

The specificity of the clonal selection theory

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Arthur M. Silverstein directed a recent paper at those “challenging” the clonal selection theory (CST) because of its obsolete notions of tolerance and self-nonself discrimination (SNS)¹. What is overlooked, according to Silverstein, is the fact that SNS and tolerance are merely “subsidiary hypotheses,” which only address “questions raised by the theory.” These should not be confused with the “core theory” or the “central hypotheses of clonal selection”: “antigen selects cells, and this results in the clonal proliferation and differentiation of these cells.” This, claims Silverstein, remains unchallenged.

In his analysis, Silverstein relies on what he believes was Macfarlane Burnet’s original conception of the CST. However, this historical interpretation is far from being evident: Burnet himself repeatedly contended that the central tenet of the CST was the fact that “no immunological reaction takes place against the normal constituents of the body.” For Burnet, this was definitely not a matter of a subsidiary hypothesis; in fact, he even defined it as an “axiom”².

At the same time, Silverstein is right to identify a conceptual fallacy prevailing in the current heated debate on the role of SNS in immunology: namely, the unqualified and

undifferentiated (indeed, interchangeable) use of the terms “SNS” and “CST.” However, it is not the distinction between central tenets and subsidiary hypotheses that is at stake. It is the different notions of immunological specificity that lie at the heart of the problem.

Nothing in immunology is more obvious than the ability of the immune system to discriminate and react specific-

ly. What is usually overlooked, however, is the fact that the concept of immunological specificity has at least two major meanings, with partially conflicting implications. On the one hand is the specificity of the immune response, on the other, the specificity of the antigen. The specificity of the immune response is that which is characteristically defined in terms of recognition, discrimination, rejection or tolerance (that is, SNS). The specificity of the antigen, in contrast, is defined in terms of epitopes (receptors or determinants). An immunological reaction may be specific, and there is some mechanism at work. But the reaction’s specificity does not necessarily have to be reducible to a single epitope or to a single clonal selection event. These are very different conceptions of specificity. The fact that in many cases the two specificities are highly correlated does not mean that they are the same thing.

The reasons for this equivocal meaning of “immunological specificity” are historical, and their tracing would require a long excursion into the origins of immunology. Important to note, however, is that the CST, in its classic form, is a statement about the relation between the notions of specificity of the reaction and of the antigen. The CST

proclaims that a specific immune response can be explained in terms of the selection of a specific clone by a specific antigen.

In this sense, it is somewhat misleading to uniformly discuss the “challengers” of the CST. For example, some of the adherents of the danger theory still seem to implicitly assume that the specificity of the reaction (albeit not the decision to react) is determined by the specificity of the antigen³. On the other hand, Irun Cohen’s conception of the “immunological homunculus” is based on a total detachment of the specificity of the antigen from that of the reaction (the latter is postulated as “emergent specificity”⁴). At the same time, it should be noted that phenomena like physiological autoimmunity and multi-signaling do not necessarily challenge the SNS scheme, as long as SNS is understood as the ability of the immune system to react specifically—regardless of the underlying mechanism.

A typical example of the implications of this confusion is the problem of adjuvants. The understanding of these peculiar reactivity pathways may profit from a careful use of the two notions of immunological specificity. Thus while the reaction to the antigen plus adjuvant may be defined as specific, this specificity must not necessarily be reducible to the specificity of the single antigen. Instead, the antigenic specificity of the antigen plus adjuvant may be considered unique.

Thus the CST may indeed still be a valid account of the way a specific antigen selects specific cells. It fails to explain, however, how this antigenic event brings about a specific immune reaction.

1. Silverstein, A.M. *Nat. Immunol.* **3**, 793–796 (2002).
2. Burnet, F.M. in *The Clonal Selection Theory of Acquired Immunity*, 32 (Cambridge University Press, Cambridge, 1959).
3. Anderson, C.C. & Matzinger, P. *Semin. Immunol.* **12**, 231–238 (2000).
4. Cohen, I.J. *Autoimmunity* **16**, 337–340 (2001).