Lymphocytes are pivotal orchestrators of the immune response, and understanding their activity in vivo is a key element in understanding the physiology of the response to infection. For example, in viral infections, activated cells of CD8 lineage, cytotoxic T-lymphocytes are important effectors for the clearance of virally infected cells. The pivotal role of lymphocytes is even more evident in disease states where lymphocyte dysfunction or depletion is the primary pathology. The archetype of such a condition would, of course, be AIDS.

Lymphocytes are very active cells. Much of our understanding of what lymphocytes do derives from studies ex vivo or in vitro. Of course, lymphocytes do many things. They proliferate in a clonal fashion in response to antigen. They probably also divide without specific stimulation, or possibly as a consequence of so-called bystander activation, in order to maintain long-term memory populations. They are also protein and peptide factories, producing both messenger molecules, such as cytokines, and effector proteins, such as antibody in the case of B-cells and perforin in the case of the cytotoxic T-lymphocytes. But what do they do in man in vivo? How active are they in health, and how is this activity altered by disease in humans?

In this issue of Clinical Science Caso et al. [1] have attempted to investigate one reflector of lymphocyte activity, protein synthesis. Such a measure is, of course, somewhat indirect and there are some complexities in the application of such methods [2]. However, this study has two important positive facets worthy of comment.

Firstly, it represents an example of the use of a traditionally ‘non-immunological’ tool to investigate immune processes. Similar stable isotope tools have been applied to investigate other aspects of the defence process, such as the production of the effector molecule NO [3] and rates of lymphocyte turnover in vivo [4]. Further application of such metabolic tools is likely to be a useful avenue to address other key immunological questions.

Secondly, this study contributes to our understanding of the link between immune function and metabolism. Such an interaction is bi-directional; the immune system is dependent upon substrate availability for its functioning, and conversely altered immune function makes a major contribution to the metabolic disturbances seen in infective states. Caso et al. [1] estimate that the lymphocyte protein fractional synthetic rate (FSR) is just over 50% higher in AIDS patients compared with controls (14.0% per day versus 9.1% per day); taken with a lymphoid mass of 300 g of protein, this additional 5% of FSR equates to about 15 g of protein per day. Such an additional requirement must be met from available substrates, although such an increase in FSR will presumably be matched by a similar increase in the lymphocyte protein degradation rate. The question of whether substrate availability ever constrains lymphocyte proliferation in vivo remains largely unanswered.

The data presented by Caso et al. [1] also shed light on the relative distribution of lymphocyte protein synthetic activity between that related to proliferation, the need to synthesize a new cell’s complement of protein, and that related to other functions, such as synthesis of export proteins. In healthy individuals turnover of the whole lymphocyte pool is probably of the order of 0.9% per day; in HIV viraemic subjects this probably rises to about 3% per day [4]. The data presented by Caso et al. [1] yield protein FSR values of approx. 9%, 8% and 14% per day in healthy subjects, asymptomatic HIV infection and AIDS respectively. Although the group definitions in these studies are not strictly comparable, some estimates may be made. It appears that in health, about one tenth of protein synthetic activity of the lymphocyte pool is probably mandated by the requirement to build new cells. In HIV infection, this rises to between 20% (using AIDS data) and almost 40% (using the asymptomatic HIV infection data). Surprisingly, the increased lymphocyte turnover in early HIV infection did not manifest as an increase in protein FSR in this group. Understanding this apparent disparity may be informative. It may be related to differing states of immune activation, as suggested by the correlation with tumour necrosis factor-α concentrations, or to the differing composition of lymphocyte pools. Whatever the answer, such results contribute to our understanding of what lymphocytes are really doing in health and disease in humans.

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