RESPONSE

Dr. Ohno gives us a pessimistic view. He challenges whether we will ever understand the immune system as an integrated whole; we wish to assure him that we, the scientific community, will, but even if we don't there remains, nevertheless, much pleasure in trying when the conversation along the way is good. Of course Protecton theory is but one part, dealing only with the humoral system, leaving us much to talk about. Ohno raises three points which are so characteristically perceptive. One of them deals with Protecton calculations directly and the other two (the "burning questions") concern T cells and their interactions with B cells.

Consider first the value of 1/3 as the probability that a joint will be in-frame. Ohno points out that, because the heptamers and octamers used as recombination signals operate over enormous distances, the probability of finding an appropriate, not spurious, site of recombination might well be 1/30 not 1/3. Haplotype (allelic) exclusion then would be totally a function of the joining mechanism (e.g., Coleclough 1983), no STOP signals being required. At its extreme, if the probability of successful fusion were low enough, 1/300, it would be possible to attain perfect or near perfect haplotype exclusion.

A highly inefficient gene fusion mechanism would eliminate most doubles. However, we point out that a careful analysis of the kappa light chain (Claverie & Langman 1984) and heavy chain (Langman & Cohn 1987) gene rearrangement patterns were consistent with a fusion efficiency of around 30% or more (not 3% or less). More generally, we note that any mechanism of haplotype exclusion that seeks to make this a perfect mechanism runs into the same question of "washout" or "displacement". When all of the B cells are functional, the available repertoire is large and cannot be maintained by evolutionary selection with a steady state antigenic load that is less than 10% of the total repertoire; at best 0.1−1.0% of the repertoire is the maximum load that can be maintained within the displacement boundary when all B cells are functional. The evolutionary selection pressure to establish and maintain haplotype exclusion is integral to the Protecton theory and if nonamer-heptamer sequences are common and represent abortive fusion sites, then the I-turn/2-turn spacer or some other as yet undescribed mechanisms must reduce the level of such abortive fusions to insignificance on both experimental and theoretical grounds; this underscores the importance of Protecton theory in suggesting likely places to obtain new insights – even if they lead to a disproof of the theory.

Ohno also takes the opportunity to question our background concepts and, although they are not critical to basic Protecton theory, we take this opportunity to comment briefly as it deals with the peptide revolution and processing. First, Ohno is concerned that, if B cells must be able to recognize carbohydrates (CHO) and a T-B cell interaction as required under Associative Recognition Theory, then the inability of T cells to process CHO means that our assumption of the key role of T-B collaboration must be wrong. This argument is as much a challenge to present day views of processing and T-cell physiology as to those of
Associative Antigen Recognition Theory! If processing is not obligatory, and current experimental findings are being grossly overinterpreted (as we will illustrate elsewhere), then Ohno’s argument does not apply. There is no way to prevent T cells from recognizing CHO and we predict it is only a question of time before this will be evident. However, we should note that if “processing” were obligatory, associative antigen recognition would, as Ohno points out, be untenable (because T-T interactions would be ruled out) but Protecton theory would remain; only the source of Signal[2] would have to be identified and shown to operate within the rules of the self-nonself discrimination (we’d enjoy a proposal for this).

Second, Ohno argues that, if the animal is tolerant to all intracellular proteins, then the Associative Antigen Recognition Theory – 1990 must be wrong. This also deals with processing inasmuch as intracellular self components as well as extracellular self and all nonself components are assumed to be processed. If this were true, Ohno argues, “the immune system unnecessarily expanded the self to an unmanageable extent.” Thus, Ohno has singled out with crystal clarity the limitations to the processing concept and we entirely agree; we go further arguing that not only is “processing” incidental but it totally lacks any conceptual underpinning, leaving the enormous body of experimental work misinterpreted. We are preparing a detailed paper on this problem. However, exactly why the finding of self tolerance to intracellular self components would disprove the Associative Antigen Recognition Theory is unclear. If we assume the argument to be that deleting the antibody repertoire specificities for intra- and extracellular antigens would create vast holes in the repertoire, such holes remain to be found. We argue that intracellular antigens are not seen by the immune system and it would not be expected to be tolerant to them. If cells lyse and these antigens appear extracellularly, an immune response to them is expected and they are eliminated as “nonself”, a process we refer to as “housekeeping”. There are many examples of response to intracellular proteins when an animal is immunized with a crossreacting antigen (e.g., Rajewsky showed that porcine LDH in a rat or rabbit elicits anti-autogenous LDH with no harmful effect).
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