

The nexus between atopic disease and autoimmunity: a review of the epidemiological and mechanistic literature†

R. L. Rabin* and A. I. Levinson†

*Center for Biologics Evaluation and Research, USFDA, Bethesda, MD, and †Pulmonary Allergy and Critical Care Division, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Accepted for publication 1 April 2008

Correspondence: R. L. Rabin, Office of Vaccines Regulation and Research, Center for Biologics Evaluation and Research, US Food and Drug Administration, 29 Lincoln Drive, Building 29, Room 203A, Bethesda, MD 20892-4555, USA. E-mail: rrabin@helix.nih.gov

†The views expressed in this report are the personal opinions of the authors and are not the official opinion of the US Food and Drug Administration or the Department of Health and Human Services.

Summary

There has been considerable interest in defining the relationship between the expression of allergic and autoimmune diseases in populations of patients. Are patients with autoimmune disease 'protected' from developing allergic (immunoglobulin E-mediated) diseases? Does the establishment of an atopic phenotype reduce the risk of the subsequent development of autoimmune diseases? Although there are clinical studies addressing this question, methodological problems, particularly in identification of atopic subjects, limits their usefulness. Moreover, an immune-based explanation of the observed epidemiological findings has relied on a paradigm that is currently undergoing increased scrutiny and modification to include newly defined effector cell subsets and the interaction between genetic and environmental factors, such as early endotoxin or mycobacterial exposure. To address this question, we reviewed a series of clinical reports that addressed coincidence or co-prevalence of atopy with four autoimmune diseases: psoriasis, rheumatoid arthritis, multiple sclerosis and type I diabetes mellitus. We present a model whereby active T helper type 1 (Th1) inflammation may suppress the development of atopy, and atopy may suppress the severity but not necessarily the onset of autoimmunity, and then discuss our model in the context of mechanisms of adaptive immunity with particular reference to the Th1/Th2 paradigms. Because the ultimate goal is to ameliorate or cure these diseases, our discussion may help to predict or interpret unexpected consequences of novel therapeutic agents used to target autoimmune or atopic diseases.

Keywords: allergy, autoimmunity, multiple sclerosis, rheumatoid arthritis, T cell subsets, type I diabetes mellitus

Introduction

There has been considerable interest in defining the relationship between the expression of allergic and autoimmune diseases in populations of patients. Are patients with autoimmune disease 'protected' from developing allergic [immunoglobulin E (IgE)-mediated] diseases? Does the establishment of an atopic phenotype reduce the risk of the subsequent development of autoimmune diseases? Although there are clinical studies addressing this question, methodological problems, particularly in identification of atopic subjects, limits their usefulness. Moreover, an immune-based explanation of the observed epidemiological findings has relied on a paradigm that is currently undergoing increased scrutiny and modification to include genetic predisposition

and its interaction with environmental factors, such as early endotoxin or mycobacterial exposure [1,2].

Until recently, the adaptive cellular immune response has been characterized broadly as being polarized in one of two directions: type 1 or type 2 [3]. Type 1 responses, directed by T helper type 1 (Th1) CD4⁺ T cells and identified by the signature cytokine interferon (IFN)- γ , are considered to protect against infections by intracellular pathogens [4], and have been incriminated in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS) and type 1 diabetes mellitus [5,6]. By contrast, type 2 responses, directed by Th2 CD4⁺ T cells and identified by the signature cytokines interleukin (IL)-4, IL-5 and IL-13, are considered to protect against helminthic infections [7] and to play major pathogenic roles in allergic diseases and

asthma [8]. Reciprocal counter-regulation of Th1 and Th2 cells [9] predicted that Th1-type autoimmune diseases and Th2-mediated allergic diseases would occur in mutually exclusive populations of patients. However, recent observations have challenged the validity of the long-standing Th1/Th2 paradigm [10], and a far more complex story explaining the immunological basis of cellular immune-mediated host defence and the pathogenesis of autoimmune and allergic diseases is emerging. The new paradigm identifies additional lymphocyte subsets, such as Th17 T cells, regulatory T cells (T_{reg}) and novel soluble factors. These help to explain experimental observations not predicted by the Th1/Th2 paradigm, and provide a new prism through which to examine the intersection of autoimmune and allergic disease [10]. In this paper, we first take a critical look at the epidemiological literature bearing on the relationship between allergic and autoimmune diseases, and then examine the findings in the context of current principles that underlie immune mediated tissue damage.

Epidemiological reports

To review the epidemiological literature addressing this issue, multiple strings were used to search through the National Library of Medicine database (Pubmed). The term 'autoimmunity' as well as each autoimmune disease was searched in combination with 'allergy', 'atopy' and 'asthma' (e.g. MS and allergy, MS and atopy, MS and asthma) with the qualifier 'human'. For purposes of this study, we used 'atopy' to mean a history of atopic dermatitis (AD), allergic rhinitis and/or asthma. While not all asthma is truly atopic – i.e. IgE-mediated – Th2-mediated adaptive responses are associated generally with asthma regardless of the levels of allergen-specific IgE.

The reports used for this review, along with the method of the study, can be found in Table 1. As expected for two sets of diseases that arise as a consequence of environmental and polygenic factors, none are perfect. Studies that were derived from national registry databases and/or questionnaires allow for a large number of study subjects, but rely on historical reports from clinicians or the subjects rather than objective diagnostic criteria. They also risk recall bias that would predispose towards a type II error – failure to infer exclusivity between autoimmunity and atopy when indeed it exists. Case-control studies include objective data [e.g. laboratory tests, skin prick tests (SPT), spirometry] but risk selection bias in the choice of control subjects. Most studies were not powered for sample size. While studies with very large numbers of subjects (> 10 000) would have survived power analysis, some of the smaller studies are clearly underpowered. If the statistical evidence did not support reported differences in the experimental and control groups [i.e. *P*-values > 0.05, or confidence intervals (CI) that overlap 1.0], we rejected those conclusions. Notwithstanding these hurdles, the reports segregated largely into comparisons of

the incidence of atopy with three autoimmune diseases that are considered historically to be Th1-mediated: MS, RA and type 1 diabetes mellitus.

Rheumatoid arthritis and atopy

Because IL-12 and IL-18 are expressed in the synovial lining in inflamed joints, RA is considered a Th1 disease [42–45]. While RA is associated with human leucocyte antigen (HLA) class II alleles [46,47] and polymorphisms that encode tumour necrosis factor (TNF) and IL-10 [48,49] genes, there are no known genetic associations with Th1 cytokines or their associated signalling molecules. RA was linked recently to a single nucleotide polymorphism (SNP) in SLC22A4, an organic cation transporter that is highly expressed in inflamed joints of mice with collagen-induced arthritis [50]. Polymorphisms in SLC22A4 have also been linked to Crohn's disease, also associated with Th1 mechanisms [51].

O'Driscoll and colleagues compared 40 subjects with RA to age-matched controls and found a similar incidence of atopy as determined by history or SPT. They also found that two of 266 atopic subjects followed in an allergy clinic had RA, a prevalence rate similar to that for RA in the general population [34]. Olsson and colleagues [38,52] found no clear associations between RA and atopy on a retrospective analysis of 281 Swedish patients treated for RA and 507 population-based controls. Although the prevalence of autoimmune and AD in the respective groups of subjects and control populations did not differ, the studies were small and probably underpowered.

In contrast, two questionnaire-based studies suggest an inverse correlation of the prevalence of self-reported atopy among cohorts who meet the American Rheumatism Association criteria for RA. Hilliquin and colleagues [36] compared 173 consecutive RA patients from their clinic to age- and sex-matched case controls and found, independent of treatment for RA, a decreased incidence and point prevalence of atopy. Rudwaleit *et al.* [37] used questions extracted from the European Community Respiratory Health Survey and the International Study of Asthma and Allergies in Children (ISAAC) protocols to analyse 728 subjects with RA from a database of university out-patient clinics and 900 controls comprised of a combination of hospital staff members and elderly patients with osteoporosis. In this study, prevalence of 'hay fever' and AD in general was decreased in the RA subjects by about 45% and 35% respectively. Most interesting was a subanalysis that found lower severity of RA among those subjects who presented with AD prior to the onset of RA.

These two studies are supported by a Dutch retrospective cohort study of 643 consecutive rheumatology patients, of whom 304 met the American College of Rheumatology criteria for RA. Allergic rhinitis was confirmed by SPT, and was less prevalent in the RA subjects (4% *versus* 8%) with a significant decrease in relative risk (0.48, 95% CI 0.25, 0.92,

Table 1. Clinical reports comparing the incidence or prevalence of autoimmunity *versus* atopy and their method of study.

1st author, reference no.	Year	Index disease	Control population	No. study subjects	No. control subjects	Methods	Conclusion	Comments
Type 1 diabetes mellitus (T1D)								
Swern [11]	1932	T1D, T2D	None	4000		Cohort	Inverse association	Interesting historical perspective
Siegel [12]	1954	T1D, T2D,	Non-DM	40	227	Hx, ID ₁ ; Cohort	n.d.	Mixed T1D + T2D
Helander [13]	1958	T1D, T2D	BA	3236	3151	Cohort	n.d. in older ↓ subjects; coincidence in younger subjects	Multiple refs of previous studies
Hermansson [14]	1971	T1D	Siblings and population controls	128	310	Medical records, physician exams; cohort	Inverse association of probands <i>versus</i> population controls, and of siblings of probands <i>versus</i> population controls	
Stromberg [15]	1995	T1D	Schoolmates	61	72	CR, Q, SPT, ID ₁ , IgE ₁ ; CC	n.d.	Atopy rates of 80–90%; better DTH in T1D subjects
Douek [16]	1999	T1D	Siblings	157	173	Q; CC	Higher wheeze control <i>versus</i> DM	
EURODIAB Substudy 2 [17]	2000	T1D	Population-based controls	1204	3606	T1D and schools, clinics registers; Q; CC	Inverse relationship T1D and atopy	See text
Kero [18]	2001	CD, T1D, RA	National registry	94, 181, 77	59 867	Cohort	Positive association between CD and asthma, and RA and asthma	Low overall prevalence of asthma 3.3%
Olesen [19]	2001	T1D	Case-controls	928	9732	Q; CC	Less AD in T1D if AD before T1D; after T1D, no difference	
Douek [20]	2002	T1D, AD, AR	Siblings	206	209	Q; CC	No association with AR, inverse association between AD and T1D	
Mattila [21]	2002	T1D	Siblings and population controls	306	506, 406	Q; CC	Weak inverse association to 'animal dust'	
Meerwaldt [22]	2002	T1D	Population survey	555	777	Q; CC	n.d.	Authors state difference, but not statistically significant
Cardwell [23]	2003	T1D	n.a.	n.a.	n.a.	Meta-analysis	Slight inverse association between asthma and T1D	
Multiple sclerosis (MS)								
Frovig [24]	1967	MS	Hospital-based practice, Norway	61	40	CR; CC	Higher incidence of allergy among subjects with MS	
Alter [25]	1968	MS	Hospital-based practice (MN, USA)	36	72	Q; CC	No difference in incidence of allergy in the MS <i>versus</i> control	
Cendrowski [26]	1969	MS	Polish epidemiological survey	300	300	CC	No difference between the two groups in the frequency of allergic diseases	
Khurshed [27]	1976	MS	Hospital-based practice, MN, USA	36	40	CC	No difference serum Total IgE between MS and control	
Warren [28]	1981	MS	Hospital-based practice	100	100	CC	Higher incidence of DM in MS population	
Casetta [29]	1994	MS	Italian epidemiological survey	104	150	CC	Slightly higher incidence of allergy in MS <i>versus</i> control	

Table 1. *Continued*

1st author, reference no.	Year	Index disease	Control population	No. study subjects	No. control subjects	Methods	Conclusion	Comments
Oro [30]	1996	MS	Non-inflammatory neuroconvulsive disorders	35	18	Q, IgE _s , IgE _s ; CC	Decreased atopy (IgE _s , MAST score, symptom scores)	
Neukirch [31]	1997	MS	French epidemiological survey	610	6926	CC	Lower incidence of allergy in MS subjects	
Solaro [32]	2001	MS	Italian epidemiological survey	312	312	CC	No difference in incidence of allergy in the MS <i>versus</i> control	
Tremlett [33]	2002	MS	Database controls, age- and sex-matched	320	320	Cohort	Decreased asthma in MS	
RA								
O'Driscoll [34]	1985	RA	Case-controls	266; 40	40	Q, SPT, IgE _s , IgE _s ; CC	RA in atopics = RA in general pop. Atopy in RA = atopy in control	
Verhoef [35]	1998	RA	RA and non-RA rheumatic diseases	304	339	Consecutive clinic patients; Q, IgE _s , ID _i ; Cohort	↓ AR in RA pts ↓ RA severity in RA alone <i>versus</i> RA + AR	See text
Hilliquin [36]	2000	RA	Case-control	173	173	Q; CC	Inverse correlation between RA and atopy	Did not define atopy or criteria for atopy
Redwaleit [37]	2002	RA, AS	Hospital staff	487, 248	536	Q; CC	Inverse RA and eczema, AR; those with atopy before RA, less severe RA	
Olsson [38]	2003	RA	Random selection	263	541	Q; CC	No statistically significant differences	
Miscellaneous Simpson [39]	2002	All atopic Dz	'Any Th1 disease'	18 307	7881	Scottish registry; total 252 538; cohort	Th1 and atopy correlate	Psoriasis and eczema concurrence account for the correlation
Sheikh [40]	2003	Lumped Th1 diseases; allergic diseases	UK Nat'l Survey	1938; 424	18 071, 6869	Q, SPT; Cohort	No differences	
Tirosh [41]	2006	Asthma	All subjects drawn from military recruits	450 000 ~	~40 000	Medical record review; cohort	Asthma protects against autoimmune disease	Well-documented study

AD, atopic dermatitis; ACD, allergic contact dermatitis; AR, allergic rhinitis; BA, bronchial asthma; CC, case-control; CD, Crohn's disease; CR, chart review; DM, diabetes mellitus (unspecified); DTH, delayed type hypersensitivity; FH, family history; Hx, history; ID_i, intra-dermal skin test for type I hypersensitivity; ID_{IV}, intra-dermal skin test for type IV hypersensitivity; IgE_s, specific serum IgE measurements; IgE_t, total serum IgE measurements; n.d., no differences between study and control populations; OR, odds ratio; Q, questionnaire; RA, rheumatoid arthritis; RDz, rheumatic diseases; SPT, skin prick testing; T1D, Type 1 diabetes mellitus; T2D, Type 2 diabetes mellitus; Urt, urticaria; ↑, Increased; ↓, Decreased; Ig, immunoglobulin.

$P < 0.05$). The subjects with both RA and allergic rhinitis had lower RA clinical scores, erythrocyte sedimentation rates (ESR) and C-reactive protein levels (CRP). Furthermore, during the pollen season, peripheral blood mononuclear cells (PBMC) from subjects with both RA and allergic rhinitis secreted less IFN- γ *in vitro* compared with PBMC from subjects with RA alone. Once the pollen season ended, IFN- γ expressed by PBMC from the dually affected subjects rose to levels similar to those from subjects with RA alone [35].

Although not without flaws, these studies taken together suggest that first, atopy is decreased in patients with RA compared with controls, and second that among those patients with both diseases, the severity of RA is decreased.

Multiple sclerosis and atopy

Multiple sclerosis is a chronic autoimmune disease in which the antigenic target is central nervous system myelin. Both CD4 and CD8 T cells are found in MS lesions, as is expression of IFN- γ and TNF. However, CD4⁺ Th1 cells have been incriminated traditionally as the major orchestrators of the acute inflammatory process. The strongest genetic linkages are with HLA class II haplotypes [53]. While several questionnaire-based studies showed no association between MS and atopy [24–29,32], two recent studies demonstrate an inverse relationship between them. Oro and colleagues [30] studied 35 MS patients and 18 control patients who were followed for non-inflammatory neuroconvulsive disorders. All patients answered questionnaires, and all but 11 MS patients had blood drawn for total and allergen-specific IgE. Allergy symptom scores and the number of positive allergen-specific IgE tests were lower among the patients with MS. Tremlett *et al.* [33] evaluated the hospital records of 320 Welsh patients and matched controls and found a lower prevalence of patients who received the diagnosis and a prescription for treatment of atopic asthma, but not AD among patients with MS.

Whether atopy may affect the clinical course of MS similar to its suggested effect on RA is difficult to determine because of the widespread use of sedating anti-histamines until 1985, when a non-sedating anti-histamine was licensed. While both sedating and non-sedating of anti-histamines are inhibitors of histamine receptor 1 (HR1), only the sedating anti-histamines cross the blood-brain barrier easily [54]. Multiple reports demonstrate a role for HR1 in generating Th1 responses [55–57] and HR1 antagonists decrease the severity of experimental autoimmune encephalomyelitis, the animal model for MS [58]. Recently, Alonso and colleagues reported a case-control study that showed an inverse correlation between MS risk and treatment of allergy with sedating, but not non-sedating anti-histamines [59]. Thus, while we may conclude an inverse relationship between MS and atopy, it must be confirmed by studies that take the use of sedating HR1 anti-histamines for atopy into account.

Type I diabetes mellitus and atopy

Type I diabetes mellitus is an autoimmune disease caused by cell-mediated immunity targeting pancreatic islet beta cells. In animal models, Th1 cytokines such as IFN- γ and IL-12 are associated with islet cell destruction [60,61], and Th2 cytokine-secreting T cells are protective [62]. Among many known autoantigens, only pro-insulin and insulin are islet-cell specific [63]. Specific T cells stimulated with pro-insulin peptides secrete IFN- γ , while cells from many controls secrete the regulatory cytokine IL-10 [64].

Type I diabetes mellitus is linked strongly with HLA class II haplotypes, some of which predispose to disease and others that protect [65]. While the HLA linkages are by far the strongest immunological risk factor, type I diabetes mellitus is also associated with polymorphisms in non-coding regions of two cytokine genes, IFN- γ [66] and IL-12 p40 [67], and an amino acid substitution in cytotoxic T lymphocyte-associated molecule 4, a co-stimulatory protein essential for attenuating cell-mediated immunity [68–70].

The earliest observations of an inverse association between diabetes mellitus and allergic diseases prompted many reports throughout the mid-20th century. While two of these are included in Table 1 for historical reference [11], only those addressing subjects with type I diabetes mellitus are considered here. A recent meta-analysis concluded a 'small but significant' decrease in asthma prevalence in children with type I diabetes mellitus [23]. Studies of interest are discussed below.

Douek and colleagues used the ISAAC questionnaire to compare 157 probands with type I diabetes mellitus to 173 unaffected siblings, and found that fewer type I diabetes mellitus subjects than controls had wheezed at all within 12 months of the study, or had multiple or speech-limiting episodes of wheezing [16]. The EURODIAB ACE Substudy 2 study group was comprised of eight centres in eastern and western Europe and reported data collected by interviews from five of the centres and by questionnaire from the other three. Probands with type I diabetes mellitus were compared with population-based controls. AD, and asthma in particular, were decreased in children with type I diabetes mellitus. Two sites in the United Kingdom, where the incidence of atopy was the highest, accounted for 40% of the diabetics and may have contributed disproportionately to the study as a whole. Furthermore, only the western European centres demonstrated the inverse relationship between type I diabetes mellitus and atopy, and the incidence of atopy was higher in the type I diabetes mellitus than controls in the Bulgarian cohort. Because atopy preceded type I diabetes mellitus, the authors' inference that atopy may protect children from type I diabetes mellitus [17] may reflect the greater prevalence of atopy in western populations.

Stromberg and colleagues [15] compared 61 Swedish children with type I diabetes mellitus to age- and sex-matched controls, and found no differences in history, SPT and total

and specific IgE. Similarly, data from a 1987 Finnish registry [18], a British health and nutrition survey [40] and a Dutch cross-sectional survey [22] found no differences in the cumulative incidence of asthma between type I diabetes mellitus patients and controls.

Perhaps the most provocative report is a retrospective case–controlled comparison of 928 Danish children with type I diabetes mellitus to a random sample of 10 000 population-based controls that found a lower cumulative incidence of AD in the diabetics [19]. Uniquely, this report showed the inverse correlation only among those diabetics who had AD prior to the onset of type I diabetes mellitus. Diabetics in whom the onset of AD followed type I diabetes mellitus were no different from controls. This study highlights a unique feature of type I diabetes mellitus relative to autoimmune diseases such as MS and RA: the pancreatic islet beta cells are diminished when type I diabetes mellitus presents [71], such that the inflammation, while not completely resolved, has diminished to a level insufficient to affect other responses. The concept of waned type 1 inflammation after clinical presentation of type I diabetes mellitus is supported by high serum levels of IL-18, IFN- γ and CXCL9 (an IFN- γ inducible chemokine) in newly diagnosed diabetics compared with those with long-standing disease [72] and low-risk controls [73]. Alternatively, defective regulatory mechanisms may make those with active type I diabetes mellitus equally prone to subsequent atopic or autoimmune disease.

Consistent with the interpretation that active type 1 inflammation protects against clinical presentation of AD is a recent analysis of almost 500 000 Israeli adults at the time of their enrolment into military service between 1980 and 2003. The diagnosis of asthma was confirmed by spirometry. Asthma prevalence and incidence were correlated inversely with a number of autoimmune diseases that were also diagnosed at enrolment [41], suggesting that those with newly diagnosed autoimmunity were less prone to have asthma.

Taken together, the studies that generalize the least and support the diagnoses with objective clinical and/or laboratory data suggest a model whereby Th1 inflammation suppresses the development of atopy [19], while Th2 inflammation suppresses the severity and perhaps the onset of some autoimmune diseases [35].

Mechanisms of type 1 and type 2 counter-regulation

As noted previously, the reciprocal counter-regulation of type 1 and type 2 pathogenic mechanisms led to the hypothesis that diseases mediated by these respective processes might not occur or would be less severe in the same patients. Evidence for the Th1/Th2 paradigm was provided originally by the observation that signature cytokines and transcription factors are both necessary and sufficient for polarization in one direction or the other. IL-12 is central to developing

Th1 responses [74] and is secreted primarily by dendritic cells (DC) in response to infection with intracellular pathogens, or stimulation of cell surface proteins such as those in the Toll-like receptor family [75]. The central role for IL-12 in the paradigm is emphasized by the biological activity of IL-18, which enhances Th1 development in the presence of IL-12, and Th2 development in its absence [76]. The finding that IFN- γ in the absence of IL-12 may similarly enhance Th2 development was surprising [77], as IL-12 shares no signalling pathways with IL-18.

The transcription factor T-bet (T-box, expressed in T cells) is expressed in Th1, but not Th2 cells [78]. T-bet transactivates the IFN- γ gene promoter [74]. T-bet itself is expressed after a sequence of events that consists of IL-12 secretion, activation in the T cell of the transcription factor signal transducer and activator of transcription-4 (STAT-4), followed by the secretion of IFN- γ by the responding T cell, and then activation of STAT-1. STAT-1 stimulates transcription of T-bet which initiates an autostimulatory positive feedback loop of subsequent IFN- γ secretion and STAT-1 activation [74]. The importance of T-bet and Th1-polarized CD4⁺ T cells in protecting against AD was demonstrated by studies conducted in T-bet knock-out mice. These animals developed spontaneously a pulmonary disease that recapitulated the clinical and pathological features of asthma [79]. A recent report associates a SNP in the 3'-untranslated region of the T-bet gene with asthma [80].

Interleukin-4 is the principal cytokine leading to the development of Th2 cells. An initial source of IL-4 may be the natural killer T (NK T) cell, which is essential for the development of asthma in a murine model [81]. GATA binding protein 3 (GATA-3) is a major Th2 regulatory factor [74] that is necessary for polarization towards the Th2 phenotype, in which cells express IL-4 and IL-5 and fails to express the β chain of the IL-12 receptor (IL-12R β) [82,83]. GATA-3 expression is repressed by the combination of IL-12 and IFN- γ and augmented by IL-4. Activated GATA-3 enhances transcription of its own gene, and represses IFN- γ and STAT-4 expression [84,85]. In the context of the differentiation of naive T cells, GATA-3 dominates T-bet independently of IL-4 and thus Th2 cells emerge. Once the T cell response has developed, however, T-bet dominates GATA-3 independent of IFN- γ [86,87].

Thymic stromal lymphopoeitin (TSLP) is the latest addition to the list of Th2 polarizing molecules [88]. Appreciated originally as a molecule produced under homeostatic conditions in the thymus, it is now clear that mucosal and skin epithelial cells also produce TSLP. TSLP conditions DC to express OX40L [89], which when presenting antigens to naive CD4⁺ T cells, promotes their differentiation to Th2 cells [90]. High concentrations of TSLP can be found in the bronchial epithelium and submucosa of allergic asthmatics and in the skin of patients with AD [91]. It has been proposed that TSLP-DC conditioned Th2 cells in these environments express an inflammatory phenotype characterized by

the production of large amounts of the classical Th2 cytokines and the proinflammatory cytokine TNF, but not the anti-inflammatory cytokine IL-10 [89]. Recent studies conducted in TSLP-deficient and TSLP-transgenic mouse models support strongly a major role for TSLP in the development and maintenance of AD [92,93].

On the other hand, TSLP-DCs also may lead to the generation of a population of a subset of anti-inflammatory Th2 cells that are distinguished by their production of the classical Th2 cytokines and IL-10, but not TNF [89,91]. For example, it appears that intestinal epithelium secretion of TSLP provides a homeostatic mechanism for counteracting the Th1 properties of commensal gut organisms through the generation of such 'tolerogenic' Th2 cells [94]. Of note, Crohn's disease has been reported to be associated with a loss of such TSLP-mediated homeostatic control [94].

The above discussion highlights current understanding of the cellular and molecular basis of the Th1 and Th2 paradigm. From the mechanistic standpoint, this discussion helps to explain why atopic and certain autoimmune disorders have been categorized as Th2- or Th1-mediated disorders.

Challenges to the Th1/Th2 paradigm

T helper type 1 cells in the pathogenesis of asthma and AD

Several studies challenge that the Th1/Th2 paradigm has served as a useful basis for thinking about the pathogenesis of autoimmune and AD. For example, Th1 cells can transfer airway hypersensitivity in an animal model of allergic asthma [95,96] and mediate inflammation during the chronic stages of AD (reviewed in [97]). In addition, it has been reported recently that Th1 cytokine secretion was associated with the size of immediate hypersensitivity skin test to allergen and bronchial hyperresponsiveness in a large cohort of affected children [98]. Furthermore, while clinical trials support a role for IFN- γ in the pathogenesis of MS [99] and TNF in RA and Crohn's disease [100], others indicate that TNF inhibitors might exacerbate MS and other demyelinating diseases [101,102]. Also, experimental models of MS and RA demonstrated that TNF and IFN- γ might have protective effects if administered after the clinical appearance of tissue destruction [103,104]. Thus, it appears that Th1 cytokines may either be pro- or anti-inflammatory in the same autoimmune disease, with the outcome dependent upon when, in the course of pathogenic events, they are introduced.

Contributions of IL-17 to immune-mediated inflammation

The emergence importance the Th17 lineage represents the latest challenge to the inviolability of the Th1/Th2 paradigm

[105,106]. Th17 cells secrete IL-17A and IL-17E, two of six members of the IL-17 cytokine family (reviewed in [107]). These cells differentiate along a pathway that is totally independent of Th1 and Th2 cells, expressing neither the Th1 transcription factors, T-bet and STAT-4, nor the Th2 transcription factors, GATA-3 and STAT-6 [97]. Th17 cells differ from naive CD4⁺ T cells in response to IL-6 secreted by stimulated DC and transforming growth factor- β secreted by T_{reg} [108,109], and are maintained by IL-23. Through expression of their signature cytokines IFN- γ and IL-4, Th1 and Th2 cells antagonize the differentiation of Th17 cells [110]. Th17 cells play a pivotal role in the pathogenesis of several autoimmune diseases, largely by induction of cytokines and chemokines that promote chemoattraction of inflammatory cells. Moreover, it is becoming clear that Th17 cells contribute to the pathogenesis of the chronic inflammation seen in several autoimmune diseases considered traditionally to be mediated by CD4 Th1 cells [111,112].

Blurring distinctions further between mechanisms contributing to autoimmunity and AD, IL-17 may contribute to the pathogenesis of asthma. Expression of IL-17 is increased in the airways of asthmatic patients and it can induce bronchial fibroblasts to produce IL-6 and IL-11 [113]. The concentration of IL-17 in sputum from asthmatics is increased, and the levels correlate with the degree of bronchial hyperresponsiveness [114]. IL-17 is also over-expressed in nasal polyps in association with increased collagen deposition [115]. These results highlight a possible contribution of IL-17 to the structural changes in the airway seen in chronic asthma. The production of IL-8 by human airway smooth muscle cells is stimulated by IL-17, suggesting a role for this cytokine in neutrophilic forms of asthma [116]. While the responsible IL-17 family members were not specified in these reports, the reagents used to identify responses induced by IL-17 suggest that Th17-derived IL-17 cytokine family members were very probably the responsible factors.

To make matters even more confusing, IL-17E is emerging as a factor in the development of allergic inflammation. IL-17E, which is now called IL-25, is expressed by murine Th2 cells and targets a novel innate immune cell to produce IL-4, IL-5 and IL-13 and the CC chemokines, CCL5 and CCL11 (eotaxin). IL-25 induces many of the features of allergic inflammation in mice, and suppresses both Th1- and Th17-mediated inflammation in some experimental models of autoimmune disease [107]. The differentiation of and interrelationships between these various CD4 T cell subsets and the potential for adverse consequences to therapeutic intervention are depicted in Fig. 1.

Emerging role of NK T cells in the pathogenesis of asthma

Whereas Th2 cytokines are still considered to be principal effector molecules in the pathogenesis of asthma, it is no longer clear that CD4⁺ T cells are the major source of these

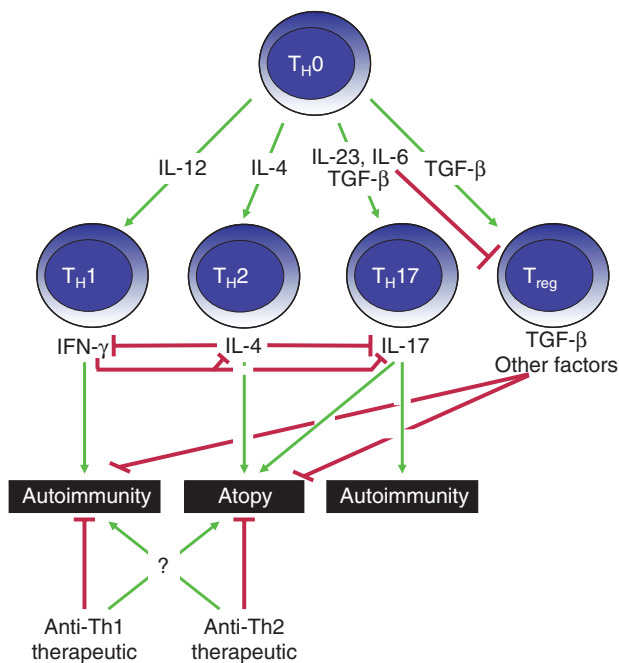


Fig. 1. Differentiation of and nexus between CD4⁺ T cell subsets. The figure depicts the diversity of CD4⁺ T cell subsets and their multiple modes of interaction. Green arrows signify positive influences and red lines inhibitory influences. All lines represent the activity of individual cytokines except in the case of T helper type 17 (Th17) cell inhibition by interferon- γ and interleukin-4 where both cytokines must act in concert. The crossed green arrows with the question mark below indicate the potential for a Th1-specific immunomodulatory agent to reveal or exacerbate a Th2 disease or vice versa. IL, interleukin; TGF, transforming growth factor; IFN, interferon.

proinflammatory molecules. As noted above, studies in mouse models of allergic asthma had indicated that NK T cells were required for the development of allergen-induced airway hyperreactivity [81]. NK T cells express features of both traditional CD4⁺ T cells and NK cells and express an invariant type of T cell receptor that recognizes glycolipid antigens in the context of CD1, a set of non-polymorphic major histocompatibility complex class I proteins. While NK T cells may express CD4, CD8, or neither CD4 nor CD8, it is primarily the CD4 expressers that secrete both Th1 and Th2 cytokines rapidly upon activation [117]. Recently, Akbari and colleagues made the striking observation that CD4⁺ NK T cells, and not classical CD4⁺ T cells, represented the dominant IL-4- and IL-13-secreting cell population in the lungs of patients with moderate to severe persistent asthma [81,118]. However, two subsequently published studies showed that while the percentage of NK T cells found in bronchoalveolar lavage fluid may be elevated, the magnitude of that increase is much lower than reported by Akbari *et al.* [119–121]. Thus, while NK T cells appear to contribute to the pathogenesis of mouse models in asthma, their importance in human asthma remains to be established.

The consensus is that NK T cells are protective in experimental animal models of autoimmune disease as well as in several types of human autoimmune disease [122]. It is considered that the NK T cells, which secrete a Th2 profile of cytokines, are those that ameliorate autoimmunity [117]. Thus, the data at hand raise the possibility that the Th2-like NK T cells may contribute to the pathogenesis of asthma, and have a salutary immunoregulatory function in autoimmune disease.

In summary, whereas the Th1/Th2 paradigm served as a useful early framework for considering the relationship between autoimmune and AD, the emergence of newly characterized proinflammatory and T_{reg} cell subsets help to explain why it can no longer be generally applied to models of the pathogenesis of autoimmune or AD. Thus, it is not surprising that the autoimmune and AD reviewed here do not adhere consistently to the yin–yang relationship predicted by this once-hallowed construct.

Conclusions

From a mechanistic standpoint, the Th1/Th2 paradigm suggested that diseases mediated by these two effector CD4⁺ T cell populations would segregate in distinct patient populations. Despite the flaws of the epidemiological studies referenced, the complex genetic and environmental factors that underlie atopy and autoimmune diseases, and modifications of the Th1/Th2 paradigm to account for newly discovered subsets of T cells such as T_{reg} and Th17 cells [114], our review supports Th1/Th2 segregation in some pairs of Th2-mediated AD and putative Th1-mediated autoimmune disorders. Because of this complexity, however, it is not surprising that this inverse relationship is neither consistent nor straightforward.

Some of the epidemiological reports suggest a model in which ongoing Th1 inflammation inhibits atopy. For example, as insulinitis diminishes, type I diabetes mellitus becomes clinically manifest and protection by Th1 inflammation against development of AD abates. Two reports of AD following anti-TNF therapy for RA [123,124] suggest that pharmacological attenuation may have the same effect. Whether or not atopy protects against autoimmunity, there is objective evidence (ESR, CRP) that, at least in RA, it can attenuate the clinical expression of autoimmunity. Because mature Th1 responses cannot be switched, transient attenuation of RA in atopic subjects during the pollen season may be due to suppressed Th1 inflammation, rather than an actual change in phenotype. For example, IL-4 secreted by mast cells may not only trigger their apoptotic death, but also suppress secretion of TNF and IL-1 β by synovial macrophages [125–127].

Even before novel selective therapeutic agents enter clinical trials, the complex relationship between Th1 and Th2 inflammation outlined here must be considered,

particularly in light of recent studies that suggest that increasing prevalence of both autoimmune and AD are due to dysfunctional regulatory mechanisms such as T_{reg} cells [128] that may control either type of pathology. In this context, a therapy that targets Th1- or Th2-specific responses may reveal underlying atopy or autoimmunity respectively. While proof of concept studies for novel therapeutic agents are performed generally in rodent strains that are susceptible for the disease under investigation, it may be worthwhile to determine, for example, whether an anti-Th2 immunomodulatory agent that treats asthma lowers the threshold for clinical presentation of DM in the non-obese diabetic mouse. Conversely, how might a potential anti-Th1 immunomodulatory therapeutic for MS affect the threshold for allergic sensitization? Finally, as clinical testing of selective therapeutics for autoimmune and AD progress towards larger pivotal trials, it would be prudent to monitor for manifestations of the onset of atopy or autoimmunity respectively, and continue post-marketing monitoring after licensure of the new drug.

References

- Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorder. *Science* 1997; **275**:77–9.
- Martinez FD. Gene–environment interactions in asthma: with apologies to William of Ockham. *Proc Am Thorac Soc* 2007; **4**:26–31.
- Paul WE, Seder RA. Lymphocyte responses and cytokines. *Cell* 1994; **76**:241–51.
- O'Garra A, Robinson D. Development and function of T helper 1 cells. *Adv Immunol* 2004; **83**:133–62.
- Skurkovich B, Skurkovich S. Anti-interferon-gamma antibodies in the treatment of autoimmune diseases. *Curr Opin Mol Ther* 2003; **5**:52–7.
- Hafler DA. Multiple sclerosis. *J Clin Invest* 2004; **113**:788–94.
- Li-Weber M, Krammer PH. Regulation of IL4 gene expression by T cells and therapeutic perspectives. *Nat Rev Immunol* 2003; **3**:534–43.
- Robinson DS. T-cell cytokines: what we have learned from human studies. *Paediatr Respir Rev* 2004; **5** (Suppl. A):S53–8.
- Sornasse T, Larenas PV, Davis KA, de Vries JE, Yssel H. Differentiation and stability of T helper 1 and 2 cells derived from naive human neonatal CD4+ T cells, analyzed at the single-cell level. *J Exp Med* 1996; **184**:473–83.
- Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007; **13**:139–45.
- Swern N. Incidence of diabetes mellitus in asthmatic patients. *J Allergy* 1932; **2**:375–8.
- Siegal S, Herzstein J. Atopy and diabetes mellitus. *J Allergy* 1954; **25**:25–7.
- Helander E. Asthma and diabetes. *Acta Med Scand* 1958; **162**:165–74.
- Hermansson B, Holmgren G, Samuelson G. Juvenile diabetes mellitus and atopy. *Hum Hered* 1971; **21**:504–8.
- Stromberg LG, Ludvigsson GJ, Bjorksten B. Atopic allergy and delayed hypersensitivity in children with diabetes. *J Allergy Clin Immunol* 1995; **96**:188–92.
- Douek IF, Leech NJ, Gillmor HA, Bingley PJ, Gale EA. Children with type-1 diabetes and their unaffected siblings have fewer symptoms of asthma. *Lancet* 1999; **353**:1850.
- The EURODIAB Substudy 2 Study Group. Decreased prevalence of atopic diseases in children with diabetes. *J Pediatr* 2000; **137**:470–4.
- Kero J, Gissler M, Hemminki E, Isolauri E. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: a register study. *J Allergy Clin Immunol* 2001; **108**:781–3.
- Olesen AB, Juul S, Birkebaek N, Thestrup-Pedersen K. Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case–control study. *Lancet* 2001; **357**:1749–52.
- Douek IF, Leech NJ, Bingley PJ, Gale EA. Eczema and Type 1 diabetes. *Diabetes Med* 2002; **19**:174–5.
- Mattila PS, Tarkkanen J, Saxen H, Pitkanen J, Karvonen M, Tuomilehto J. Predisposition to atopic symptoms to inhaled antigens may protect from childhood type 1 diabetes. *Diabetes Care* 2002; **25**:865–8.
- Meerwaldt R, Odink RJ, Landaeta R *et al.* A lower prevalence of atopy symptoms in children with type 1 diabetes mellitus. *Clin Exp Allergy* 2002; **32**:254–5.
- Cardwell CR, Shields MD, Carson DJ, Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. *Diabetes Care* 2003; **26**:2568–74.
- Froviq AG, Presthus J, Sponheim N. The significance of allergy in the etiology and pathogenesis of multiple sclerosis. *Acta Neurol Scand* 1967; **43**:215–27.
- Alter M, Speer J. Clinical evaluation of possible etiologic factors in multiple sclerosis. *Neurology* 1968; **18**:109–16.
- Cendrowski W, Wender M, Dominik W, Flejsierowicz Z, Owsianowski M, Popiel M. Epidemiological study of multiple sclerosis in western Poland. *Eur Neurol* 1969; **2**:90–108.
- Ansari KA, Yokoyama MM, Rand A. Circulating IgE, allergy and multiple sclerosis. Serum levels of IgE, other immunoglobulins and complement (C's) in patients with multiple sclerosis in exacerbation and other neurologic diseases. *Acta Neurol Scand* 1976; **53**:39–50.
- Warren S, Warren KG. Multiple sclerosis and associated diseases: a relationship to diabetes mellitus. *Can J Neurol Sci* 1981; **8**:35–9.
- Casetta I, Granieri E, Malagu S *et al.* Environmental risk factors and multiple sclerosis: a community-based, case–control study in the province of Ferrara, Italy. *Neuroepidemiology* 1994; **13**:120–8.
- Oro AS, Guarino TJ, Driver R, Steinman L, Umetsu DT. Regulation of disease susceptibility. decreased prevalence of IgE-mediated allergic disease in patients with multiple sclerosis. *J Allergy Clin Immunol* 1996; **97**:1402–8.
- Neukirch F, Lyon-Caen O, Clanet M, Bousquet J, Feingold J, Druet P. Asthma, nasal allergies, and multiple sclerosis. *J Allergy Clin Immunol* 1997; **99**:270–1.
- Solaro C, Messmer Uccelli M, Guglieri P *et al.* Prevalence of atopy in multiple sclerosis patients: a case–control study. *J Neurol* 2001; **248**:239–40.
- Tremlett HL, Evans J, Wiles CM, Luscombe DK. Asthma and multiple sclerosis: an inverse association in a case–control general practice population. *Q J Med* 2002; **95**:753–6.
- O'Driscoll BR, Milburn HJ, Kemeny DM, Cochrane GM, Panayi GS. Atopy and rheumatoid arthritis. *Clin Allergy* 1985; **15**:547–53.

- 35 Verhoef CM, van Roon JA, Vianen ME, Bruijnzeel-Koomen CA, Lafeber FP, Bijlsma JW. Mutual antagonism of rheumatoid arthritis and hay fever; a role for type 1/type 2 T cell balance. *Ann Rheum Dis* 1998; **57**:275–80.
- 36 Hilliquin P, Allanore Y, Coste J, Renoux M, Kahan A, Menkes CJ. Reduced incidence and prevalence of atopy in rheumatoid arthritis. Results of a case–control study. *Rheumatology (Oxford)* 2000; **39**:1020–6.
- 37 Rudwaleit M, Andermann B, Alten R *et al.* Atopic disorders in ankylosing spondylitis and rheumatoid arthritis. *Ann Rheum Dis* 2002; **61**:968–74.
- 38 Olsson AR, Wingren G, Skogh T, Svernell O, Ernerudh J. Allergic manifestations in patients with rheumatoid arthritis. *APMIS* 2003; **111**:940–4.
- 39 Simpson CR, Anderson WJ, Helms PJ *et al.* Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general practice data. *Clin Exp Allergy* 2002; **32**:37–42.
- 40 Sheikh A, Smeeth L, Hubbard R. There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: lack of support for the hygiene hypothesis. *J Allergy Clin Immunol* 2003; **111**:131–5.
- 41 Tirosh A, Mandel D, Mimouni FB, Zimlichman E, Shochat T, Kochba I. Autoimmune diseases in asthma. *Ann Intern Med* 2006; **144**:877–83.
- 42 Mosaad YM, Metwally SS, Auf FA, Abd ELSEER, el-Deek B, Limon NI, el-Chennawi FA. Proinflammatory cytokines (IL-12 and IL-18) in immune rheumatic diseases: relation with disease activity and autoantibodies production. *Egypt J Immunol* 2003; **10**:19–26.
- 43 Radstake TR, Roelofs MF, Jenniskens YM *et al.* Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by proinflammatory cytokines interleukin-12 and interleukin-18 via interferon-gamma. *Arthritis Rheum* 2004; **50**:3856–65.
- 44 Dinarello CA. Interleukin-18 and the pathogenesis of inflammatory diseases. *Semin Nephrol* 2007; **27**:98–114.
- 45 Lipsky PE. Rheumatoid arthritis. In: Kasper DL, Braunwald E, Fauci AS *et al.*, eds. *Harrison's principles of internal medicine*, 17th edn. New York: McGraw-Hill, 2008:2083–92.
- 46 Newton JL, Harney SM, Wordsworth BP, Brown MA. A review of the MHC genetics of rheumatoid arthritis. *Genes Immun* 2004; **5**:151–7.
- 47 Orozco G, Rueda B, Martin J. Genetic basis of rheumatoid arthritis. *Biomed Pharmacother* 2006; **60**:656–62.
- 48 Hajeer AH, Hutchinson IV. TNF-alpha gene polymorphism: clinical and biological implications. *Microsc Res Tech* 2000; **50**:216–28.
- 49 Padyukov L, Hytonen AM, Smolnikova M *et al.* Polymorphism in promoter region of IL10 gene is associated with rheumatoid arthritis in women. *J Rheumatol* 2004; **31**:422–5.
- 50 Tokuhira S, Yamada R, Chang X *et al.* An intronic SNP in a RUNX1 binding site of SLC22A4, encoding an organic cation transporter, is associated with rheumatoid arthritis. *Nat Genet* 2003; **35**:341–8.
- 51 Rioux JD, Daly MJ, Silverberg MS *et al.* Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. *Nat Genet* 2001; **29**:223–8.
- 52 Reckner Olsson A, Skogh T, Wingren G. Comorbidity and lifestyle, reproductive factors, and environmental exposures associated with rheumatoid arthritis. *Ann Rheum Dis* 2001; **60**:934–9.
- 53 Hauser SL, Oksenberg JR. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. *Neuron* 2006; **52**:61–76.
- 54 Montoro J, Sastre J, Bartra J *et al.* Effect of H1 antihistamines upon the central nervous system. *J Invest Allergol Clin Immunol* 2006; **16** (Suppl. 1):24–8.
- 55 Packard KA, Khan MM. Effects of histamine on Th1/Th2 cytokine balance. *Int Immunopharmacol* 2003; **3**:909–20.
- 56 Takahashi HK, Iwagaki H, Mori S, Yoshino T, Tanaka N, Nishibori M. Histamine inhibits lipopolysaccharide-induced interleukin (IL)-18 production in human monocytes. *Clin Immunol* 2004; **112**:30–4.
- 57 Jutel M, Watanabe T, Klunker S *et al.* Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature* 2001; **413**:420–5.
- 58 Dimitriadou V, Pang X, Theoharides TC. Hydroxyzine inhibits experimental allergic encephalomyelitis (EAE) and associated brain mast cell activation. *Int J Immunopharmacol* 2000; **22**:673–84.
- 59 Alonso A, Jick SS, Hernan MA. Allergy, histamine 1 receptor blockers, and the risk of multiple sclerosis. *Neurology* 2006; **66**:572–5.
- 60 Debray-Sachs M, Carnaud C, Boitard C *et al.* Prevention of diabetes in NOD mice treated with antibody to murine IFN gamma. *J Autoimmun* 1991; **4**:237–48.
- 61 Trembleau S, Penna G, Gregori S, Giarratana N, Adorini L. IL-12 administration accelerates autoimmune diabetes in both wild-type and IFN-gamma-deficient nonobese diabetic mice, revealing pathogenic and protective effects of IL-12-induced IFN-gamma. *J Immunol* 2003; **170**:5491–501.
- 62 Tisch R, Wang B, Weaver DJ *et al.* Antigen-specific mediated suppression of beta cell autoimmunity by plasmid DNA vaccination. *J Immunol* 2001; **166**:2122–32.
- 63 Notkins AL. Immunologic and genetic factors in type 1 diabetes. *J Biol Chem* 2002; **277**:43545–8.
- 64 Arif S, Tree TI, Astill TP *et al.* Autoreactive T cell responses show proinflammatory polarization in diabetes but a regulatory phenotype in health. *J Clin Invest* 2004; **113**:451–63.
- 65 Melanitou E, Fain P, Eisenbarth GS. Genetics of type 1A (immune mediated) diabetes. *J Autoimmun* 2003; **21**:93–8.
- 66 Awata T, Matsumoto C, Urakami T, Hagura R, Amemiya S, Kanazawa Y. Association of polymorphism in the interferon gamma gene with IDDM. *Diabetologia* 1994; **37**:1159–62.
- 67 Morahan G, Huang D, Ymer SI *et al.* Linkage disequilibrium of a type 1 diabetes susceptibility locus with a regulatory IL12B allele. *Nat Genet* 2001; **27**:218–21.
- 68 Nistico L, Buzzetti R, Pritchard LE *et al.* The CTLA-4 gene region of chromosome 2q33 is linked to, and associated with, type 1 diabetes. *Belgian Diabetes Registry. Hum Mol Genet* 1996; **5**:1075–80.
- 69 Hirschhorn JN. Genetic epidemiology of type 1 diabetes. *Pediatr Diabetes* 2003; **4**:87–100.
- 70 Waterhouse P, Penninger JM, Timms E *et al.* Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4 [see comments]. *Science* 1995; **270**:985–8.
- 71 Powers AC. Diabetes mellitus. In: Braunwald E, Fauci AS, Isselbacher KJ *et al.*, eds. *Harrison's principles of internal medicine*, 17th edn. New York: McGraw-Hill, 2008:2275–304.
- 72 Nicoletti F, Conget I, Di Mauro M *et al.* Serum concentrations of the interferon-gamma-inducible chemokine IP-10/CXCL10 are augmented in both newly diagnosed Type I diabetes mellitus patients and subjects at risk of developing the disease. *Diabetologia* 2002; **45**:1107–10.
- 73 Nicoletti F, Conget I, Di Marco R *et al.* Serum levels of the interferon-gamma-inducing cytokine interleukin-18 are increased

- in individuals at high risk of developing type I diabetes. *Diabetologia* 2001; **44**:309–11.
- 74 Finotto S, Glimcher L. T cell directives for transcriptional regulation in asthma. *Springer Semin Immunopathol* 2004; **25**:281–94.
 - 75 Trinchieri G, Pflanz S, Kastelein RA. The IL-12 family of heterodimeric cytokines. new players in the regulation of T cell responses. *Immunity* 2003; **19**:641–4.
 - 76 Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. Interleukin-18 regulates both Th1 and Th2 responses. *Annu Rev Immunol* 2001; **19**:423–74.
 - 77 Pernis A, Gupta S, Gollob KJ *et al.* Lack of interferon gamma receptor beta chain and the prevention of interferon gamma signaling in TH1 cells. *Science* 1995; **269**:245–7.
 - 78 Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH. A novel transcription factor, T-bet, directs Th1 lineage commitment. *Cell* 2000; **100**:655–69.
 - 79 Finotto S, Neurath MF, Glickman JN *et al.* Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. *Science* 2002; **295**:336–8.
 - 80 Raby BA, Hwang ES, Van Steen K *et al.* T-bet polymorphisms are associated with asthma and airway hyperresponsiveness. *Am J Respir Crit Care Med* 2006; **173**:64–70.
 - 81 Akbari O, Stock P, Meyer E *et al.* Essential role of NKT cells producing IL-4 and IL-13 in the development of allergen-induced airway hyperreactivity. *Nat Med* 2003; **9**:582–8.
 - 82 Szabo SJ, Dighe AS, Gubler U, Murphy KM. Regulation of the interleukin (IL)-12R beta 2 subunit expression in developing T helper 1 (Th1) and Th2 cells. *J Exp Med* 1997; **185**:817–24.
 - 83 Rogge L, Barberis-Maino L, Biffi M *et al.* Selective expression of an interleukin-12 receptor component by human T helper 1 cells. *J Exp Med* 1997; **185**:825–31.
 - 84 Ouyang W, Ranganath SH, Weindel K *et al.* Inhibition of Th1 development mediated by GATA-3 through an IL-4-independent mechanism. *Immunity* 1998; **9**:745–55.
 - 85 Usui T, Nishikomori R, Kitani A, Strober W. GATA-3 suppresses Th1 development by downregulation of Stat4 and not through effects on IL-12Rbeta2 chain or T-bet. *Immunity* 2003; **18**:415–28.
 - 86 Zhou M, Ouyang W. The function role of GATA-3 in Th1 and Th2 differentiation. *Immunol Res* 2003; **28**:25–37.
 - 87 Skapenko A, Leipke J, Niesner U *et al.* GATA-3 in human T cell helper type 2 development. *J Exp Med* 2004; **199**:423–8.
 - 88 Soumelis V, Reche PA, Kanzler H *et al.* Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002; **3**:673–80.
 - 89 Ito T, Wang YH, Duramad O *et al.* TSLP-activated dendritic cells induce an inflammatory T helper type 2 cell response through OX40 ligand. *J Exp Med* 2005; **202**:1213–23.
 - 90 Wang YH, Ito T, Wang YH *et al.* Maintenance and polarization of human TH2 central memory T cells by thymic stromal lymphopoietin-activated dendritic cells. *Immunity* 2006; **24**:827–38.
 - 91 Liu YJ, Soumelis V, Watanabe N *et al.* TSLP: an epithelial cell cytokine that regulates T cell differentiation by conditioning dendritic cell maturation. *Annu Rev Immunol* 2006; **25**:193–219.
 - 92 Al-Shami A, Spolski R, Kelly J, Keane-Myers A, Leonard WJ. A role for TSLP in the development of inflammation in an asthma model. *J Exp Med* 2005; **202**:829–39.
 - 93 Zhou B, Comeau MR, De Smedt T *et al.* Thymic stromal lymphopoietin as a key initiator of allergic airway inflammation in mice. *Nat Immunol* 2005; **6**:1047–53.
 - 94 Rimoldi M, Chieppa M, Salucci V *et al.* Intestinal immune homeostasis is regulated by the crosstalk between epithelial cells and dendritic cells. *Nat Immunol* 2005; **6**:507–14.
 - 95 Hansen G, McIntire JJ, Yeung VP *et al.* CD4(+) T helper cells engineered to produce latent TGF-beta1 reverse allergen-induced airway hyperreactivity and inflammation. *J Clin Invest* 2000; **105**:61–70.
 - 96 Randolph DA, Carruthers CJ, Szabo SJ, Murphy KM, Chaplin DD. Modulation of airway inflammation by passive transfer of allergen-specific Th1 and Th2 cells in a mouse model of asthma. *J Immunol* 1999; **162**:2375–83.
 - 97 Allam JP, Novak N. The pathophysiology of atopic eczema. *Clin Exp Dermatol* 2006; **31**:89–93.
 - 98 Heaton T, Rowe J, Turner S *et al.* An immunoepidemiological approach to asthma: identification of *in-vitro* T-cell response patterns associated with different wheezing phenotypes in children. *Lancet* 2005; **365**:142–9.
 - 99 Panitch HS, Hirsch RL, Schindler J, Johnson KP. Treatment of multiple sclerosis with gamma interferon: exacerbations associated with activation of the immune system. *Neurology* 1987; **37**:1097–102.
 - 100 Braun J, Sieper J. Overview of the use of the anti-TNF agent infliximab in chronic inflammatory diseases. *Expert Opin Biol Ther* 2003; **3**:141–68.
 - 101 Feldmann M, Steinman L. Design of effective immunotherapy for human autoimmunity. *Nature* 2005; **435**:612–19.
 - 102 van Oosten BW, Barkhof F, Truyen L *et al.* Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody cA2. *Neurology* 1996; **47**:1531–4.
 - 103 Jacob CO, Holoshitz J, Van der Meide P, Strober S, McDevitt HO. Heterogeneous effects of IFN-gamma in adjuvant arthritis. *J Immunol* 1989; **142**:1500–5.
 - 104 Liu J, Marino MW, Wong G *et al.* TNF is a potent anti-inflammatory cytokine in autoimmune-mediated demyelination. *Nat Med* 1998; **4**:78–83.
 - 105 Harrington LE, Mangan PR, Weaver CT. Expanding the effector CD4 T-cell repertoire: the Th17 lineage. *Curr Opin Immunol* 2006; **18**:349–56.
 - 106 Weaver CT, Harrington LE, Mangan PR, Gavrieli M, Murphy KM. Th17: an effector CD4 T cell lineage with regulatory T cell ties. *Immunity* 2006; **24**:677–88.
 - 107 Weaver CT, Hatton RD, Mangan PR, Harrington LE. IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu Rev Immunol* 2007; **25**:821–52.
 - 108 Bettelli E, Carrier Y, Gao W *et al.* Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature* 2006; **441**:235–8.
 - 109 Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity* 2006; **24**:179–89.
 - 110 Wynn TA. T(H)-48: a giant step from T(H)1 and T(H)2. *Nat Immunol* 2005; **6**:1069–70.
 - 111 Dong C. Diversification of T-helper-cell lineages: finding the family root of IL-17-producing cells. *Nat Rev Immunol* 2006; **6**:329–33.
 - 112 McFarland HF, Martin R. Multiple sclerosis: a complicated picture of autoimmunity. *Nat Immunol* 2007; **8**:913–19.
 - 113 Molet S, Hamid Q, Davoine F *et al.* IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. *J Allergy Clin Immunol* 2001; **108**:430–8.

- 114 Barczyk A, Pierzchala W, Sozanska E. Interleukin-17 in sputum correlates with airway hyperresponsiveness to methacholine. *Respir Med* 2003; **97**:726–33.
- 115 Molet SM, Hamid QA, Hamilos DL. IL-11 and IL-17 expression in nasal polyps: relationship to collagen deposition and suppression by intranasal fluticasone propionate. *Laryngoscope* 2003; **113**:1803–12.
- 116 Wuyts WA, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE, Demedts MG, Verleden GM. Interleukin-17-induced interleukin-8 release in human airway smooth muscle cells: role for mitogen-activated kinases and nuclear factor-kappaB. *J Heart Lung Transplant* 2005; **24**:875–81.
- 117 Yu KO, Porcelli SA. The diverse functions of CD1d-restricted NKT cells and their potential for immunotherapy. *Immunol Lett* 2005; **100**:42–55.
- 118 Akbari O, Faul JL, Hoyte EG *et al.* CD4+ invariant T-cell-receptor+ natural killer T cells in bronchial asthma. *N Engl J Med* 2006; **354**:1117–29.
- 119 Pham-Thi N, de Blic J, Le Bourgeois M *et al.* Enhanced frequency of immunoregulatory invariant natural killer T cells in the airways of children with asthma. *J Allergy Clin Immunol* 2006; **117**:217–18.
- 120 Thomas SY, Lilly CM, Luster AD. Invariant natural killer T cells in bronchial asthma. *N Engl J Med* 2006; **354**:2613–16;author reply –6.
- 121 Vijayanand P, Seumois G, Pickard C *et al.* Invariant natural killer T cells in asthma and chronic obstructive pulmonary disease. *N Engl J Med* 2007; **356**:1410–22.
- 122 Linsen L, Thewissen M, Baeten K *et al.* Peripheral blood but not synovial fluid natural killer T cells are biased towards a Th1-like phenotype in rheumatoid arthritis. *Arthritis Res Ther* 2005; **7**:R493–502.
- 123 Mangge H, Gindl S, Kenzian H, Schauenstein K. Atopic dermatitis as a side effect of anti-tumor necrosis factor-alpha therapy. *J Rheumatol* 2003; **30**:2506–7.
- 124 Chan JL, Davis-Reed L, Kimball AB. Counter-regulatory balance: atopic dermatitis in patients undergoing infliximab infusion therapy. *J Drugs Dermatol* 2004; **3**:315–18.
- 125 Shelburne CP, Ryan JJ. The role of Th2 cytokines in mast cell homeostasis. *Immunol Rev* 2001; **179**:82–93.
- 126 Bonder CS, Dickensheets HL, Finlay-Jones JJ, Donnelly RP, Hart PH. Involvement of the IL-2 receptor gamma-chain (gammaC) in the control by IL-4 of human monocyte and macrophage proinflammatory mediator production. *J Immunol* 1998; **160**:4048–56.
- 127 Oskeritzian CA, Wang Z, Kochan JP *et al.* Recombinant human (rh)IL-4-mediated apoptosis and recombinant human IL-6-mediated protection of recombinant human stem cell factor-dependent human mast cells derived from cord blood mononuclear cell progenitors. *J Immunol* 1999; **163**:5105–15.
- 128 Bacchetta R, Gambineri E, Roncarolo MG. Role of regulatory T cells and FOXP3 in human diseases. *J Allergy Clin Immunol* 2007; **120**:227–35;quiz 36–7.