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Repertoire Purging by Medium Concentration Self-Macromolecules is the Major Factor Determining Helper and Suppressor Repertoire Differences

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Interest in helper and suppressor epitopes has been growing rapidly. It is now generally accepted that most antigens present structures (epitopes) to the immune system which are recognized preferentially by different sets of lymphocytes, as shown in Fig. 1. These sets belong to the effector compartment containing B cells, Tc cells (cytotoxic cells), and delayed-type hypersensitivity-mediating T cells (not shown), or to the regulatory compartment containing Th and Ts cells (helper and suppressors). Structures preferentially recognized by Th cells are termed helper epitopes, and so on, and the balance of the two types of regulatory epitope is known to be an important factor in determining the outcome of at least some immune responses. The presence of even a single suppressor epitope may be enough to prevent a response from occurring. The fullest analysis of an antigen along these lines has been carried out on lysozyme [1] and β-galactosidase [18, 9], and other antigens which have been examined in this way include ferredoxin [19] and tumour antigens [5, 7]. Note however that cleavage of serum albumin does not yield fragments with distinct helper and suppressor epitopes [2, 4].

Understanding the nature of helper and suppressor epitopes is a matter of importance to leukaemia research because it could link tumour idiotype to membership

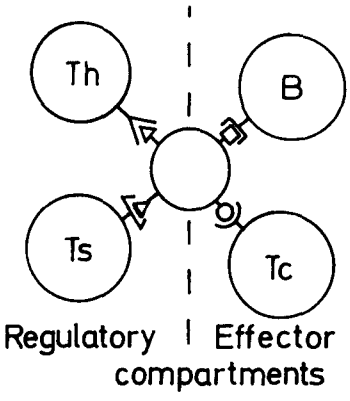

Fig. 1. How a vaccine looks to T cells. Th–Ts repertoire differences are potentially valuable

of a lymphocyte set, and also because of its relevance to any future tumour immunotherapy. It is important to immunological diseases at large, because it is likely to help explain why particular types of antigen tend to generate a harmful response. And at the present time it is most obviously important to development of the new generation of vaccines. This is an area of great excitement because these vaccines, based on bioengineering, promise to control and eventually eradicate the major tropical diseases. Of course one needs to exercise caution in evaluating this promise and as yet engineered vaccines are only just entering veterinary trials, but there is no doubt that this hope has given new heart to vaccine research. What is now being done, world-wide, is to take a parasite such as the plasmodium of malaria, clone cDNA into an expression vector, and screen for antibody-defined antigens [6, 7]. A complementary approach is to screen for antibody-reactive synthetic peptides [11]. Both

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of these strategies concentrate initially on the ability of vaccine molecules to interact with the effector compartment, simply because antibodies and to a lesser extent cytotoxic T cell clones are the only practical screening agents. But in the long run this is too limited an approach, particularly for the major tropical diseases all of which are long-term and characteristically display an ineffective host response. Surely the main hope is for a vaccine which can perturb this balance between parasite and host, through manipulation of the regulatory compartment.

The nature of suppressor and helper epitopes is still poorly understood. I wish here to offer a contribution towards a general theory of what makes them different from one another. Any discussion of the problem should start with a distinction between differences based on antigen processing and differences based on the receptor repertoire of lymphocytes. As regards the former, interpretations have tended to diverge, with some authors emphasizing the importance of relatively crude factors such as the gross anatomical localization of antigen, while others emphasize the importance of the interaction of fragments of antigen with particular cell receptors. Thus chemical modification can greatly effect anatomical localization [3], and the route of immunization or form in which a determinent is administered can greatly influence which sets of lymphocyte respond [14]. On the other hand it has been suggested that peptide fragments of antigens associate selectively with particular major histocompatibility complex components, and thus determine which regulatory cells respond to "aggretope selection" [10]. Or suppressor cells may resemble B cells rather than helper cells in their interaction with antigen, and consequently tend to respond to conformational rather than sequence determinants [12]. These are fascinating questions, but we have little hard information with which to answer them.

In contrast there is something more definite to say about repertoire differences between helper and suppressor cells, even if at present this is of a rather general character. Thanks to recent advances in our understanding of the interactions of four

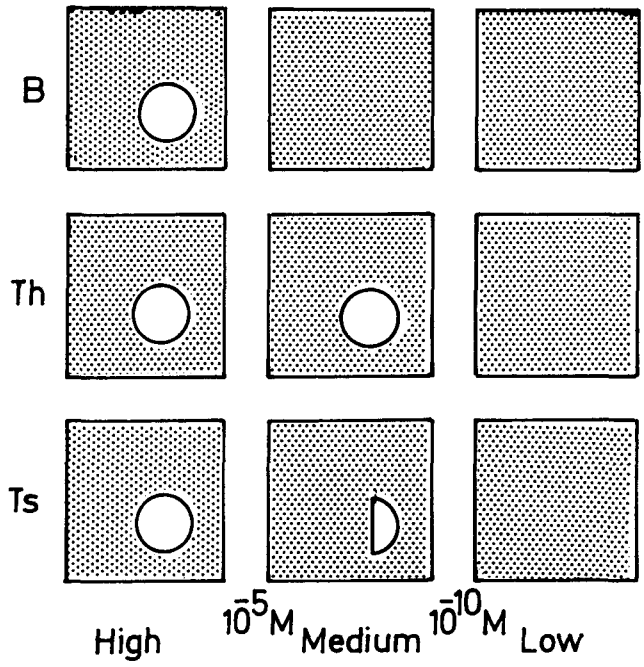

Fig. 2. Only medium concentration self-macromolecules generate Th–Ts repertoire differences (see text for details)

proteins with the immune system as they occur naturally, we can begin to define what is probably the main factor responsible for moulding this repertoire difference. The proteins in question are C5, a complement component, F, a liver and serum protein of unknown function, AFP, α-fetoprotein, and Tg, thyroglobulin. The argument is summarized in Fig. 2, which requires some explanation. Each stippled area represents the repertoire of antigen receptors for a set of lymphocytes (each dot representing, as it were, a single clone of cells). The circles represent holes punched out of the repertoire by tolerance of a single self-protein; it is assumed that self-tolerance results from purging the repertoire of clones reactive with self-proteins. The top row describes what happens to B cells: their repertoire is purged only by proteins which occur in the body at high concentrations, over 10^{-5} *M*, such as serum albumin or the constant part of immunoglobulin. The next row deals with helper T cells: their repertoire is purged by proteins occurring down to lower levels of concentration, 10^{-10} *M*, but no doubt there are still other molecules which occur at concentrations too low to be noticed at all by the immune system, and for which no purging occurs. Thyroglobulin is an example at the bor-

Table 1. Documentation of reactivity of the main lymphocyte sets to four medium concentration self-proteins

	C5	F	AFP	Tg
B cells	+±	++	++	++
Th cells	−	−	−	−
Ts cells	+	+		+
Concentration in body fluid (*M*)	10^{-7} M	10^{-6} M	10^{-9} M	10^{-15} M
References	[5]; Y. Borel, personal communication	[12, 20]	[15, 16]	[17, 18]

derline between the medium and low ranges of concentration: it purges the helper cell repertoire to a significant extent, but incompletely. At the bottom come suppressor T cells: their repertoire is no more than partially purged by proteins occuring at medium concentrations, as exemplified by the proteins F and C5. The important point is that purging of helper and suppressor cells occurs down to different levels, and that this difference defines a medium concentration range at which their repertoires must differ. No other factor can be identified which is known to generate a difference between their repertoires. This does not mean that other factors do not operate, but simply that at present we do not know what they are. For instance at the time of writing there is a suspicion, but at present no more than that, that helper and suppressor T cells draw from different sets of V genes. The evidence for the medium concentration range that is crucial to this argument is cited in Table 1 for the four proteins C5, F, AFP and Tg, and is discussed in greater detail elsewhere [13].

What are the practical consequences? It is ironic that this, the only definite piece of information which we have about the helper-suppressor epitope difference should produce so little in the way of practical advice about how to design a particular epitope. Even if we knew the full three-dimensional structure of the proteins listed in Table 1 we would only be a little nearer this goal. From this point of view research on differential antigen processing perhaps has more to offer, even if so far its achievements have been small. For the time being immunologists will be kept busy cloning genes and synthesizing peptides of potential value in vaccines. More and more of these new products will enter immunization trials without much rhyme or reason, and as they do so we shall no doubt acquire empirical information about which kinds of structure are good immunogens as distinct from ones which merely react well with antibodies. It will be important to have some kind of theoretical framework into which this information will fit. I believe that medium concentration self-proteins as defined here will be an important part of that framework.

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