Yes	
			haplotype	Yes	
IFN5	12q21	Total IgE	(CA)n intron 1	Yes	[57]
PHF11	13q14	Total IgE	Haplotype	Yes	[58]
ILRA	14q12	Allergic asthma	Ile50Val	Yes	[59]
IL21R		Total IgE		Yes	[59]
CARD15	16q12	Allergic rhinitis	2104C/T	Yes	[60]
		Allergic rhinitis, AD	2722G/C	Yes	
		Atopy, total IgE	3020insC	Yes	
RANTES	17q21	Asthma (mild-moderate)	−28C/G	No	[61]
		Asthma severity	−28C/G	Yes	[62]
Eotaxin-1	17q21	Total IgE	Ala23Thr	Yes	[48]
		Total IgE in AD	−426C/T	Yes	[63]
ADAM 33	20p13	Asthma	Haplotype	Yes	[64]

BHR, bronchial hyperresponsiveness; AD, atopic dermatitis; FVC, forced vital capacity; FEV, forced expiratory volume in 1 second.

From: Halapi and Hakonarson, *Curr. Opin. Pulm. Med.* 10:22, 2003

Summary

1. Asthma is a chronic disease of the airways characterized by reversible airway obstruction, bronchial hyperreactivity, chronic inflammation, and mucus hypersecretion.
2. The allergic response is characterized by an early phase, dominated by degranulation of mast cells, followed by a late phase, involving T cells and eosinophils.
3. Asthma is accompanied by up-regulation of leukocyte adhesion molecules and the presence of multiple pro-inflammatory mediators, including chemokines, prostaglandins, leukotrienes, adenosine, and toxic products released from eosinophil granules.
4. Asthma is a prototypical Th2 disease, with increased production if IL-4 and IL-13, and STAT6 activation. The immunobiology of asthma is highly complex, but includes defects in the anti-viral response in airway epithelia.
5. The hygiene hypothesis states that asthma may arise from an imbalance in the Th1 and Th2 lymphocyte populations, possibly from differences in exposure to Th1-polarizing stimuli early in life.
6. An alternative view is that asthma arises from a defect in immune regulation. Insufficient production of Tregs may predispose to airway sensitization and atopy.
7. Future insights into the cellular immunology and genetics underlying asthma offer hope for future therapeutics.