Review Article

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Genetics of asthma: current research paving the way for development of personalized drugs

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Asthma is a complex genetic disorder involving the interplay between various environmental and genetic factors. In this review, efforts have been made to provide information on the recent advances in these areas and to discuss the future perspective of research in the area of developing personalized drugs using pharmacogenomic approach. Atopic asthma is found to be strongly familial, however the mode of inheritance is controversial. A large number of studies have been carried out and a number of candidate genes have been identified. In addition, a number of chromosomal regions have been identified using genome-wide scans, which might contain important unknown genes. It has been shown in studies carried out in different populations that the genetic predisposition varies with ethnicity. In other words, genes that are associated with asthma in one population may not be associated with asthma in another population. In addition to the involvement of multiple genes, gene-gene interactions play a significant role in asthma. The importance of environmental factors in asthma is beyond doubt. However, it remains controversial whether a cleaner environment or increased pollution is a trigger for asthma. Despite the increasing prevalence of the disorder, only a limited number of therapeutic modalities are available for the treatment. A number of novel therapeutic targets have been identified and drugs are being developed for better efficacy with less side-effects. With the rapid progress in the identification of genes involved in various ethnic populations combined with the availability in future of well-targeted drugs, it will be possible to have appropriate medicine as per the genetic make-up of an individual.

Key words Asthma - chemokines - immunoglobulin E - interleukins - pharmacogenomics

Asthma is a chronic inflammatory disorder of the airways of the lungs. Many cells and cellular elements, including mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils and epithelial cells are involved in the process. The inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing in susceptible individuals, particularly in the night or early in the morning[1]. These episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or with treatment. The infiltration of leukocytes, particularly eosinophils, into the lungs and release of vasoactive mediators from mast cells set the stage for asthmatic inflammation. Two functional alterations are typically associated with asthma. These include variable airway obstruction and bronchial hyperresponsiveness. The narrowing of the airways is associated with smooth muscle contraction, airway wall thickening, oedema and increased mucus secretion[1,2]. Along with these, there is denudation of the airway epithelium and collagen deposition beneath the basement membrane[3]. Several quantitative traits are associated

with the asthma phenotype. These include forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), airway hyperresponsiveness by methacholine challenge, serum total immunoglobulin E (IgE), serum immunoglobulin E specific to certain allergens, eosinophil counts in the peripheral blood, and skin prick test to a panel of locally predominant environmental allergens[4-6].

Studies over the last 25 years have clearly demonstrated that both genetic and environmental factors determine the phenotypic expression of asthma[7]. It affects nearly 155 million individuals the world-over[8]. In an epidemiological study conducted in India, approximately 10-15 per cent of the Indian population, particularly women and children (under 5 yr of age), were found to be affected by atopic asthma[9]. It has been estimated that around 34 per cent of the total man-days lost are due to asthma and other airway disorders[9]. The rising incidence of asthma over the past decades suggests that environmental and lifestyle factors are important[8].

Biochemical pathways involved in the pathogenesis of asthma

The biochemical pathways involving atopic asthma have been studied in great detail. Basically, two types of airway responses are initiated on allergen challenge of an appropriately sensitized asthmatic individual[10]. The early phase is characterized with an acute bronchospasmatic event that begins 15-30 min after exposure and resolves over time. The process initiates with the recruitment of a subtype of CD4+ T cells, Th2, which produce predominantly interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13)), at the site of immune activation[10,11]. IL-4 along with IL-13 induces B cells to produce immunoglobulin E (IgE)[12,13]. IL-13 also induces mucus secretion from the goblet cells[14,15]. IL-5 in association with interleukin-3 (IL-3) and granulocyte-monocyte colony stimulating factor (GMCSF) helps eosinophils to grow, mature and infiltrate into the lungs[16-18]. Thus, asthma is mainly associated with an increase in Th2 cytokines both in the broncoalveolar lavage (BAL) and serum and with increased IgE levels in the sera[19,20]. Crosslinking of IgE receptor present on mast cells by fresh exposure of allergens initiates this acute phase. The late phase response begins 4-6 h after the initial insult and causes prolonged symptomology. The infiltration of leukocytes, particularly eosinophils, into the lungs and release of vasoactive mediators from mast cells set the stage for asthmatic inflammation[20]. Along with cytokines, chemokines play a major role in asthma pathogenesis as they are potent leukocyte chemoattractants, cell activating factors, and histamine-releasing factors. In particular, the eotaxin subfamily of chemokines and their receptor CC chemokine receptor 3 (CCR3) have emerged as central regulators of the asthmatic response[21,22]. Recent studies have provided an integrated mechanism for understanding the coordinate interaction between IL-13 and chemokines in the pathogenesis of asthma[23]. Finally, structural alterations, including airway wall thickening, lung fibrosis, mucus metaplasia, hyperplasia and hypertrophy of the myocyte are certain features which are generally observed in the airway of asthmatics[2,3].

Contribution of genes in the pathogenesis of asthma

Asthma is a complex disorder of multi-factorial origin. Atopic asthma in children is found to be strongly familial and a genetic basis is indicated by familial aggregation and the identification of candidate genes and chromosomal regions linked to asthma risk[24]. The risk of a first-degree relative of an asthmatic individual being asthmatic is two to almost six times higher than the risk for an individual from the general population to develop the disease[24-26]. Both shared genes and shared environment account for such a huge risk. Twin studies have shown that the incidence of asthma is significantly higher in monozygotic twins than dizygotic twins[27-29]. It has earlier been shown that atopic asthma was influenced by a few genes with moderate effects[30]. Similarly few other studies have implicated the maternal inheritance of atopy[31]. A previous study has suggested that early breast-feeding may increase the risk of allergic disease in genetically susceptible children[32].

Although asthma has a significant heritable component, the mode of inheritance is controversial

due to the complex nature of the disorder. In a study conducted in Taiwan, it was concluded that a history of asthma in parents is a strong risk factor for asthma in the offspring[33]. Under the assumption of applied segregation, it was reported that at least one major gene exists that could be involved in the development of allergy. In addition, a polygenic/ multifactorial (genetic and environmental factors) influence with a recessive component inheritance may be involved in the pathogenesis of asthma[33]. Further, there are gene-gene interactions that may lead to increased risk of developing asthma[8,34,35].

Polymorphisms in several candidate genes have been found to be associated with asthma and allergic disorders (Table I). Atopy was linked to a genetic marker on chromosome 11q13[36,37]. In different independent studies, polymorphism in the beta chain of high-affinity receptor for IgE (FcεRI-β) in the same chromosomal location was found to be associated with asthma, atopy, bronchial hyper-responsiveness and severe atopic dermatitis[37,38]. A significant association of total serum IgE concentrations and asthma with genetic markers within the *IL4* gene cluster (5q31.1) has been established[39,40]. Interestingly, this region, contains a large number of important candidate genes that encode IL4, IL13, IRF1, IL9, CD14, IL-12β and β_2-adrenergic receptor[39]. Recently, polymorphisms have been recognised in several of these genes which may contribute to the pathophysiology of allergic diseases[41,42]. It has been proposed that these genes are co-ordinately expressed due to the presence of some common regulatory motifs, therefore, polymorphisms within this cluster could be due to linkage disequilibrium with other known or unknown genes[39]. In a preliminary study conducted in the Indian population, it has been observed that polymorphisms in the proximal promoter and a CA repeat in intron 2 of *IL4* are less likely to be associated with asthma (Nagarkatti and Ghosh, unpublished data).

Chromosome 12q is another interesting region for both asthma and atopy because of the presence of several candidate genes encoding IFN-γ[43,44], signal transducer and activator of transcription (STAT6)[45-49], a mast cell growth factor and a β-subunit of nuclear factor-Y. Studies with Afro-Caribbean and Caucasian populations found an association of serum IgE and asthma to markers on chromosome 12q[50]. Earlier studies in several populations have observed that *IFN-g* gene was linked to atopy and asthma[43,44]. Recent studies carried out in the Indian population have shown a significant positive association of $(CA)_n$ repeat in *IFN-g* with asthma phenotype and serum IgE levels[43]. *STAT-6* plays a major role in the initiation of signals from activated Th2 cells, specifically through IL-4 and IL-13 receptors[48]. In a study conducted in the Indian population, novel polymorphisms in the *STAT6* gene had been identified[51]. Using a novel CA repeat region in the proximal promoter region [denoted as R1] and a previously identified CA repeat in the 5′-UTR [denoted as R3], it has been demonstrated that a haplotype, containing 17 CA repeats at the R1 locus and 15 CA repeats at the R3 locus was significantly associated with asthma in the Indian population (Nagarkatti and Ghosh, unpublished data).

A polymorphism in the *IL4Ra* coding region has been associated with asthma[52]. Also, polymorphism in TNF-α has been found to be associated with asthma[53]. An increased risk of aspirin-induced asthma is found to be associated with polymorphism in the leukotrine C4 synthase (*LTC4S*) promoter[54]. There is a significant difference in the linkage in candidate genes among various ethnic populations. Studies of asthma conducted in Japan, UK, and USA have implicated chromosome 5q as the region containing one or more susceptibility genes for asthma[55-58]. However, in studies conducted in Australian, Finnish, British, Scottish and German populations, chromosome 5q did not be appeared to be linked with asthma or atopy[59-63]. These studies on candidate genes have been mostly done on limited sample sizes. For the utility of these studies a large-scale epidemiological study is required to classify various classes of allergies and asthma.

In addition to studies on candidate genes, several genome-wide searches have been carried out. In this approach, genetic markers throughout the genome are mapped in family members and are used to identify chromosomal regions that are co-inherited

Table I. Major chromosomal locations with prime candidate genes

Chromosomal location	Candidate gene	Function	Association obtained
5q31.1-33.3	*IL3, IL4, IL5, IL13, IL9, CSF2, CD14*	IgE class switching, eosinophil, basophil and mast cell maturation	BHR, asthma, atopy
	ADRB2	G-protein receptor	Total IgE, BHR, Asthma, atopy
	GRL	Modulates inflammation	Asthma, atopy
6p2l.3	*HLAD*	Antigen presentation	Specific IgE, IgE
	TNF-a	Mediates inflammation	Asthma
11q13	*FceRIb*	Signal transduction	BHR, asthma, IgE, high eosinophils counts, allergic dermatitis, atopy
	FGF3	Cellular proliferation	
12q14.3-24.1	*IFN-g*	Inhibits IL4 production	Total IgE, BHR, asthma, atopy
	SCF	Produces IL4	
	NFYb	Upregulates IL4 transcription	
	STAT6	Cytokine transcription factor	
14q11.2-13	*TCR-a, TCR-d*	Interacts with MHC complex	BHR, asthma, IgE
	NFKb-1	Activates immunoregulatory genes	
16pl2.1-11.2	*IL4RA*	Signal transduction and activation	Atopy, IgE
2q33	*CD28, CTLA4*	Antigen presentation	Atopy, asthma
20p13	*ADAM33*	Membrane anchored metalloprotease	Asthma

BHR, bronchial hyper responsiveness

with a particular phenotype such as asthma, bronchial hyperresponsiveness (BHR), or a positive SPT. The data gathered from these studies where the linkage has been verified in at least two populations, have been summarised (Table II). Attempts are underway to locate the genes in these regions by fine mapping. *ADAM33* is an important gene located on 20p13 identified as a result of such fine mapping[63].

Contribution of environment to the pathogenesis of asthma

In addition to genes, environmental factors, such as allergens, food, childhood viral infection *etc*., also play significant roles in causing asthma. The incidence of asthma is rising with an alarming rate in developed as well as in the developing countries. It has been postulated that the immune deviation resulting in asthma takes place much earlier *in utero*[74]. Depending on the genetic status of the mother during pregnancy and exposure to various allergens, it is possible that the child may be born with an intrinsic propensity to be atopic.

Genetically predisposed children when exposed to environmental allergens develop asthma even in very early phase of life[75]. Evidence of polymorphism in the *CD14* (LPS receptor) gene supports this hypothesis[41]. In a recent study conducted in Canada, it has been shown that daily visits to a local hospital due to asthma increased significantly with increases in level of pollens and pollution in the air[76]. Similarly, in a study carried out in US, it has been shown that with increase in air pollution levels in Cincinatti, Cleveland and Columbus, the visits to the asthma clinic increased significantly[77]. In a study carried out in Palestinian children it has been shown that familial atopic diseases are predictors of asthma in children, however the indoor environment, such as the presence of cats, dogs, *etc*., also play a major role[78].

In contrast, it has also been shown that the prevalence of asthma in the western countries is increasing even though the environment is cleaner than earlier[79,80]. For example, the incidence of atopic disorders including asthma in East Berlin increased after the unification of Germany[81-84]. Similarly, many surveys have identified an inverse relationship between prior microbial exposure and the development of atopy[79]. Further, it has been seen that respiratory allergy appears less frequently in people exposed to orofaecal and food-borne microbes. Thus, improved hygiene, early infection and antibiotic use, and semi-sterilized diet may facilitate atopy by influencing exposure to commensals and pathogens that stimulate cell populations such as gut associated lymphoid tissue[85,86]. It is, therefore, proposed (hygiene hypothesis) that the cleaner environment in the western countries is not favourable for providing signals for Thl development, especially in children born of atopic parents[79].

The underlying reason of these apparently contradictory observations is not understood as yet. Nevertheless, it seems very likely that environment is only a triggering factor. A genetically predisposed individual will develop the disorder anyway once the ‘proper’ environmental exposure is provided irrespective of the specific nature of the trigger. Therefore, the identification of the environmental factors that trigger asthma offers the possibility of prevention of disease.

Current mode of asthma therapy

A large number of drugs are now available (Table III), which help to control the signs and symptoms of asthma[87,88]. The anti-leukotrines are the newest class of anti-asthmatic drugs available. Although, they do not provide any quick relief, they help to control the symptoms of asthma in the long-term.

Despite the introduction of such new agents, corticosteriods are the anti-inflammatory drugs of choice for the majority in the treatment of asthma[89]. Both intravenous and oral forms are available and are equally effective in the treatment of mild to severe asthma[89,90]. However, when inhaled, the dose is not sufficient to cause complete relief. Moreover, the therapy is associated with side effects like kidney, liver failure, increased hunger, compromised immune system, high blood pressure, *etc*.

Table II. Major chromosomal locations identified in various genome-wide scans in various populations

Chromosome	Location	Study population	Sample size	Phenotypes	Statistical method/ Programme used	LOD score/ *P* value
1p	D1S468	Hutterites[64]	693 Inbred	Strict asthma	LR (χ^2)/TDT	*P*=0.0002
	1p36.2	Japanese[4]	67 ASP	Severe allergic rhinitis, Total IgE	GENEHUNTER	*P*<0.002 *P*<0.002
2p	D2S1780	Chinese[6]	2551 individuals	Slope BHR	Unified Haseman Elston method	*P*=0.00002
2q	D2S2944	Hutterites[64]	693 Inbred	SPT cockroach	LR(χ^2)/TDT	*P*=0.00004
	D2S116	German[65]	156 ASP	Total IgE	GENEHUNTER	*P*=0.0016
	173-210 cM from pter	Dutch[11,66]	1174 individuals	Total IgE Eosinophils	Linkage	LOD=1.96 LOD=1.49
3p	D3S3564	Hutterites[64]	693 Inbred	Loose asthma	LR (χ^2)/TDT	*P*=0.00004
	3p24.1	Japanese[4]	67 ASP	Total IgE	GENEHUNTER	*P*<0.001
4q	D4S1467	Chinese[6]	2551 individuals	SPT	Unified Haseman	*P*=0.0003
	4q24-27	Danish[67]	33 ASP	Allergic rhinitis	MAPMAKER/SIBS	LOD=2.83
	D4S2417 -D4S408	Japanese[68]	65 ASP	Mite sensitive asthma	MAPMAKER/SIBS	MLS=2.7
	D4S426	Busselton[69]	172 ASP	Slope BHR	Haseman-Elston sib pair Technique	*P*<0.0005
5p	D5S268	French[70]	297 ASP	Slope BHR	GENEHUNTER	*P*=0.001
	D5S1470	Hutterites[64]	693 Inbred	BHR	LR (χ^2)/TDT	*P*=0.001
5q	D5S820	Japanese[68]	65 ASP	Mite-sensitive asthma	MAPMAKER/SIBS	MLS=4.8
	D5S2014	Hutterites[64]	693 Inbred	Asthma symptoms	LR (χ^2)/TDT	*P*=0.0009
	130-172 cM from pter	Dutch[11,66]	1174 individuals	Total IgE	Linkage	LOD=2.73
	5q33.1	Japanese[4]	67 ASP	Total IgE	GENEHUNTER	*P*<0.001
6p	D6S276	Busselton[69]	172 ASP	Eosinophils, Atopy, Total IgE	Haseman-Elston sib pair Tehnique	*P*<0.0001 *P*<0.005 *P*<0.05
	30-40 cM from pter	Caucasians[71,72]	CSGA (266 Families)	Asthma	Multi-point analysis	LOD=1.91
	D6S276 D6S291 D6S426 D6S291	German[65]	156 ASP	Total IgE, RAST Eosinophils, Asthma	GENEHUNTER	*P*=0.0012 *P*=0.0011 *P*=0.0005 *P*=0.0081
	D6S1959-D6S2439	Japanese[68]	65 ASP	Mite-sensitive asthma	MAPMAKER/SIB	MLS=2.1
7p	D7S484 D7S2250 D7S484/ D7S2250	Busselton[69]	172 ASP	BHR, Total IgE, Eosinophils	Haseman-Elston sib pair Technique	*P*<0.0005 *P*<0.005 *P*<0.05

Contd...

	7p14-15	Finnish[73]	220 affected	IgE, Asthma	Non-parameteric linkage	$P<0.0001$
	D7S484	French[70]	297 ASP	Eosinophils	GENEHUNTER	$P=0.002$
7q	98-109 cM from pter	Dutch[11,66]	1174 individuals	Total IgE, SPT aeroallergens	Linkage	LOD=3.36 LOD=1.04
11q	FCER1B	Busselton[69]	172 ASP	Skin test index, Total IgE	Haseman-Elston sib pair Technique	$P<0.00005$ $P<0.005$
	D11S2002	African-American[71,72]	CSGA (266 families)	Asthma	ASP two-locus analysis, Conditional analysis	LOD=2
12q	D12S366 D12S78-D12S79	French[70] Japanese[68]	297 ASP 65 ASP	Eosinophils Mite-sensitive asthma	GENEHUNTER MAPMAKER/SIBS	$P=0.0003$ MLS=1.9
	111-134 cM from pter	Dutch[11,66]	1174 individuals	Total IgE	Linkage	LOD=2.46
	12q24.2	Japanese[4]	67 ASP	Total IgE	GENEHUNTER	$P<0.001$
13q	D13S787	Hutterites[64]	693 Inbred	Asthma symptoms	LR (χ^2)/TDT	$P=0.0006$
	D13S175-D13S217/ D13S153	Japanese[68]	65 ASP	Mite-sensitive asthma	MAPMAKER/SIBS	MLS=2.4/2.0
	6-45 cM from pter	Dutch[11,66]	1174 individuals	Total IgE SPT	Linkage	LOD=2.28 LOD=1.27
	D13S153	Busselton[69]	172 ASP	Atopy	Haseman-Elston sib pair Technique	$P<0.001$
	D13S170	French[70]	297 ASP	Eosinophils	GENEHUNTER	$P=0.002$
16p	D16S412	Chinese[6]	2551 individuals	Forced vital capacity	Unified Haseman Elston method	$P=0.0006$
	16p12.3	Japanese[4]	67 ASP	RAST (orchard grass)	GENEHUNTER	$P<0.001$
16q	D16S289	Busselton[69]	172 ASP	Total IgE, Slope BHR	Haseman-Elston sib pair Technique	$P<0.0005$ $P<0.05$
	D16S539	Hutterites[64]	693 Inbred	SPT (molds)	LR (χ^2)/TDT	$P=0.0008$
17q	D17S250	French[70]	297 ASP	SPT, Asthma	GENEHUNTER	$P=0.001$ $P=0.003$
	62-100 cM from pter	Dutch[11,66]	1174 individuals	Eosinophils, SPT (Mite)	Linkage	LOD=1.97 LOD=1.21
19q	D19S900	Hutterites[64]	693 Inbred	BHR	LR (χ^2)/TDT	$P<0.001$
	D19S433	Chinese[6]	2551 individuals	BHR	Unified Haseman-Elston method	$P=0.002$

The numbers in superscript denote references

IgE, Immunoglobulin E; BHR, Bronchial hyperresponsiveness; SPT, Skin Prick Test; RAST, Radio allergo sorbent test; LR, Likelihood ratio; TDT, Transmission disequilibrium test; ASP, Affected sib pair; CSGA, Collaborative Study on Genetics of Asthma; LOD, Log of odds; pter, Genetic distance (cM) based on Marshfield map

Table III. Major classification for types of drugs used in asthma therapy

Drug type	Mechanism of action	Route of administration	Example
Bronchodialators	Relax smooth muscles in the airways		
Beta-adrenergics		Inhaled, subcutaneous, oral	Epinephrine, Isoproteronol
Methyl-xanthines		Oral/iv	Theophylline/Amino-phlline
Anti-cholinergics		Inhaled only	Atropine, Atrovent
Anti-Inflammatory drugs	Decrease cellular response of inflammation		
Corticosteroids			
		Oral; Intramuscular; intravenous	Beclomethasone, Dexamethasone
Mediator-release inhibitors		Inhaled only	Nedocromil sodium
Anti-leukotrine drugs		Oral only	

Additionally, in 25 per cent of the cases there may be resistance to treatment with the intensity of side-effects increasing.

Response to asthma therapy varies with individual's genetic make-up

Various clinical trials have shown that there is considerable variation in the treatment response from individual to individual. These differences may be due to genetic variations between individuals along with variable expression of metabolic enzymes and receptors for drugs[91]. These factors contribute in the varying efficacy of the treatment regime. For example, patients with polymorphisms in the core promoter of *ALOX5* leading to decreased promoter activity *in vitro*, have failed to respond to treatment with *ALOX5* inhibitors like ABT-761[92]. It has been noted that the promoter of *ALOX5* contains 3-6 copies of Sp-1 binding sites. Only individuals with wild type *ALOX5* promoter (5 Sp-1 binding sites in both chromosomes) responded to the therapy, whereas individual with mutant alleles (any other combination other than 5) failed to show any improvement of lung function when treated with ABT-761. Thus scanning of the *ALOX5* promoter for Sp-1 binding sites will provide the opportunity to administer the drug according to the genetic make-up of the individual. Sanak and Szczeklik[54] have described a polymorphism in the leukotriene C4 synthase (*LTC4S*) promoter that resulted in higher risk of asprin-induced asthma. This genetic variant may also alter the response to treatment with drugs directed against leukotrines. Similarly, variations in the β2-adrenergic receptor (*ADRB2*) does not lead to the loss of functionality of the receptor, however, the response of patients to treatment with drugs varies from individual to individual[93]. Drysdale *et al*[84] have demonstrated that only a limited number of *β2AR* haplotypes can be found in several ethnic groups[94]. Also, transfection studies have shown that certain haplotypes were associated with a better response to β2-agonist drugs.

Future perspective

The goal of current therapy for asthma is to render the patient as symptom-free as possible and to reduce or eliminate the need for rescue therapy and hospitalisation. Even with the availability of a large range of drugs, most patients show considerable heterogeneity in terms of the type and extent of inflammatory response, response to environmental triggers and degree of atopy[95,96]. A major challenge in asthma therapy has therefore been the identification of novel therapeutic targets, which are safer and more specific in their action. The major abnormality in asthma is the presence of activated CD4+-Th2 cells, eosinophils and increased levels of certain Th2 cytokines. These findings, therefore, suggest that most asthmatics may benefit from an approach that targets the mechanism of allergic sensitisation and inflammation[97,98]. A few of these novel strategies are listed in Table IV.

Table IV. Novel strategies for the inhibition and prevention of asthma

Target	Agent
Prenvention of T-cell activation	Anti-CD4 CTLA4
Prevention of reversal of Th2 expression	
Inhibition of Th2 cytokines	Anti-IL4
	STAT6 inhibition
	Anti-IL5
	GATA inhibition
	Anti-IL9
	Soluble ILI3Rα
Promotion of Th1 cytokines	IFN-γ
	IL12
	IL18
Immunotherapy	Specific Immunotherapy Peptide immunotherapy *Mycobacterium vaccae* vaccination CpG
Inhibition of downstream mediators	
Anti-inflammatory cytokines	IL10 IL1Rα
Inhibition of eosinophil migration and activation	CCR3 Antagaonist CCR3 Antisense Met-RANTES
Blocking cell adhesion molecules	VLA4 inhibitor ICAM-1 inhibitor
IgE inhibition	Monoclonal anti-IgE (E25)

STAT, signal tranducer and activator of transcription; IFN, Interferon; IL, Interleukin; CCR, chemokine receptor; Met-RANTES, Methionine-regulated on activation, normal T cell expressed and secrefed; VLA, very late antigen; ICAM, Intercellular cell adhesion molecule; CTLA, cytotoxic T lymphocyte antigen

Recent advances in the techniques for the synthesis and manufacture of monoclonal antibodies, synthetic peptides and peptidomimetic small molecules have increased the potential for the creation of specific inhibitors of immune processes in allergic inflammation[97]. While preliminary data from studies on these agents appear promising, these agents will have to endure rigorous evaluation of efficacy, long-term safety and minimal side effects along with cost effectiveness. The advancement in the understanding of the genetic predisposition for asthma in various ethnic populations is likely to change its classification and future treatment. The future will thus see an era of predictive and preventive medicines with the marketing of tailor-made medicines to suit the genetic make-up of individuals.

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