


THE AUTOLOGOUS MIXED LYMPHOCYTE REACTION AND DENDRITIC CELLS

LYMPHOCYTES from human peripheral blood are activated in culture by autologous, mononuclear cells [1, 2]. In rheumatoid arthritis and systemic lupus erythematosus [3–5] and some other diseases, particularly those with a lymphoproliferative or autoimmune basis, this autologous mixed leucocyte reaction (AMLR) using cells from peripheral blood is abnormally low [6–12]. However, in inflammatory arthritis there may be a high stimulation of syngeneic blood lymphocytes by mononuclear cells isolated from joint fluids [13–15]. Potent stimulation of autologous lymphocytes is caused by antigen-presenting dendritic cells (DC) [16]. These also acquire foreign antigens and can initiate lymphocyte responses [17, 18]. In the light of such findings, a major component of the AMLR may reflect the acquisition of antigens by DC and their presentation to T lymphocytes. Clustering of T lymphocytes around antigen-bearing DC is a prerequisite for the initiation of primary proliferative responses to antigen in vitro [18, 19]. A similar aggregation of T cells around the interdigitating cells within the paracortex of lymph nodes appears to be the route of primary antigenic stimulation in vivo [20]. Since DC surrounded by T lymphocytes are also found in the synovial membranes of patients with inflammatory arthritis, the redistribution and compartmentalization of antigen-bearing dendritic cells and of lymphocytes responsive to these antigens could initiate and promote the inflammatory reactions within the joint.

The characteristics of induction of the AMLR are similar to those for producing immune stimulation by many antigens. Immune-associated (Ia), class II antigens are required; the responses as measured are Ia-restricted; the cells which initially respond are T cells and Ia positive antigen-presenting cells, particularly dendritic cells, are potent stimulators [1, 2, 12, 16, 21]. The dendritic cells in question are bone-marrow derived [17] and may represent up to 2% of the peripheral blood mononuclear cells [22, 23]. They are present in small numbers in most tissues of the body where they may be tissue-specific, as exemplified by the Langerhans’ cells of the skin [18, 20]. Particularly after exposure to antigen, dendritic cells normally travel as ‘veiled cells’ in the afferent lymph to the paracortex of the lymph nodes where they become interdigitating cells of the T-dependent zones [18, 20]. These are distinct from the follicular dendritic cells of the B-dependent areas which arise in situ from fibroblastic reticulum cells [24]. In patients with inflammatory arthritis, however, DC are increased in the synovial membranes and fluids compared with noninflammatory tissues [25–31]. DC in the joints are distinct from fibroblasts which have been described as ‘dendritic’ in morphology [28].
The AMLR has previously been considered separate from the presentation of foreign antigen to lymphocytes because it occurs in the absence of deliberate exposure to antigen [1, 2]. It has been suggested that the presentation of antigens from fetal calf serum supplementing the culture medium can contribute to the AMLR [21]. Two lines of evidence support the idea that acquisition of antigens in vivo by DC and the presentation of these antigens to lymphocytes may form a basis for the AMLR. Firstly, mice from the specific pathogen-free unit at the Clinical Research Centre had low numbers of DC in their lymph nodes and these, when added in small numbers to syngeneic lymphocytes, caused no stimulation. Following skin painting with contact sensitizers, the numbers of DC in the lymph node increased and caused high levels of stimulation of syngeneic lymphocytes. These DC were potent at initiating specific delayed hypersensitivity when transferred to normal syngeneic recipients [32, 33]. Secondly, on following the levels of syngeneic stimulation in mice over several years in the absence of deliberate immunization, there have been three occasions when mice showed increases in the number of dendritic cells together with higher levels of syngeneic stimulation. On two of these occasions, infection with Sendai virus was also detected. Similarly, increases in stimulation of peripheral blood lymphocytes by autologous veiled cells from rabbits followed either hyperimmunization with antigen or infection [18]. An AMLR may thus reflect the level of presentation to the immune system of foreign antigen acquired by the dendritic cells either by deliberate immunization or from opportunistic exposure.

Evidence from animals with autoimmune diseases shows that DC may present not only foreign antigen but also autoantigens. Rats were given the autoimmune disease experimental allergic encephalomyelitis by administration of brain antigen in complete Freund's adjuvant. Transfer of small numbers of DC from these animals to normal syngeneic recipients induced symptoms of the disease [34]. This suggests that in this disease, autoantigen is being continuously presented to the immune system on DC.

The evidence for involvement of DC in the development of inflammatory arthritis in humans is circumstantial. The dendritic cells are present in increased numbers in the synovium and in the synovial fluid [23–28]. In some patients, DC from synovial fluid can produce high levels of stimulation of syngeneic lymphocytes from peripheral blood [31] supporting the idea that dendritic cells with antigen may be providing a continuing stimulus to the lymphocytes within the joints. Low AMLR with stimulator cells from peripheral blood may reflect a lack of antigen-presentation and be correlated with the poor accessory function of blood 'monocytes' [35, 36]. Direct evidence for a role of DC with antigen in the production of arthritis has been obtained from studies in mice. *Chlamydia trachomatis* organisms or small numbers of DC exposed in vitro to *C. trachomatis* were injected intravenously into normal syngeneic recipients. DC with antigen caused arthritis which was not seen with antigen alone (unpublished observations). DC with antigen may, therefore, travel to the joints. In reactive arthritis, the lymphocytes within the joint fluids, while responding poorly to nonspecific mitogens [37, 38], show a response to the putative antigens which is higher than that in peripheral blood, suggesting that there is an accumulation of antigen-responsive lymphocytes within the joint [39]. The joints may therefore harbour DC able to present antigen and lymphocytes responsive to antigen.

This discussion has centred on the activities of DC as stimulators of the AMLR. They may be essential for the development of primary immune responses. Once the initial phase of primary stimulation has occurred other cells may present antigen to the activated T cells [19] and this may also be the basis for the capacity of cell types other than the DC to stimulate the AMLR [12].

The AMLR may thus have wider implications than those of measuring the responses to self 1a-determinants alone. It may provide a method for assessing the distribution of cells presenting antigen and of lymphocytes responsive to these antigens. On this basis it would appear that in inflammatory arthritis, DC possessing antigen are sequestered within the joints where they are able to present antigen to T lymphocytes. If this is the case, it still leaves unidentified the source and nature of the antigen and the cause of the accumulation of the cells within the joint. However, it provides a new impetus for studying the AMLR. It could also produce a possible route of attack in the continuing search for methods of immunotherapy as illustrated by the use of cyclosporin A to block antigen presentation by DC [40].

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PRECAUTIONS: Use with care in patients with a history of severe renal or hepatic insufficiency, asthma, sensitivity to aspirin or other non-steroidal anti-inflammatory agents (NSAIs), incipient or actual congestive heart failure. Modification of dosage may be necessary in concurrent therapy with highly protein-bound drugs, e.g., anticoagulants, sulphonamides and hypoglycaemic agents.

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OVERDOSAGE. Supportive and symptomatic therapy.

PRESENTATION AND PACKAGING. Surgam 300mg tablets and sachets in packs of 60. Surgam 200mg tablets in bottles of 100.

LEGAL CATEGORY. POM.

BASIC NHS PRICES. Surgam 300mg £11.85 per pack of 60. Surgam 200mg £15.76 per pack of 100.

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