EDITORIAL

Therapeutic vaccines

In this age of antimicrobial chemotherapy, the huge amount of work on immunotherapy undertaken before the Second World War has become almost totally forgotten. Sir Almroth Wright, for example, devoted much of his time to the development of therapeutic, as well as prophylactic, vaccines and was portrayed as Sir Bloomfield Bonington in Shaw's play *The Doctor's Dilemma* with his cry of 'stimulate the phagocytes'. Ironically, it was in Wright's department at St Mary's Hospital, London, that Alexander Fleming discovered penicillin, thereby paving the way to the chemotherapeutic approach to infectious disease.

Once again, however, interest is turning towards the therapy of infectious disease by stimulation of the immune defence mechanisms – for two reasons. First, necessity: there are alarming reports worldwide of drug and multidrug resistance in a wide range of bacterial and protozoal diseases with some micro-organisms being resistant to almost all known agents. In the case of tuberculosis, outbreaks of multidrug resistant disease seriously threaten the control of this affliction in many countries a mere two decades after the widespread introduction of short-course chemotherapy.

Secondly, our understanding of the immune system has reached a point at which the design of immunotherapeutic agents, as well as prophylactic vaccines, can be based on rational principles. Although it is well known that harmful hypersensitivity reactions occur in allergic disorders, it is not generally realised that inappropriate immune reactions are responsible for most of the tissue damage and other pathological phenomena in many chronic infectious diseases. Indeed, it is possible to vaccinate an animal in such a way that the outcome of experimental infection is worse than in unvaccinated animals. In tuberculosis, there is ample evidence that the efficacy of Bacille Calmette-Guérin (BCG) varies greatly from region to region; in a large study in South India it appeared to induce a slight predisposition to disease rather than protection [1]. This variation is largely due to previous sensitisation of the population by exposure to environmental mycobacteria [2].

The existence of more than one pattern of reactivity in tuberculosis had been suspected since Koch's pioneering work on Old Tuberculin as an immunotherapeutic agent and has been the subject of considerable controversy [3]. The argument centred on whether

the protective immunity and the tissue-destroying reactions represent distinct phenomena or differ only in degree. One problem was that apparently qualitatively different reactions are both transferable by T cells and both are associated with positive tuberculin reactivity. This subject has become clearer in recent years with the finding that T cells are not only divisible according to cluster differentiation (CD) antigens but according to their maturation pathways, of which there are two, producing Th1 and Th2 helper T cells which secrete different cytokines [4]. In general, a Th1 response is required for protection against chronic intracellular parasitism, as this facilitates detection and lysis of immunologically effete cells packed with pathogens and their containment or destruction by activated macrophages, usually aggregated into granulomas. A Th2 response favours antibody formation and gross tissue necrosis, which may be required for the elimination of very large extracellular parasites, notably worms.

The numerous epitopes of complex pathogens are often regarded as being like the biblical sheep and goats, with some conferring protection and others mediating virulence and immunopathology. The reason for this is largely historical. Most of the early vaccines were for the prevention of acute infections in which protection depends on production of antibody to species- or to strain-specific toxins or factors blocking phagocytosis of the pathogens. However, there is no reason to assume that a 'protective' epitope of an intracellular pathogen such as the tubercle bacillus should have such specificity. Indeed, BCG, an attenuated strain of *Mycobacterium bovis*, not only protects against tuberculosis, but also against leprosy and lymphadenitis due to environmental mycobacteria, indicating that shared bacterial components are involved in the induction of protection [1, 5].

Nevertheless, the dogma of the specific protective antigen is firmly entrenched and much fruitless effort has been spent on isolating single epitopes and studying the nature of the immune response elicited by them. It now appears likely that, rather than a broad spectrum of immune responses being elicited by the complex array of epitopes in a given pathogen, the whole organism elicits a remarkably unified response; a phenomenon termed 'coherence' [6]. It also seems likely that the nature of the coherent response is determined by adjuvants, which have direct effects on the functions of the macrophage and the antigen-presenting cell [7].

Adjuvants including peptidoglycans, polyanions, lipoproteins and lipopolysaccharides, have a profound effect on the Th1/Th2 ratio by two principal, and probably closely interacting, mechanisms. One involves the release of cytokines, from macrophages and other cells, that affect the maturation pathway [4]. Thus, for example, interleukin 12 (IL-12) and IL-10 drive, respectively, Th1 and Th2 maturation. Another mechanism involves an effect, directly or *via* cytokines, on tissue enzymes that convert prohormones into active metabolites which influence the Th1/Th2 ratio. Glucocorticoids, by inhibiting the transcription of Th1 cytokines, favour Th2 maturation while metabolites of dehydroepiandrosterone (DHEA) are antiglucocorticoid and may also directly enhance Th1 maturation [8–10].

In the long struggle between pathogens and the mammalian immune system, there would have been a strong evolutionary drive for the latter to select the best possible response to a given pathogen and this strategy usually succeeds. In the case of tuberculosis in immunocompetent persons, only one in 10 of those infected eventually develops clinically evident disease. As the bacillus must be eliciting a highly successful response in the other nine, it is necessary to ask what is different in those who do not control or contain the infection.

T cell maturation pathways tend to be 'locked in' to one or other type but there are mechanisms for a Th1 to Th2 switch in chronic infections, with detriment to the host [6]. These include changes in the glucocorticoid/DHEA ratio due to effects of cytokines and disease-related stress on the hypothalamo-pituitary-adrenal axis and a direct effect of circulating tumour necrosis factor on the adrenal gland [9].

In tuberculosis, a Th1 response favours protection while a Th2 (or mixed Th1 and Th2) response causes the massive and inappropriate tissue destruction responsible for the formation of lung cavities in which the tubercle bacilli may freely replicate and gain access to the cough spray, thereby infecting other persons [11]. Accordingly, a shift towards Th1 responsiveness should be beneficial. This may be achieved with a strain of *M. vaccae* which not only contains the adjuvant compound or compounds, but also the common mycobacterial antigens [12]. A heat-killed suspension of this organism is effective against drug-susceptible and multidrug-resistant tuberculosis when used as an adjunct to antimicrobial chemotherapy [13, 14].

Can *M. vaccae* be used as an immunotherapeutic agent for other chronic infectious diseases, for example, by introducing epitopes of unrelated pathogens by genetic recombination [15]? In fact, there is anecdotal evidence that *M. vaccae* is effective alone in unrelated infections, perhaps by recognition of markers

of stress on infected cells rather than pathogen-specific antigen. All cells contain small amounts of 'heat-shock proteins' (HSP), most of which are normally involved in the folding and assembly of newly synthesised proteins. In circumstances of stress, such as heat shock or intracellular parasitism, the quantity of HSPs increases greatly and they are presented on the cell surface where they serve as targets for 'hunter-killer' cells [16].

Patients with tuberculosis and leprosy have a diminished ability to respond to the common mycobacterial antigens [17, 18], as have tuberculin positive HIV-infected persons, patients with rheumatoid arthritis and persons in the silent phase of Chagas' disease (South American trypanosomiasis) [19, 20]. These common antigens include HSPs.

The modulation of immune recognition of HSPs by bacterial adjuvants suggests that immunotherapeutic agents may have a place in the treatment of autoimmune disease and cancer. HSPs are highly conserved so that one from a mycobacterium is structurally and antigenically similar to its human analogue. One of the paradoxes of immunology is that the conserved HSPs are immunodominant and thus, whether of exogenous or endogenous origin, are potentially capable of inducing 'anti-self' or autoimmune responses. Normally this is controlled by a complex immunoregulatory network but the high incidence of autoimmune disease indicates that this network can easily malfunction [16]. It seems that *M. vaccae* immunotherapy may, in some circumstances, correct such a malfunction, as has been demonstrated in psoriasis and psoriatic arthropathy [21].

Another group of diseases involving Th2 cytokines and IgE are the atopic or allergic conditions such as urticaria, hay fevers and extrinsic asthma [22]. An obvious therapeutic strategy is to incorporate the relevant epitope of an allergen into a Th1 adjuvant by genetic recombination or chemical conjugation.

Bacterial products have long been used as therapeutic agents in cancer. The first of these were the 'Coley toxins', extracts of streptococci and *Serratia* species, which showed some efficacy against sarcomas. Neonatal BCG vaccination also confers considerable protection against leukaemia and other childhood cancers [23]. It has also been used in the treatment of cancers, either alone or as a carrier for tumour antigens, although with variable results and frequent serious side effects. It is probable that the efficacy of BCG, and the severity of side effects, depend on whether there is a predetermined Th1 or Th2 response and that more consistent results, with minimal side effects, would be obtained by use of *M. vaccae*. This reasoning is based on the hypothesis that an important component of antitumour immunity is recognition and cytotoxicity of stressed cancer cells expressing HSPs on

their surface [24]. Thus, murine tumour cell lines transfected with, and expressing, a mycobacterial 65-kDa HSP lost their ability to cause tumours and induced a cytotoxic immunity to the analogous untransfected cancer cells [25]. Preliminary studies of *M. vaccae* immunotherapy in cancer patients are being conducted.

It is evident that therapeutic vaccines with Th1 adjuvant activities are likely to act in several different ways. First, they down-regulate inappropriate Th2-driven responses that cause immunopathology in a range of chronic infections characterised by intracellular parasitism. Secondly, they induce a Th1 response leading to macrophage activation and granuloma formation. Thirdly, they appear to facilitate a regulated recognition of HSPs thereby suppressing autoimmune phenomena, but also facilitating the recognition of stressed, abnormal cells expressing HSPs on their surfaces. Fourthly, they reduce Th2-mediated allergic responses. Thus they have the potential to treat chronic infections, autoimmune disease, cancer and allergy, which make up a very large part of the ills that afflict mankind. Finally, there is increasing evidence that vasculitis, which is an important component in the immunopathology of many diseases and a causative factor in arteriosclerosis, is triggered by Th2 cytokines and thus amenable to immunotherapeutic intervention. Although Th1 activity appears beneficial in a wide range of disorders, there are circumstances in which this may not be desirable. Thus down-regulation of Th1 activity without stimulating Th2-driven antibody formation is likely to prolong homograft survival [7], while a specific Th2 response may be required for protection against helminth infection.

The wide range of activity of adjuvants, notably those driving Th1 responses, with or without the presence or addition of specific antigen, suggests that these agents may lead to as significant and far-reaching a therapeutic revolution in the 21st century as antimicrobial drugs did in the 20th century.

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