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Two unresolved problems facing models of the Self–Nonself discrimination

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HIGHLIGHTS

- Priming effector T-helpers.
- Associative Recognition of Antigen.
- Tolerance versus unresponsiveness.

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ABSTRACT

Although the Associative (linked) Recognition of Antigen (ARA) model for a Self (S)–Nonself (NS) discrimination, now over 50 years old, is built on a solid conceptual and experimental base, two unsettled questions remain.

1. How is ARA accomplished for T–T interactions?
2. How does the immune system get started?

In examining these questions, unanticipated aspects of the ARA Model itself had to be reconsidered. This essay spells out these problems and suggests possible solutions.

1. Introduction

The subject of this essay arises from the Associative (linked) Recognition of Antigen (ARA) model (Cohn, 2005b, 2007, 2012b), which is an updated version of the 1970 Two Signal model (Bretscher and Cohn, 1970). Unfortunately, there still exist two problems posed by this model that are under debate. These are:

1. The origin of priming effector T-helpers (eTh).
2. The parameters of T–T interactions mediated via antigen-presenting cells (APC).

The adaptive immune system must be able to respond to ligands with which it has had no prior experience. In order to do this, it generates a large repertoire that is random with respect to the property Self (S) or Nonself (NS). In order to be functional this repertoire must be sorted by purging anti-S leaving as a residue anti-NS. As this process must operate at the level of cells that express as receptors either anti-S or anti-NS, each newborn antigen-responsive cell upon encountering a ligand, S or NS, is faced with a decision between inactivation and activation. This decision is referred to as the S–NS discrimination. The ARA ("Two Signal") model under analysis here, while supported by extensive experimental evidence, is founded on a simple logic that is its strength, namely that on encountering a ligand, a decision between two pathways requires two signals. The origin of these two signals is central and as we will see, in the end, must be answered by a solution to Problem 1.

The receptors, TCR and BCR, recognize as ligands, epitopes, not antigens, which are collections of linked epitopes. The ridding and biodestructive effector output of the immune system operates on antigens, not epitopes. As this response must be independent and coherent for each antigen, there must be a way that the immune system knows which epitopes are linked on that antigen and whether that antigen is to be treated as S or NS. In other words, there must be a relationship between what is recognized and what is ridded. Thus, the necessity for a solution to Problem 2 is posed.

In order to place these two questions in perspective, the frameworks provided by both the ARA model (Cohn, 2012b) and the

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Stepwise Model (Cohn, 2014) of T-cell polyreactivity, must be understood. They will be summarized where appropriate.

2. The ARA or linked recognition model

Referring to Fig. 1, under the ARA model (Cohn, 2015a), the naïve antigen-responsive cells (initial state or i-cells), iT and iB, require two signals to be activated (the galvanized or g-state), the first step on the pathway to effectors. Signal 1 delivered via the receptor, TCR or BCR, when it binds its ligand, puts the i-cell on an inactivation pathway, the first step of which is the a-state (anticipatory, aT/B). The continued delivery of Signal 1 results in inactivation. There is a window before irreversibility sets in when the delivery of a second signal to an a-state cell by an effector T-helper (eTh) results in activation. The requirement of Signals1+2 for activation guarantees that no cell can be activated that, in principle, could not have been inactivated. This dual requirement acts as insurance against autoimmunity. The differentiation of g-state cells to effectors (eT/B) is controlled by processes that were germline selected, whereas the S–NS discrimination is controlled by somatic selection.

As Signals 1+2 are also required for the activation of the aTh itself, a problem arises as to the origin of the initial or primer eTh that are required for the aTh to gTh transition necessary for differentiation to eTh. The eTh are also required to activate all other iT and iB cells.

3. The primer problem

The iTh are born in thymus where they undergo a first step of Signal 1 driven negative selection. The iTh-cells that leave the thymus are of two categories, anti-Nonself (NS) and anti-Self (S). The ligand for the latter is uniquely peripheral S (not expressed in thymus). Thus two steady state populations are exported to the periphery. The iTh anti-NS that do not encounter NS, simply turnover. The steady state level of these peripheralized iTh anti-NS is referred to as the 'immune boundary', whereas that of the iTh anti-S is referred to as the 'autoimmune boundary' (Cohn and Langman, 1990). These latter encounter peripheral S, which puts them on a Signal 1-driven inactivation pathway (i.e., the anticipatory or a-state). The aTh anti-NS require eTh anti-NS to be activated. What is the origin of the primer eTh anti-NS?

4. Two proposed solutions to the primer problem

Solution 1: in order to face this question, we proposed an antigen-independent pathway, iTh to eTh (Cohn, 1983, 1992; Cohn et al., 2002; Langman et al., 2003) initiated before the iTh encounter NS and continued throughout life. Consequently, for the iTh in the immune boundary, there is a defined rate, steady state, stochastic conversion to eTh. The result is an immune boundary that is largely iTh with a steady state fraction that is primer eTh. The iTh and the primer eTh in the immune boundary cover the same anti-NS repertoire but at different multiplicities of recognition.

What is true of the immune boundary must also apply to the autoimmune boundary. In order to deal with this potential problem of autoimmunity, we took advantage of the fact that all i-cells in this boundary are engaged by peripheral S and receiving Signal 1 (i.e., are in the aTh-state). The postulate that Signal 1 inhibits the antigen-independent stochastic conversion of aTh to eTh, results in an autoimmune boundary that is lacking in primer eTh anti-S.

This postulate is essential because some iTh anti-S are derived in the periphery from iTh anti-NS in the immune boundary by receptor revision (discussed in Cohn (2014)). These peripherally derived iTh anti-S are simply melded into the autoimmune boundary where they are, in large measure, blocked from undergoing the primer pathway.

Solution 2: Bretscher (2014, 1999) has proposed an antigen-dependent model for the origin of primer eTh, which is important because it balances and clarifies thinking. He bases his proposal on the well-established fact that the B-cell processes antigen and can serve as an antigen-presenting cell for Class II MHC-restricted T-cell responses (Avalos and Ploegh, 2014).

The elements of his proposal are:

1. The primer eTh-cells only appear during a neonatal window when iTh-cells are born with a minimal effector activity, insufficient to activate aTh-cells but sufficient to cooperate with each other to yield primer eTh-cells that can activate aTh.
2. In order to deal with the Self–Nonself discrimination, the cooperative interaction between them is mediated solely via BCR-uptake of antigen and subsequent processing. As B-cells have undergone the S–NS discrimination, the BCR-uptake is assumed to provide a ligand display that is, in essence, uniquely NS. This, in addition, permits an interaction in ARA if the B-cell presents BCR-uptake antigen uniquely.

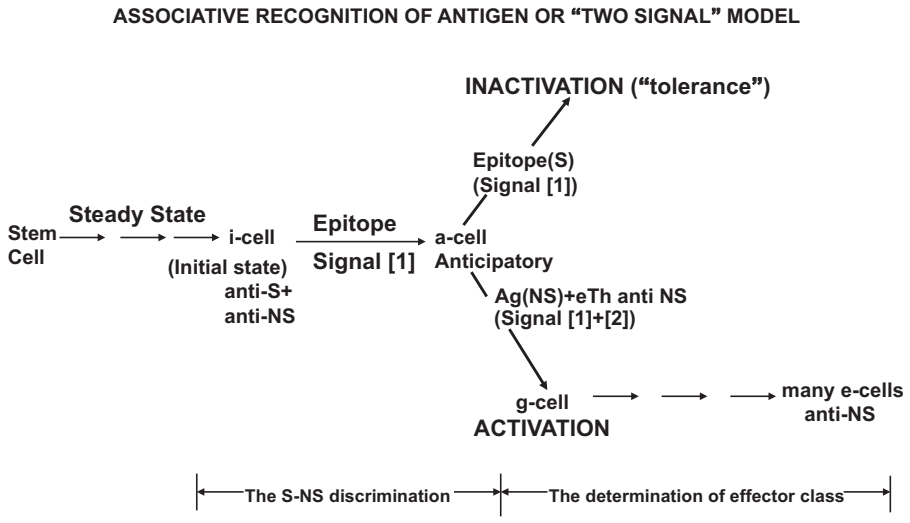

Fig. 1. The pathway of induction of antigen-responsive cells to effectors (see text).