

# Self/Nonsel—Immune Recognition and Signaling

## A new journal tackles a problem at the center of immunological science

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Launching a new journal is always a risky affair. It reminds one of the scene from *King Henry IV* in which Glendower says, “I can call spirits from the vasty deep” and Hotspur replies, “But will they come when you do call for them?” In this instance, I believe that the editors can have confidence that readers will come.

Self/nonself discrimination is at the very core of immunology. It can be argued that with the appearance of the two different adaptive immune systems in the agnathans and the jawed vertebrates some 500 mya, solving the self/nonself problem became perhaps the most critical driving force in the evolution of the modern immune system. Indeed, it is a reasonable hypothesis that the need to limit self-reactivity was of sufficient importance that it drove the evolution of the immune system very close to the “one cell—one antibody” (or one T cell receptor, TCR) ideal that was at the heart of the revolutionary proposals by David Talmage<sup>1</sup> and MacFarlane Burnet<sup>2</sup> just over 50 years ago that set immunology on its current course, which legions of scientists have pursued without waver.

Self-reactivity of immune receptors is by no means rare. It has been shown that the majority of the most primitive B cells express self-reactivity and these self-reactive cells are gradually replaced or purged as the B cell passes through its various stages of development.<sup>3</sup> Indeed, the frequency of mature B cells that have “edited”  $\kappa$  chains is estimated to be in excess of 25%.<sup>4</sup> If we add an unknown proportion of cells that were eliminated because they failed editing, self-reactivity among the primary B cell repertoire could easily have been a property of the majority of B cells.

The T cell walks an even more perilous path. It has adopted self-reactivity as a requirement for passing into the selected repertoire; the process of thymic positive selection is based on the TCR of the developing T cell being able to recognize some self-peptide/MHC complex (pMHC) with a sufficient affinity to rescue it from the apoptosis of neglect. While the highest affinity cells are then purged, it may still be asked why the system takes such a risk. The two classes of answers are that T cells that recognize any particular pMHC are more likely to recognize a pMHC containing a foreign peptide than would a randomly generated TCR and thus it is advantageous to select self-reactive cells. Indeed, Kappler and Marrack and their colleagues<sup>5</sup> and Garcia et al.<sup>6</sup> have provided data that clearly supports the argument that TCR  $\alpha$  and  $\beta$  chains have undergone an evolutionary selection process to make them more likely to generate TCRs with pMHC reactivity. The other argument is that T cell survival in the periphery requires signals derived from periodic TCR interaction with pMHC and there is no point in selecting cells whose receptors lack this self-reactivity since they will fail to survive. Grossman and I argued that such self-reactivity would also provide a self-referential marker allowing T cells to “tune” their reactivity and thus to assure appropriate discrimination between self- and foreign antigens.<sup>7</sup> Indeed, both ideas may be correct and may have both played a role in evolutionary selection of self-recognition as an intimate element of repertoire generation. Either way, it places virtually the whole of the “T cellome” in the theoretically dangerous position of being self-reactive.

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Another way to judge the importance of avoiding or controlling self-reactivity is to list the number of distinct mechanisms that have developed to control the process. Of course, there is negative selection in the thymus weeding out the potential bad actors; this is reinforced by the remarkable capacity of the thymus, through the agency of AIRE,<sup>8</sup> to transcribe a multiplicity of genes that for all other purposes are regarded as specific to an individual peripheral tissue, insulin being an obvious example.

In the periphery, there is evidence that pMHC on resting DC may either eliminate or induce anergy upon interaction with T cells bearing cognate TCRs.<sup>9</sup> The general phenomenon of clonal anergy provides a mechanism to silence potentially dangerous peripheral T cells. And, of course, the development of regulatory T cells, themselves selected to be self-reactive, provides yet another powerful mechanism to limit the action of self-reactive conventional T cells.

Equally remarkable is the process through which TCRs distinguish ligands and transduce signals. The equilibrium constants of TCRs for pMHC complexes seem remarkably low when compared with the  $K_a$ 's of  $10^{10} M^{-1}$  or greater often observed for affinity-matured antibody. And yet despite low affinity and, presumably, a very limited number of pMHC/TCR contacts, T cells make a robust response and clearly distinguish agonist, partial agonist and antagonist ligands. They do this even though the differences in the affinity/avidity of binding of these

ligands to their cognate TCR are relatively modest.<sup>10</sup> The signal amplification mechanisms the T cell uses for this purpose and its decision-making strategies, sorting stimulatory and inhibitory ligands, are among the most exciting and challenging problems in receptor biology and cell signaling.

Furthermore, the process of antigen-recognition/reactivity goes on in a remarkable structure, the immunological synapse, in which, through the dynamic grouping and reassortment of cell surface and bridging molecules, the decisions about how to react are played out. When Bob Seder and I suggested the concept of a synapse, it was for the relatively simple function of concentrating cytokines secreted by one cell and acting on its partner.<sup>11</sup> The complexity of the synapse and its central role in immune discrimination represents a far more sophisticated recognition machine than we had envisaged.

Not only do we need a more detailed understanding of these processes, we can confidently anticipate entirely new developments that may completely alter our view of the processes of recognition and response. It is also important to remind ourselves that research in immunology is not only a search to know how the system works but to use this information for the development of new therapies for autoimmune, autoinflammatory and immunodeficiency diseases as well as for the design of new generations of preventive vaccines that can deal with some of the still uncontrolled scourges of mankind and of effective therapeutic vaccines

for cancer, chronic infection and even for other applications.

Clearly, these subjects and a set of related problems illustrated by the contents of this first issue of *Self/Nonsel—Immune Recognition and Signaling* should provide the editors with more than enough exciting articles to fill their pages—printed and electronic. More importantly, by providing a venue specializing in this subject, the journal should fulfill the true function of scientific publications, the advancement of knowledge and its translation into applications that can benefit humankind.

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