Analysis of T Cell Clones in Rheumatoid Arthritis

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Introduction

Like most active autoimmune disease, rheumatoid arthritis (RA) joints are infiltrated by numerous activated T cells. These coexist in close proximity to cells bearing human leucocyte antigen (HLA) class I and especially the HLA class II determinants that are universally present on all antigen-presenting cells. Thus there has been speculation, based on histopathological criteria that RA joints appear to be sites of on going active immune responses [9, 10].

Investigation of other autoimmune diseases has revealed that in the majority of diseases, the immunohistological appearance is very similar. In endocrine autoimmune disease, extensive class II expression was noted, extending to epithelial cells which normally do not express HLA class II antigens [7]. This 'aberrant' expression on the tissue target cells of the autoimmune process led to the hypothesis that the target cells expressing autoantigens are the important antigen-presenting cells involved in the perpetuation of the autoimmune response and that immune mediators are responsible for maintaining the class II expression [1]. Whether they are also involved in the initiation of the autoimmune response is a different question, which cannot be readily addressed experimentally. In contrast the former can, and has been, tested successfully.

Testing of the concept, which is illustrated in Fig. 1, was performed in several ways, using Graves' disease as the model, due to the relatively large and cellulary operative samples available. First, it was demonstrated that products of T cells, such as interferon-γ (IFNγ), can induce target cell (thyroid follicular cell, TFC) expression of class II antigens [22]. Second, purified TFC from Graves’ disease were shown to be able to present synthetic peptide antigens to histocompatible

Abbreviations: AMLR: Autologous mixed lymphocyte reaction; BSF-2: B-cell stimulatory factor-2, also known as IFNβ2 or IL-6; GM-CSF: granulocyte macrophage colony stimulating factor; IFNγ: interferon-γ; IFNα: interferon-α; IL-1: interleukin-1; IL-2: interleukin-2; LT: lymphotoxin or TNFβ; PBL: peripheral blood lymphoid cells; RA: rheumatoid arthritis; TFC: thyroid follicular cells; TGFβ: transforming growth factor β; TNF: tumour necrosis factor

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T cell clones [13]. Third, cloning of the T cells infiltrating Graves’ thyroids has revealed a high frequency of autoreactive clones, reactivated by autologous TFC, but not allogeneic TFC, or autologous peripheral blood lymphoid cells (PBL) [12]. In this context, it is interesting that trials of human interferon-α (IFNα), which has been shown to augment class II expression in vivo, have revealed a high incidence of autoimmune side effects, particularly thyroiditis (e.g., [8]). These findings are readily compatible with the hypothesis under test (Fig. 1).

In RA there are a multitude of cell types in the inflamed synovium, and unlike thyroiditis there is no clear cut target of the autoimmune process. To date it has not been defined precisely which cell types express HLA class II [4] and thus could be important antigen-presenting cells in this disease. However, the coexistence of abundant HLA class II and activated T cells makes the concept developed for endocrine autoimmunity a reasonable hypothesis to account for the perpetuation of the autoimmune response in RA. This has led us to investigate the nature of the T cells in RA joints in more detail, by cloning the cells which were activated in vivo.

**T Cell Infiltrate in RA Joints**

There are two potential sources of T cells from RA joints, either those present in the synovial fluid (SF), or those present in the synovial membrane. Published studies and our own experience indicates that the types of T cells in these two types of biopsies are different, e.g., there are far more CD8 cells in SF than in the membrane; in SF the CD4/CD8 ratio is approximately equal, whereas in the membrane CD4 cells predominate (e.g., Brennan et al., unpublished).

One of the problems of studying clones of T cells is to determine whether a given panel reflects the activated cells from which that panel was derived. Thus it is essential for us to study the composition of RA joint T cells in some detail to be able to answer this question.

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**Fig. 1.** Overall scheme of mutual cell interaction. **IFNγ:** Interferon-γ; **TNF:** tumour necrosis factor; **LT:** lymphotoxin; **IL-1:** interleukin-1