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REVIEW

A shadow of Epstein–Barr virus in the pathogenesis of atopic diseases

H. OKUDAIRA*, H. SHUTO†, C. SHUTO‡, T. CHIBA§, H. AKIYAMA§, I. OHTA* and G. MATSUZAKI*

*Department of Allergy and Rheumatology, Graduate School of Medicine, Tokyo University, †Ekibiru-iin Sengendai Hospital, ‡Ohbukuro-iin Hospital, and §SRL Inc., Tokyo, Japan

Introduction

In 1923, Coca and Cook presented a concept of 'atopy' defined as 'the immunological mechanism responsible for hayfever and asthma with a hereditary cause'. Thus in the background of so-called atopic diseases, an immunological abnormality based on some hereditary trait was assumed to exist. Since this original paper, there have been numerous reports that support the presence of genetic or familial trait(s) that cause the development of atopic diseases, and the interest of the majority of researchers has focused on elucidation of the 'atopic trait' and/or the genetic mechanisms of atopy. However, many investigators, and epidemiologists in particular, have continued to be suspicious about the genetic heritage of atopic diseases.

In order to clarify the influence of genetics on the development of atopic diseases, twin studies are of great importance. If an atopic trait is mediated by a single 'atopy gene' or polygenes for atopy, the concordance rate of atopic diseases between monozygotic twins, whose genetic constitution is assumed to be exactly the same, should be around 100%. Edfors-Lubs in Sweden [1] performed a large scale study of 7000 twin pairs and reported that the symptom-specific concordance rates in the monozygotic group were: asthma 19.0%, hayfever 21.4% and eczema 15.5%. The concordance in general (for asthma, hayfever or eczema) was as low as 25.3% in the monozygotic group. From these observations, they concluded that the environmental component is much larger than the hereditary component, as alluded to above. These investigations suggest that there is no *major* 'atopy gene' that plays a decisive role in the development of atopic diseases. The prevalence of atopic diseases in so-called developed countries has risen over the past several decades, which is too short a period for genetic change to take place. Furthermore, this rise has occurred irrespective of race and geographical features. These facts strongly suggest that the rise is due not to genetic factors but to environmental factor.

Correspondence: H. Okudaira, Department of Allergy and Rheumatology, Graduate School of Medicine, Tokyo University, Tokyo, Japan.

The familial nature of atopic diseases does not necessarily imply that they are caused by inherited genetic factors. Various genetic effects have been recognized that may predispose to an atopic state, but these known genes or genetic loci do not account for all of the familial clustering of atopic disorders. The failure to develop a simple, consistent, and universal model of inheritance is most simply explained if we accept that atopic diseases develop dependent on strong environmental influences [2].

The Th1/Th2 concept [3]

In 1986, Mosmann and colleagues reported that most cloned lines of murine $CD4^+$ T cells could be classified into two groups, Th1 and Th2, based on the cytokines they produced and their related functional activities [4]. Since then, the subset model has evolved to encompass several newly discovered cytokines and many new observations, as reviewed extensively elsewhere [5–11]. Th1 cells are now defined by their production of interleukin 2 (IL-2), interferon γ (IFN-γ) and tumour necrosis factor β (TNF-β), and Th2 cells are defined by their production of IL-4, IL-5, IL-6, IL-10 and IL-13; both cell types produce IL-3, TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Th2 dominance and bacterial/viral infection

Recently, it was shown that IL-12 [12–14] produced mainly by cells of monocyte-macrophage origin plays an important role in the suppression of INF-γ synthesis by Th1

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type cells. Production of IL-12 is enhanced by bacterial or viral infection to suppress so-called Th2 type responses. It has also been reported that IL-12 production is down-regulated by IL-10 [15], originally found to be one of the Th2 cytokines. It seems that the Th1/Th2 cytokine *milieu* is oppositely regulated by Th1 and Th2 type cytokines. It is therefore possible that any factors that affect regulation of the Th1/Th2 cytokine system may induce a chain reaction that leads to the dominance of Th1 or Th2 cytokines.

IL-5 central hypothesis on eosinophilic inflammation in asthma and atopic dermatitis [16]

The role of chronic eosinophilic inflammation of the bronchial mucosa and skin has been recognized in the pathophysiology of asthma and atopic dermatitis (AD), respectively [17,18]. Activated T cells and T cell cytokines, including especially IL-5, have been strongly implicated in the local accumulation and activation of eosinophils [19,20]. Several animal studies have shown that tissue infiltration of eosinophils is dependent on IL-5 produced by T cells [21,22]. The number of $CD4^+$ T cells expressing IL-5 mRNA is increased in the bronchial mucosa of symptomatic asthmatics [20], is correlated with the number of activated eosinophils and is further increased upon allergen inhalation challenge [23,24]. IL-5 is the predominant eosinophil-active cytokine present in bronchoalveolar lavage fluid (BALF) obtained during allergen-induced late-phase reaction [25]. Oral prednisolone therapy reduced serum IL-5 concentration [26] and the number of IL-5 mRNA-expressing cells in BALF [27], in parallel with clinical improvement.

Antigen-dependent T cell receptor (TCR)-mediated signal and IL-2R-mediated signal in human IL-5 synthesis [28]

We have recently reported that human helper T cell clones that produce IL-5 in response to antigenic stimulation also produce IL-5 in response to IL-2 [29]. All of the Der f II (a major allergen of house dust mite) specific T cell clones established from atopic asthmatic patients produced both IL-2 and IL-4 upon activation by antigen. It was also found that recombinant(r) IL-2 induced gene expression and protein synthesis of IL-5 in T cell clones that produce IL-5 upon antigenic stimulation. The human IL-5 promoter/enhancer-luciferase gene construct transfected to T cell clones was clearly transcribed in response to IL-2. Moreover, IL-5 production by T cell clones stimulated with a TCR-mediated signal was completely abrogated by anti-IL-2 neutralizing antibody, suggesting that IL-5 synthesis of human helper T cells is profoundly dependent on IL-2. IL-4 was not transcribed in response to IL-2, reflecting well the absence of IL-4 protein production in response to rIL-2. In contrast, IL-4 was clearly transcribed in response to antigen and other TCR-mediated stimuli [28]. It was also suggested that the TCR signal is mediated by quite distinct pathways from those mediating the IL-2R signal. So it is now an intriguing question as to whether IL-2-induced IL-5 synthesis is inhibited by glucocorticoid as effectively as TCR-mediated IL-5 synthesis. We showed that glucocorticoid inhibited IL-2-induced cytokine synthesis and proliferation of helper T cells [28].

Different cytokine spectra in BALF of atopic and non-atopic asthmatics [30]

In 1992, Walker et al. reported that significantly different cytokine spectra were found in BALF in the two types of asthma (Fig. 1). BALF of atopic asthmatics showed increased levels of IL-4 and IL-5, while in the BALF of non-atopic asthmatics IL-2 and IL-5 predominated. The close correlation of IL-5 level with BAL eosinophilia in both types of asthma seems to suggest that IL-5 is a common essential cytokine for the development of

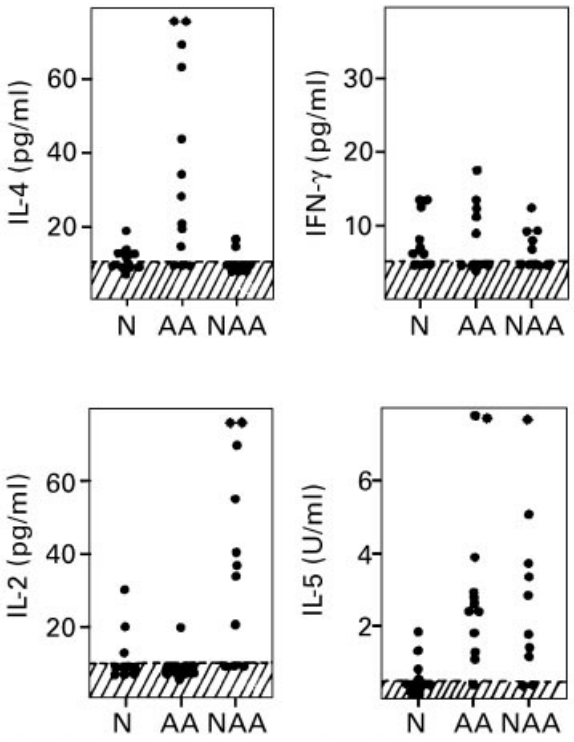


Fig. 1. Cytokine levels in concentrated BAL fluid. BAL fluid from 10 normal individuals (N) and 10 allergic (AA) and 10 non-allergic asthmatics (NAA) were concentrated 18-to 20-fold. IL-4 and INF-γ were measured by sandwich ELISA, and IL-2 and IL-5 by proliferation assays using cytokine-specific cell lines. The crosshatched area represents the detection limit of the assays used. (Cited from Walker *et al*. [30].)

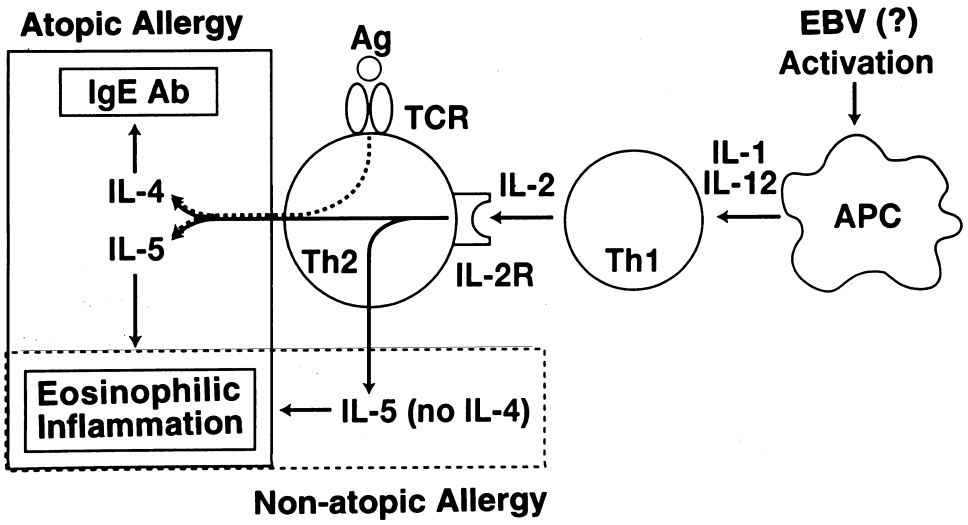


Fig. 2. Schematic model for the pathogenesis of atopic and non-atopic allergic diseases on the basis of findings in the cellular and cytokine *milieu*. A delineation of the relationship between atopic and non-atopic diseases and their distinct features has been attempted.

characteristic eosinophilic inflammation in the two types of asthma. It is fascinating to speculate that hyper-production of IL-2 from Th1 cells stimulated by IL-1 and/or IL-12 released from highly activated macrophages leads to the development of non-atopic or 'intrinsic' atopic diseases.

It is well known that Epstein–Barr virus (EBV) is one of the most potent macrophage activators. Since IL-2R-mediated IL-5 production does not accompany IL-4 production, which is essential for IgE antibody formation, the 'intrinsic' nature (eosinophilic inflammation without IgE antibody formation [31]) of the non-atopic type of asthma may well be explained. In the absence of IL-2R-mediated signals strong enough for the manifestation of IL-5-dependent eosinophilic inflammation by themselves, additional signal(s) delivered by allergen through TCR may activate Th0/Th2 cells to synthesize IL-4 and IL-5 [28], which induce allergen-specific eosinophilic inflammation and IgE antibody formation as features of 'extrinsic' allergy (Fig. 2).

Atopic and non-atopic asthma may well be defined as 'TCR signal dominant' and 'IL-2R signal dominant' asthma, respectively. However, since TCR signals and IL-2R signals are not mutually exclusive and the two factors may coexist and synergise in most asthmatics, it may be merely artificial to divide asthmatics clearly into the two subtypes as suggested by several investigators [32].

Possible role of EBV in the pathogenesis of atopic diseases

In the investigation of the pathogenesis of atopic diseases, there are exiting reports that the BCRF1 (*Bam*H1, C fragment, rightward reading frame 1) gene product of EBV has 84% homology of its DNA sequence and significant functional similarity to human (h)IL-10, and it has been designated viral IL-10 (v-IL-10) [33,34]. Thus, we speculated that EBV may have some important role in the development of atopic diseases.

The screening of more than 40 B cell lines suggested that the secretion of IL-10 is associated with the mature and pre-plasmocytic stages of B cell development, since none of the pro-B, pre-B, or myeloma cell lines tested was able to produce IL-10. The report also indicated an association between the presence of the EBV genome and the secretion of hIL-10 [35]. Mature human B cell lines were able to produce hIL-10, and this secretion appeared to be at least partially correlated with EBV expression, since 24 of the 26 hIL-10-secreting cells were EBV positive. Besides, it should be stressed that only low levels of vIL-10 could be detected in the supernatants of a restricted number of EBV-infected cell lines.

In 1994, Nakagomi *et al*. reported that the EBV latent membrane protein-1 (LMP1) can induce hIL-10 production in B lymphoma cell lines [36]. In 1990, Paul *et al*. reported that normal human B cells that have been transformed by EBV constitutively produce IL-5 [37]. Baumann *et al*. further reported evidence that IL-5-producing EBV-transformed B cells specifically bind IL-5, are growth-inhibited by neutralizing anti-IL-5 antibody, and are capable of responding to IL-5 by augmented proliferation. Thus, EBV-transformed B cells probably produce and use IL-5 in an autocrine fashion to induce chronic eosinophilic inflammation [38].

Increased serum levels of antibodies to EBV in patients with atopic disease [39,40]

In 1981, Strannegard and Strannegard [40] found no

increased frequency of seropositivity or increased antibody titres to a number of viruses (varicella-zoster virus, herpes simplex virus), other than EBV, in atopic individuals. In a subsequent study, this finding was corroborated [39]. Thus, EBV antibodies occurred at higher titres and at a higher frequency in atopic individuals of all ages studied than in non-atopic controls. In the Strannegard's study, an increased EBV antibody titre was observed in atopic children with AD and asthma as well as rhinoconjunctivitis [40]; that is, in all groups of classical atopic disease. Of particular interest was the finding that the increased EBV antibody titres occurred in AD patients irrespective of whether the dermatitis was active or healed. Thus, it appears that the increased antibody level is not a consequence of disease manifestations but may rather reflect basic immunological disturbances that are associated with the atopic phenotype [41]. However, such disturbances might be expected to result in abnormal antibody responses not only to EBV, but also to other viruses. Since the abnormality in the studies was confined to EBV antibodies, one has to consider the possibility that EBV is in some way connected with the pathogenesis of atopic diseases.

Immortal IgE antibody-forming cells transformed by EBV may participate in persistent IgE antibody formation in patients with atopic diseases [42]

Persistent IgE antibody formation is one of the characteristic features of atopic patients. IgE antibody titre in the serum of ragweed-sensitive hayfever patients is maintained for an entire year after exposure to allergens during the pollen season [43]. Persistent antibody formation is also obtained in high responder mice after a single injection of a minute dose of a potent immunogen together with an appropriate adjuvant [44]; the antibody level is maintained for several months without a booster injection. It was shown that both IgE and IgG antibody levels to a potent immunogen in high responder mice can be maintained for at least 2 months after 1000 R whole-body irradiation [42]. As reported by us, 1000 R irradiation is sufficient to deplete B memory cells of both IgE and IgG isotypes. Since helper T cells are radio-resistant [45,46], the lack of secondary response in the irradiated mice would be due to either depletion or inactivation of B memory cells. The lack of B memory cells in the irradiated animals suggests that recruitment of B memory cells to become antibody-forming cells by either residual antigen or anti-idiotype antibody is not responsible for the maintenance of their antibody level. This idea is supported by the observations of Grobler *et al.* [47] that germinal centres in mouse lymph nodes were destroyed by 600 R whole-body irradiation, but that antibody production persisted despite the disappearance of germinal centres.

The question arose as to how antibody levels could be maintained without the recruitment of B memory cells to the status of antibody-forming cells. We have demonstrated antibody-forming cells in the spleen of recipients of antigen-primed cells which showed a persistent adoptive antibody response. Important findings on *in vitro* antibody formation were that antibody titres in culture supernatants continued to increase for 14 days and that irradiation of cell donors with a lethal dose of X-rays or exposure of splenic cells to X-irradiation before culture failed to affect antibody formation [42]. Depletion of T cells in the splenic cell suspension or the addition of antibodies to the culture did not affect antibody formation. These findings strongly suggest that radio-resistant non-apoptotic antibody-forming cells are responsible for the long-lasting antibody formation *in vitro* and *in vivo* (Fig. 3).

The bcl-2 proto-oncoprotein expression induced by IL-10 inhibits B cell apoptosis

The *bcl-2* gene was originally identified [48–50] as the locus linked to the immunoglobulin heavy chain locus by the 14;18 chromosome translocation associated with lymphomas of follicular centre B-cell origin [51,52]. The *bcl-2* may be the paradigm of an oncogene that promotes cell survival rather than proliferation.

It was shown that IL-10, which can be produced by EBV infection as stated before, is a crucial factor involved in prolonged cell survival. Indeed, IL-10 enhanced purified splenic B cell survival. This increased viability was most striking when separated germinal centre cells (GCC) were studied, since the latter cells undergo apoptosis after brief *in vitro* culture. This effect was associated with the induction of *bcl-2* protein expression as shown by fluorescence analysis of unseparated or large splenic (GCC) B cells cultured in the presence of IL-10 [53].

Altogether, these results suggest that IL-10 is a potent factor able to rescue GCC from apoptosis by inducing the synthesis of *bcl-2* protein. The *bcl-2* prolongs cell survival by blocking programmed cell death [54]. In normal tissues, *bcl-2* protein expression is topographically confined to the long-lived recirculating B cells from the follicular mantle and is absent from the centroblasts and centrocytes destined to die [55–57].

Further experiments were performed to investigate whether the control of *bcl-2* expression could be mediated by lymphokines other than IL-10. It was demonstrated that IL-2 and IL-4 induced transient expression of *bcl-2* which was detectable in a fraction of GCC [53]. Interestingly, addition of anti-IL-10 antibodies abolished this effect, suggesting that IL-10 was responsible for this upregulation of *bcl-2* expression. It is noteworthy that EBV is, to date, the only agent to induce IL-10 production in B cells [58].

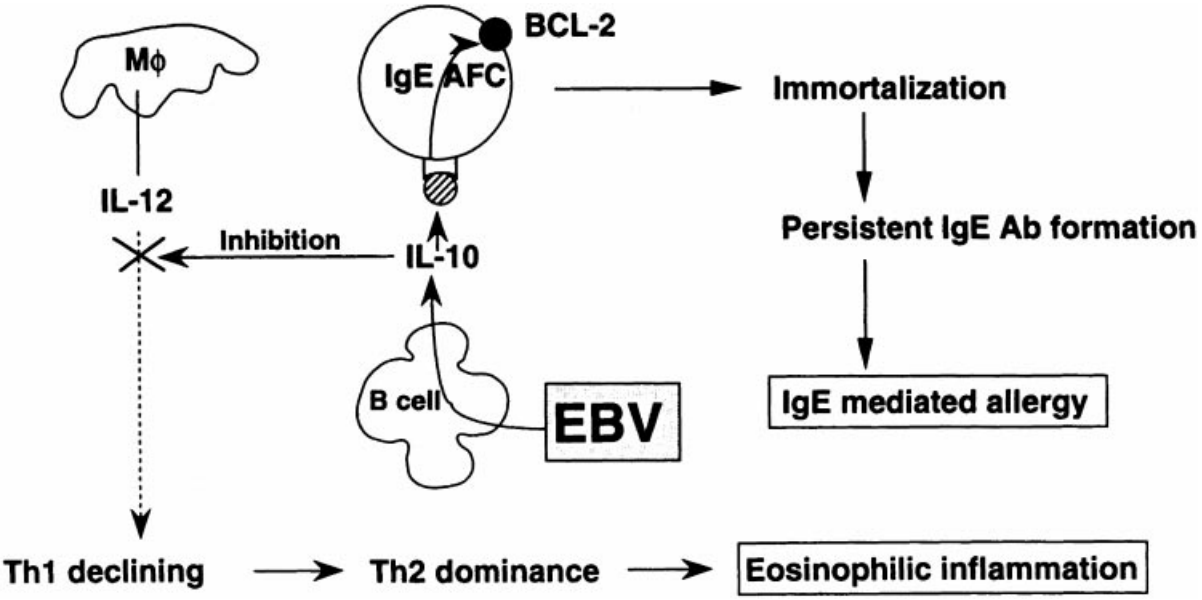


Fig. 3. Schematic model for the induction of non-apoptotic long-lasting IgE antibody forming cells by EBV infection.

Further investigations are clearly required, but it may be reasonable to speculate that persistent IgE antibody formation in atopic patients could be mediated by immortal antibody-forming cells which have been infected with EBV to express *bcl-2* proto-oncoprotein molecules through the activity of IL-10, a considerable part of which is induced by EBV.

Conclusion

Nowadays, the prevalence of atopic diseases in so-called developed countries is estimated to exceed 30%. Furthermore, it may well reach over 50% within two generations. Based on such facts, the so-called 'atopic predisposition' can not be thought of as an abnormal genotype consisting of certain 'atopic gene(s)' that a minority of unfortunate people possess. Rather, the gene(s) that cause atopic diseases must reside in the common human gene repertoire; several environmental factors could cause the over-expression of some constitutive gene(s), this leading to the development of atopic diseases. The authors consider that over-expression and production of Th2 cytokines may be a key event. The recent rise in prevalence of atopic diseases in developed countries may be mediated by a change of Th2 polarization due to the recent decrease in environmental factors that favour Th1 polarization, such as bacterial and viral infections. The atopic trait seems not to be a genotype that determines the development of an atopic disease on an all–or–nothing basis. The familial nature of atopic diseases is of course undeniable, but this does not necessarily mean that atopic diseases are genetic in nature. For example, if a parent suffers from tuberculosis, the possibility that his or her children will develop tuberculosis is markedly increased, despite tuberculosis being a truly infectious disease.

The strong association between EBV expression and hIL-10 production by a human B cell line is consistent with the results recently obtained with human B cell lines derived from patients with acquired immuno-deficiency syndrome or Burkitt lymphoma [59]. A model, now widely accepted, is that the EBV-infected cells are long-lived; they are perhaps the very cells that were originally infected or their progeny [60]. It was reported that B cell lines were derived easily from peripheral blood mononucleated cells of AD patients without depletion of T cells or treatment with an immunosuppressant, cyclosporin A [61]. This may suggest an unusually high load of EBV-infected cells in the circulation.

In light of these considerations, EBV is suggested to play a pathogenetic role in the development of atopy. However, several other factors such as *Staphylococcus aureus* infection may play a similar role to EBV infection [62]. In fact, in this investigation, the authors found that not all atopic individuals had EBV infection. Thus, it only remains an attractive hypothesis that EBV infection may promote the development of eosinophilic inflammation of atopic diseases by inducing an increased amount of IL-2 and/or IL-5.

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References

1 Edfors-Lubs M-L. Allergy in 7000 twin pairs. Acta Allergol 1971; 26:249–85.

2 Okudaira H. Why atopic diseases prevail in developed countries. ACI Int 1998; 10:110–21.

3 Kelso A. Th1 and Th2 subsets: paradigms lost? Immunol Today 1995; 16:374–9.

4 Mosmann TR, Cherwinski H, Bond MW et al. Two types of murine helper T cells clones. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 1986; 136:2348–57.

5 Mosmann TR, Coffman RL. Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. Annu Rev Immunol 1989; 7:145–73.

6 Gajewski TF, Schell SR, Nau G et al. Regulation of T-cell activation: differences among T-cell subsets. Immunol Rev 1989; 111:79–110.

7 Swain SL, Bradley LM, Croft M et al. Helper T-cell subsets: phenotype, function and the role of lymphokines in regulating their development. Immunol Rev 1991; 123:115–44.

8 Coffman RL, Varkila K, Scott P et al. Role of cytokines in the differentiation of CD4+ T-cell subsets in vivo. Immunol Rev 1991; 123:189–207.

9 Mosmann TR, Schumacher JH, Street NF et al. Diversity of cytokine synthesis and function of mouse CD4+ T cells. Immunol Rev 1991; 123:209–29.

10 Seder RA, Paul WE. Acquisition of lymphokine-producing phenotype by CD4+ T cells. Annu Rev Immunol 1994; 12:635–73.

11 Romagnani S. Lymphokine production by human T cells in disease states. Annu Rev Immunol 1994; 12:227–57.

12 Kobayashi M, Fitz L, Ryan M et al. Identification and purification of natural killer cell stimulatory factor (NKSF), a cytokine with multiple biological effects, on human lymphocytes. J Exp Med 1989; 170:287–845.

13 Trinchieri G. Interleukin-12: a cytokine produced by antigen-presenting cells with immunoregulatory functions in the generation of T-helper cells type 1 and cytotoxic lymphocytes. Blood 1994; 84:4008.

14 Trinchieri G, Scott P. The role of interleukin 12 in the immune response, disease and therapy. Immunol Today 1995; 15:460.

15 Moore KW, Vieira P, Fiorentino DF et al. Homology of cytokine synthesis inhibitory factor (IL-10) to the Epstein–Barr virus gene BCRFI. Science 1990; 248:1230–4.

16 Okudaira H, Mori A. Simple understanding and optimistic strategy for coping with atopic diseases. Int Arch Allergy Immunol 1998; 117:11–9.

17 Jeffery PK, Waldlaw AJ, Nelson FC et al. Bronchial biopsies in asthma. An ultrastructural, quantitative study and correlation with hyperreactivity. Am Rev Respir Dis 1989; 140:1745–53.

18 Gleich GJ, Adolphson CR. The eosinophilic leukocyte. Structure Function Adv Immunol 1986; 39:177–253.

19 Kay AB. 'Helper' (CD4+) T cells and eosinophils in allergy and asthma. Am Rev Respir Dis 1992; 145:S22–6.

20 Hamid Q, Azzawi M, Ying S et al. Expression of mRNA for interleukin-5 in mucosal bronchial biopsies from asthma. J Clin Invest 1991; 87:1541–6.

21 Gulbenkian AR, Egan RW, Fernandez X et al. Interleukin-5 modulates eosinophil accumulation in allergic guinea pig lung. Am Rev Respir Dis 1992; 146:263–6.

22 Mauser PJ, Pitman A, Witt A et al. Inhibitory effect of the TRFK-5 anti-IL-5 antibody in a guinea pig model of asthma. Am Rev Respir Dis 1993; 148:1623–7.

23 Robinson DS, Ying S, Bentley AM et al. Relationships among numbers of bronchoalveolar lavage cells expressing messenger ribonucleic acid for cytokines, asthma symptoms, and airway methacholine responsiveness in atopic asthma. J Allergy Clin Immunol 1993; 92:397–403.

24 Robinson D, Hamid Q, Bentley A et al. Activation of CD4+ T cells, increased TH2 type cytokine mRNA expression, and eosinophil recruitment in bronchoalveolar lavage after allergen inhalation challenge in patients with atopic asthma. J Allergy Clin Immunol 1993; 92:313–24.

25 Ohnishi T, Kita H, Weiler D et al. IL-5 is the predominant eosinophil-active cytokine in the antigen-induced pulmonary late-phase reaction. Am Rev Respir Dis 1993; 147:901–7.

26 Corrigan CJ, Haczku A, Gemou-Engesaeth V et al. CD4 T-lymphocyte activation in asthma is accompanied by increased serum concentrations of interleukin-5. Effect of glucocorticoid therapy. Am Rev Respir Dis 1993; 147:540–7.

27 Robinson D, Hamid Q, Ying S et al. Prednisolone treatment in asthma is associated with modulation of bronchoalveolar lavage cell interleukin-4, interleukin-5, and interferon-γ cytokine gene expression. Am Rev Respir Dis 1993; 148:401–6.

28 Mori A, Suko M, Kaminuma O et al. A critical role of IL-2 for the production and gene transcription of IL-5 in allergen-specific human T cell clones. Int Immunol 1996; 8:1889–95.

29 Mori A, Suko M, Tsuruoka N et al. Allergen-specific human T cell clones produce IL-5 upon stimulation with Th1 cytokine, IL-2. Int Arch Allergy Immunol 1995; 107:220–2.

30 Walker C, Bode E, Boer L et al. Allergic and nonallergic asthmatics have distinct patterns of T-cell activation and cytokine production in peripheral blood and bronchoalveolar lavage. Am Rev Respir Dis 1992; 146:109–15.

31 Rackemann FM. A working classification of asthma. Am J Med 1947; 3:601–6.

32 Humbert M, Durham SR, Ying S et al. IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against 'intrinsic' asthma being a distinct immunopathologic entity. Am J Respir Crit Care Med 1996; 154:1497–504.

33 Nagafuchi S, Otsuka T, Niho Y. Chronic EB virus infection and cytokine: IL-2, interferon gamma, and BCRF1 gene product (viral IL-10). Intern Med 1993; 32(12):945–7.

34 Miyazaki I, Cheung RK, Dosch HM. Viral interleukin 10 is critical for the induction of B cell growth transformation by Epstein–Barr virus. J Exp Med 1993; 178:439–47.

35 McDonnell TJ, Deane N, Platt FM et al. bcl-2-immunoglobulin transgenic mice demonstrate extended B cell survival and follicular lymphoproliferation. Cell 1989; 57:79–88.

36 Nakagomi H, Colcetti R, Bejarno MT et al. The Epstein–Barr

virus latent membrane protein-1 (LMP1) induces interleukin-10 production in Burkitt lymphoma lines. Int J Cancer 1994; 57:240–4.
37 Paul CC, Keller JR, Armpriester JM et al. Epstein–Barr transformed B-lymphocytes produce interleukin-5. Blood 1990; 75:1400–3.
38 Baumann M, Paul CC. Interleukin-5 is an autocrine growth factor for Epstein–Barr virus-transformed B lymphocytes. Blood 1992; 79:1763–7.
39 Rystedt I, Strannegard IL, Strannegard O. Increased serum levels of antibodies to Epstein–Barr virus in adults with history of atopic dermatitis. Int Arch Allergy Appl Immunol 1984; 75:179–83.
40 Strannegard IL, Strannegard O. Epstein–Barr virus antibodies in children with atopic disease. Int Arch Allergy Appl Immunol 1981; 64:314–29.
41 Strannegard O, Strannegard IL. T-lymphocyte numbers and function in human IgE-mediated allergy. Immunol Rev 1978; 41:149–70.
42 Okudaira H, Ishizaka K. Reaginic antibody formation in the mouse. XI. Participation of long-lived antibody-forming cells in persistent antibody formation. Cell Immunol 1981; 58:188–201.
43 Lichtenstein LM, Ishizaka K, Norman PS et al. IgE antibody measurements in ragweed hay fever. Relationship to clinical severity and the results of immunotherapy. J Clin Invest 1973; 52:472–82.
44 Vaz EM, Vaz NM, Levine BB. Persistent formation of reagins in mice injected with low doses of ovalbumin. Immunology 1971; 21:11–5.
45 Kontiainen S, Mitchison NA. Blocking antigen-antibody complexes on the T-lymphocyte activation during in vitro incubation before adoptive transfer. Immunology 1975; 28:523–33.
46 Tew JG, Self CH, Harold WW et al. The spontaneous induction of anamnestic antibody synthesis in lymph node cell cultures many months after primary immunization. J Immunol 1973; 111:416–23.
47 Grobler P, Buerki H, Cottier H et al. Cellular bases for relative radioresistance of the antibody-forming system at advanced stages of the secondary response to tetanus toxoid in mice. J Immunol 1974; 112:2154–65.
48 Tsujimoto Y, Finger LR, Yunis J et al. Cloning of the chromosome breakpoint of neoplastic B cells with the t (14; 18) chromosome translocation. Science 1984; 226:1097–99.
49 Bakhshi A, Jensen JP, Goldman P et al. Cloning the chromosomal breakpoint of t (14; 18) human lymphomas: clustering around JH on chromosome 14 and near a transcriptional unit on 18. Cell 1985; 41:889–906.
50 Cleary ML, Sklar J. Nucleotide sequence of a t (14; 18) chromosomal breakpoint in follicular lymphoma and demonstration of a breakpoint–cluster region near a transcriptionally active locus on chromosome 18. Proc Natl Acad Sci USA 1985; 82: 7439–43.
51 Tsujimoto Y, Cossman J, Jaffe E et al. Involvement of the bcl-2 gene in human follicular lymphoma. Science 1985; 228:1440–3.
52 Aisenberg AC, Wilkes BM, Jacobson JO. The bcl-2 gene is rearranged in many diffuse B-cell lymphomas. Blood 1988; 71:969–72.
53 Liu YJ, Cairns J, Holder MJ et al. Recombinant 25-kDa CD23 and interleukin 1 alpha promote the survival of germinal center B cells: evidence for bifurcation in the development of centrocytes rescued from apoptosis. Eur J Immunol 1991; 21:1107–14.
54 Vaux DL, Cory S, Adams JM. Bcl-gene promotes haemopoietic cell survival and cooperates with c-myc to immortalize pre-B cells. Nature 1988; 335:440–2.
55 Danneman PJ, Michael JG. Regulation of reaginic antibody production in mice. I. Suppression by antigen of IgE antibody production in vitro. J Exp Med 1977; 146:1534–48.
56 MacLennan IC, Gray D. Antigen-driven selection of virgin and memory B cells. Immunol Rev 1986; 91:61–85.
57 Nunez G, London L, Hockenbery D et al. Deregulated Bcl-2 gene expression selectively prolongs survival of growth factor-deprived hemopoietic cell lines. J Immunol 1990; 144:3602–10.
58 Rousset F, Garcia E, Defrance T et al. Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes. Proc Natl Acad Sci USA 1992; 89:1890–3.
59 Hockenbery D, Nunez G, Millman C et al. Bcl-2 is an inner mitochondrial membrane protein that blocks programmed cell death. Nature 1990; 348:334–6.
60 Korsmeyer SJ. Bcl-2 initiates a new category of oncogenes: regulators of cell death. Blood 1992; 80:879–86.
61 Bird AG, McLachlan SM, Britton S. Cyclosporin A promotes spontaneous outgrowth in vitro of Epstein–Barr virus-induced B cell lines. Nature 1981; 289:300–1.
62 Herz U, Bunikowski R, Renz H. Role of T cells in atopic dermatitis. Int Arch Allergy Immunol 1998; 115:179–90.