EFFECTOR CD4$^+$ T LYMPHOCYTES IN THE PRODROME OF POLYARTHRITIS

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Abstract

The inoculation of a single dose of Complete Freund's Adjuvant (CFA) in Dark Agouti rats induces a polyarthritis that resembles rheumatoid arthritis (RA) in humans. The specific role of T cells in the pathogenesis of RA is controversial but a considerable body of evidence suggests that the joint destruction is mediated by T cells within the synovium, which may activate other cells such as macrophages and fibroblasts that are more directly implicated in articular damage. To gain a further understanding of the mechanisms involved in the development of T cell-mediated polyarthritis, the activation and phenotype of $CD4^+$ T cells during the prodrome of adjuvant-induced arthritis (AA) has been investigated in rats.

Research in the Arthritis Research Laboratory has demonstrated previously that activated $CD4^+$ T cells in the thoracic duct (TD) lymph of rats during the late prodromal phase of AA (9 days after inoculation) have the capacity to enter both normal and inflamed joints after the adoptive transfer to syngeneic recipients. Furthermore, these activated $CD4^+$ T cells can transfer disease to naive recipient rats. The arthritogenic population is contained within a subset of $CD4^+$ T cells that expresses CD25, MHC class II, CD134 and CD71.

The delay in onset of AA after inoculation with adjuvant (9-10 days) or adoptive transfer of arthritogenic TD lymphocytes (4-6 days) suggests that progressive differentiation or selection of effector cells is required before disease can be expressed. This study has charted the emergence of activated and arthritogenic $CD4^+$ T cells in the inguinal and popliteal lymph nodes draining the site of inoculation, in the TD lymph and in the joints of the hind paws. In the lymph nodes and TD lymph, the proportion of $CD4^+$ T cells expressing activation markers such as CD25, MHC Class II, CD134 and CD71 and adhesion molecules such as ICAM-1 increased within 3 days following inoculation of CFA and these levels remained elevated throughout the early stages of AA. Arthritogenic lymphocytes were present in the TD lymph by the fourth day after inoculation of CFA. Interestingly, the disease transferred to recipients by lymphocytes from a donor on the fourth day post-inoculation followed similar kinetics to that transferred by TD lymphocytes harvested from donors at later time points. Very few $CD4^+$ T cells were detected in the hind paws during the prodrome of AA, whereas a dramatic influx was observed by day 9 and even more so at day 12 post-inoculation, when joint inflammation

was usually moderate to severe. These $CD4^+$ T cells in the inflamed hind paws had an effector phenotype.

A method was developed for detecting the cytokine production by individual T lymphocytes under conditions that reflected the cytokine production by these cells *in vivo*. This technique revealed that $CD4^+$ T cells from arthritic rats produced more interferon (IFN)-γ than interleukin (IL)-4, suggesting that this disease was mediated by T helper type –1 cells. $CD4^+$ T cells from inflamed joints were prolific producers of IFN-γ, suggesting that this pro-inflammatory cytokine may have played a crucial role in disease pathology. However, when a monoclonal antibody was used to block IFN-γ produced by either transferred arthritogenic lymphocytes or host cells in the active disease, the arthritis was markedly exacerbated, indicating that this cytokine also has down-regulatory effects at an important stage during the development of the inflammatory response.