Thorax 1992;47:127–128

Scientific updates in respiratory medicine *Series editor: D J Shale*

Introduction

This issue of *Thorax* sees the start of a new feature presenting scientific updates in respiratory medicine. This will consist of a series of short reviews focusing on developments, mainly in the basic sciences, with implications for the understanding of respiratory diseases or their future management. Each review is selected by the writer, who has a research interest in the scientific area from which the review is derived. This will ensure an up to date content and relevance to respiratory medicine.

Seven reviewers will produce updates from across the spectrum of respiratory medicine, including oncology, asthma, pharmacology, molecular biology, immunology, and epidemiology. The first review, by Ron du Bois, outlines current understanding of how T lymphocytes recognise antigen and how such knowledge may lead to new options for management in interstitial lung disease. Future reviews will feature new host defence proteins and somatic gene treatment for α_1 antitrypsin deficiency and cystic fibrosis.

DJ SHALE
Section of Respiratory Medicine,
University of Wales College of Medicine,
Llandough Hospital,
Penarth,
South Glamorgan, CF6 1XX

How T cells recognise antigen: implications for lung diseases

R M du Bois

For many years histology and differential cell counts on bronchoalveolar lavage fluid have shown the lymphocyte to be a prominent component of inflammation in the lower respiratory tract in conditions such as fibrosing alveolitis, sarcoidosis, and extrinsic allergic alveolitis.[1 2] More recently lymphocytes have been implicated in diseases that affect the airways predominantly, notably asthma and bronchiectasis.[3 4]

Lymphocytes can be broadly subdivided into B cells, which are responsible for antibody mediated immune responses, and T cells, which are responsible for a range of immune responses including delayed hypersensitivity, B cell "help," and cytotoxicity. T cells have an extensive repertoire of surface receptors which often reflect functional state (for example, CD25+ cells indicate an activated state).

Perhaps not surprisingly, several lung diseases that appear to have a strong immune component have been associated with the presence of T cells, many of which are activated. Recognition of antigen by T cells is the first step in a highly complex process that results in the generation of cytokines, inflammatory cell chemotaxis and activation, and, ultimately, the release of a wide range of other mediators that are responsible for inflammation within the lower respiratory tract.[5]

T cells recognise antigen only when it is presented by an antigen presenting cell.[6] Antigen presented on the surface of such cells in association (as a complex) with class I major histocompatibility complex (MHC) molecules (HLA-A, B, and C) is recognised by CD8+ suppressor-cytotoxic T cells. Antigen complexed with class II MHC molecules (predominantly HLA-DR, but also possibly DP or DQ) will be recognised by CD4+ helper-inducer T cells. The MHC-antigen complex is identified by T cell antigen receptors, which are most commonly of the α/β form.[5] This nomenclature denotes that the receptor on the T cell surface consists of two glycoprotein chains (a 40–50 kDa α chain and a 40–45 kDa β chain) linked by disulphide bonds and that it is associated with the CD3 group of molecules, present on all mature T cells and necessary for surface signal transduction. The T cell antigen receptor structure closely resembles that of an immunoglobulin molecule. Each chain consists of a variable region and a constant region. The variable region contains a hypervariable segment, which confers antigen specificity on the molecule. Both the α and the β chains of the T cell antigen receptor have many individual members, which are grouped into families (for example, Vβ1, Vβ2, etc) based on gene sequences that are common to all members of an individual family. Theoretically up to 10^{13} α/β T cell receptor variants could exist.[5]

Recent studies have emphasised the impor-

Interstitial Lung Disease Unit, Royal Brompton National Heart and Lung Hospital, London SW3 6NP
R M du Bois
Reprint requests to:
Dr du Bois

tance of the T cell antigen receptor not only for the molecular biologist intent on understanding T cell repertoires and regulation of the inductive phase of the immune response but also for the clinical scientist. There is now a real possibility that a fuller understanding of the part played by T cells in the earliest phases of inflammation may provide new approaches to disease management.

Studies of T cells from the lungs and blood of a subgroup of patients with active sarcoidosis show that a specific family of T cell antigen receptors (Vβ8) are used preferentially by lymphocytes from such patients.[7] Interestingly, the sequences of many of these molecules were identical, implying a common triggering mechanism. This suggests that an antigen driven process, acting through the T cell antigen receptor, is responsible for the activation and amplification of selected T cells. A similar observation has been made in rheumatoid arthritis, a specific family of T cells (Vβ14) being found in the joints but not the blood of patients with active disease.[8] These clinical observations are consistent with findings from an animal model of extrinsic allergic encephalomyelitis,[9] in which hypersensitivity responses to myelin basic protein are responsible for an immune response that results in demyelination. The immune response is limited to T cells bearing receptors with distinct variable regions. Treatment of the animals with monoclonal antibodies directed against the variable regions Vβ8 and Vβ13 results in a sustained deletion of those families of T cells and protection against extrinsic allergic encephalomyelitis.[10]

Tolerance to antigen stimulation has also been induced in T cells from an atopic individual. In these studies O'Hehir *et al* have shown that T cell clones, specifically reactive to house dust mite allergens of *Dermatophagoides pteronyssinus* and *D farinae*, were inactivated by pretreatment with *Staphylococcus aureus* enterotoxins, which act as "superantigens" and render the T cell antigen receptor unresponsive to the natural ligand.[11] This induction of tolerance was receptor family specific. Although such studies have been performed in vitro, they have implications for diseases where the triggers are known, such as occupational asthma and extrinsic allergic alveolitis, and for disorders in which specificity of T cell triggering can be found without definitive antigen recognition, as in autoimmune or granulomatous lung diseases.[12] If treatments could be designed to remove or minimise the effectiveness of a particular T cell clone, it is likely that the most important component of the antigen driven inductive phase of the inflammation would be removed.

It is too early to say whether such a theoretical, albeit attractive, approach to human disease will be possible in the near future; but treatment of human disease with antibodies against the lymphocyte receptors CD3 and CD4 has been undertaken and these antibodies are far less specific than antibodies directed against the T cell antigen receptor. The fact that such an approach is being considered so soon after the discovery of T cell antigen receptors is an acknowledgment of the speed at which scientific advances can be made since the development of sophisticated molecular and cellular biological techniques of investigation.

1 Campbell DA, Poulter LW, Janossy G, du Bois RM. Immunohistological analysis of lung tissue from patients with cryptogenic fibrosing alveolitis suggesting local expression of immune hypersensitivity. *Thorax* 1985; **40**:405–11.

2 Crystal RG, Bitterman PB, Rennard ST, Hance AJ, Keogh BA. Interstitial lung diseases of unknown cause: disorders characterised by chronic inflammation of the lower respiratory tract. *N Engl J Med* 1984;**310**:154–65, 235–44.

3 Azzawi M, Bradley B, Jeffery PK, Frew AJ, Wardlaw AJ, Knowles G, *et al*. Identification of activated T lymphocytes and eosinophils in bronchial biopsies in stable atopic asthma. *Am Rev Respir Dis* 1990;**142**:1407–13.

4 Lapa e Silva JR, Guerreiro D, Noble B, Poulter LW, Cole PJ. Immunopathology of experimental bronchiectasis. *Am J Respir Cell Mol Biol* 1989;**1**:297–304.

5 Saltini C, Richeldi L, Holroyd KJ, du Bois RM, Crystal RG. Lymphocytes. In: Crystal RG, West JB, eds. *The Lung: scientific foundations*. New York: Raven Press, 1991.

6 Berzofsky JA. Structural basis of antigen recognition by T-lymphocytes. *J Clin Invest* 1988;**82**:1811–7.

7 Moller DR, Konishi K, Kirby M, Balbi B, Crystal RG. Bias toward use of a specific T-cell receptor β-chain variable region in a subgroup of individuals with sarcoidosis. *J Clin Invest* 1988;**82**:1183–91.

8 Paliard X, West SG, Lafferty JA, Clements JR, Kappler JW, Marrack P, *et al*. Evidence for the effects of a superantigen in rheumatoid arthritis. *Science* 1991;**253**:325–9.

9 Kumar V, Kono DH, Urban JL, Hood L. The T-cell receptor repertoire and autoimmune diseases. *Annu Rev Immunol* 1989;**7**:657–82.

10 Zaller DM, Osman G, Kanagawa O, Hood L, Prevention and treatment of murine experimental allergic encephalomyelitis with T-cell receptor Vβ-specific antibodies. *J Exp Med* 1990;**171**:1943–55.

11 O'Hehir RE, Aguilar BA, Schmidt TJ, Gollnick SO, Lamb JR. Functional inactivation of Dermatophagoides spp (house dust mite) reactive human T-cell clones. *Clin Exp Allergy* 1991;**21**:209–15.

12 Cooke A. Is there restricted T cell receptor usage in autoimmune disease? [editorial review]. *Clin Exp Immunol* 1991;**83**:345–6.