Perspective

Mechanisms of Immunological Tolerance

H. ROBSON MACDONALD

A SEMINAL FEATURE OF THE IMMUNE SYSTEM IS ITS ABILITY to distinguish self from nonself. The responsibility for this discrimination lies with the T cell antigen receptor (TCR) αβ heterodimer that recognizes small peptide fragments of foreign antigens that are physically associated with polymorphic self proteins encoded within the major histocompatibility complex (MHC).

Immunological tolerance is the failure of T cells to respond to self antigens. Three mechanisms have been invoked to explain this phenomenon, involving either elimination, nonresponsiveness, or active suppression of the autoreactive clones. Experimental attempts to distinguish between these mechanisms have been controversial because functional assays used to measure autoreactive cells can be subject to a number of artifacts. Recently these objections have been swept away by three concurrent developments: (i) the construction of transgenic mice bearing specific TCRs, (ii) the demonstration that some TCR β-chain variable (V_β) domains confer preferential reactivity to specific self and foreign antigens, and (iii) the identification of the T cells bearing specific TCRs with monoclonal antibodies. As a consequence of this progress, there is now direct evidence that cells bearing autoreactive TCRs are eliminated during development and that deletion normally occurs within the microenvironment of the thymus gland (*1, 2*). This establishes clonal deletion as a major mechanism for the maintenance of self tolerance. But is it the only mechanism?

All aspects of self tolerance cannot easily be explained by clonal deletion. If deletion always occurs intrathymically (a dogma not challenged by any recent data), T cells that develop extrathymically or that react with tissue-specific antigens presumed to be absent (or ineffectively presented) in the thymus would not be eliminated. Recent papers address this problem from various viewpoints. By taking advantage of several well-established correlations between V_β domains and antigen reactivity, these studies show that putatively autoreactive TCRs are not always clonally deleted and in some cases even may be associated with the development of autoimmunity.

The necessity of the thymus for effective clonal deletion is directly confirmed by both Hodes *et al.* (*3*) and Fry *et al.* (*4*) in this issue. Comparing genetically athymic (nu/nu) mice and their control littermates, both groups found that "forbidden" $V_\beta3^+$ and $V_\beta11^+$ T cells (reactive with the self antigens Mls-2^a and I-E, respectively) were present in the athymic animals. Taking advantage of the reactivity of these same V_β domains with staphylococcal enterotoxin A (SEA), Fry *et al.* also found that $V_\beta3^+$ and $V_\beta11^+$ T cells from athymic mice could be expanded by SEA stimulation in vitro. One might expect such undeleted clones to preferentially respond to self antigens and provoke symptoms of autoimmunity in the athymic animals; however, neither group noted any such abnormalities, a finding consistent with the general health of athymic mice maintained under pathogen-free conditions.

A possible link between autoimmunity and the failure of clonal deletion was found in a related model system by Smith *et al.* (*5*). These authors (among others) noted previously that thymectomy 3 to 6 days after birth led to an increased incidence of autoimmune disease in certain mouse strains (*6*). They further demonstrated that, in the most susceptible of these strains (B6AF1), $V_\beta11^+$ (I-E reactive) cells that should normally be deleted (because these mice express I-E) were highly enriched in adult mice that had undergone neonatal thymectomy. What remains to be established in this system is a direct (causative) link between autoimmunity and $V_\beta11$ expression. Since a significant proportion of potentially autoreactive cells are present after birth even in strains that are not prone to autoimmunity (*7*), it is not clear whether these cells simply persist in neonatally thymectomized mice or are actively selected by autoantigens. Comparable thymectomy experiments in strains not normally susceptible to autoimmunity will be required to resolve this issue.

None of the aforementioned studies directly addresses alternative mechanisms of establishing self tolerance. This question is elegantly pursued by Ramsdell *et al.* (*8*) in this issue. This group has established radiation bone marrow chimeras in which the self antigen necessary for clonal deletion (Mls-1^a or I-E) is only expressed on the radioresistant host (stromal) component of the thymus and is apparently not presented (at least in functional form) on donor hematopoietic-derived cells. Clonal deletion of Mls-1^a or I-E reactive ($V_\beta6^+$ or $V_\beta17a^+$) cells does not occur in such chimeras [a finding noted independently by Speiser *et al.* (*9*)]; nevertheless, thymic or peripheral T cells bearing these TCRs do not respond to autoantigens either in vitro (in mixed leukocyte cultures) or in vivo (in a graft versus host assay). The authors propose that this functionally nonresponsive ("anergic") state results from the interaction of developing T cells with autoantigens presented by (radioresistant) thymic cortical epithelium. Although the biochemical basis of this anergy will require further study, Ramsdell *et al.* hint that failure to produce the growth-promoting cytokine interleukin-2 may account for at least part of the hyporeactivity, a conclusion that is supported by another recent report (*10*).

These recent findings need to be reconciled in a consistent model for the induction and maintenance of immunological tolerance to self antigens. It seems clear that clonal deletion normally requires the thymus and (at least for certain antigens such as Mls-1^a) only occurs as a result of high avidity interactions between developing autoreactive T cells and hematopoietic thymic components. What is less clear is the fate of T cells that escape this clonal deletion mechanism, either because they fail to transit the thymus or because the self antigens they recognize are not presented by the appropriate thymic components. As this series of papers reveals, nondeleted autoreactive cells can show a perplexing variety of behavior patterns in vitro and in vivo, ranging from benign (anergy) to highly aggressive (autoimmunity). Understanding this complexity will ultimately require a better knowledge of the molecular nature of the self antigens themselves, as well as their manner of presentation under physiological (or pathological) conditions.

The author is a member of the Ludwig Institute for Cancer Research, Lausanne Branch, Epalinges, Switzerland.

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