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DISCUSSION FORUM

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On the nature of signal 1 delivered to lymphocytes: A critical response to some considerations put forward in support of the quantum model of T cell activation

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Abstract

The original Two Signal Model of lymphocyte activation stated that antigen-dependent lymphocyte cooperation is required for lymphocyte activation, whereas a single or a few antigen-specific lymphocytes can be inactivated by antigen. A virtue of this model is its ability to account for peripheral tolerance. Both the activation and inactivation of lymphocytes were envisaged to require the lymphocytes' antigen-specific receptors to interact with antigen, leading to signal 1. We consider here the proposition that the sensitivity to antigen concentration for the generation of signal 1, to support both differentiation processes, is the same. This situation optimizes the reliability of peripheral tolerance and minimizes the effects of lymphocyte inactivation in decreasing the diversity of the lymphocytes. We consider the broader implications of this Principle of Parsimonious Sensitivity in regulating the activity of lymphocytes.

KEYWORDS

lymphocyte differentiation, lymphocyte sensitivity to antigen, signal 1 for lymphocytes

1 | PROLOGUE

This paper is written in response to the one by MH Manjili and SH Manjili, entitled 'The Quantum Model of T-cell activation: Revisiting immune response theories'.[1] An assessment of the plausibility of any new model involves an assessment of alternative models that currently exist, as well as an assessment of the novel grounds on which the new model is proposed. Manjili and Manjili, in proposing their new model, describe and argue against an alternative model that I and my colleagues have proposed for how naive CD4 T cells are activated and inactivated.[2–4] I suggest their comments do not reflect a correct appreciation of this model, as outlined below. I therefore feel obliged to respond. I do not address here their discussion of other alternative and current models, nor the novel grounds on which their new model is based.

2 | THE ORIGINAL TWO SIGNAL MODEL OF LYMPHOCYTE ACTIVATION

I briefly outline my current view to provide context. This is necessary as this model,[2] though unchanged in essence for more than 50 years, has been given different and more detailed formulations[3,4] as more information at the level of the system, and at the cellular and molecular levels, has become available.

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We proposed the original Two Signal Model in 1970 to explain how antigens may activate and inactivate mature lymphocytes to result in what we now recognize as peripheral tolerance. It had been previously proposed that tolerance to self-antigens is a consequence of their early presence in the developmental *history* of an individual, before lymphocytes are generated, and their continuous presence thereafter.[5,6] I refer to this proposition as The Historical Postulate.[4] Our proposal was formulated to be in accord with this postulate. We proposed that the activation of lymphocytes requires their antigen-mediated cooperation, whereas antigens interacting with a single or with only a few lymphocytes would inactivate them. We argued that these propositions provide an explanation of (peripheral) tolerance consistent with The Historical Postulate. Lymphocytes specific for peripheral self-antigens are inactivated, as generated, one or a few at a time, by virtue of the continuous presence of peripheral self-antigens. Lymphocytes specific for a foreign antigen accumulate in its absence. When the antigen impacts the immune system, it can mediate the lymphocyte cooperation that leads to lymphocyte activation and an immune response.[2]

We proposed that both the activation and inactivation of a lymphocyte require antigen to interact with the lymphocyte's antigen-specific receptors, resulting in signal 1. A target lymphocyte, to be activated, must also receive signal 2, whose delivery is initiated when the cooperating 'helper lymphocyte' recognizes antigen.[2] We refer to this model as The Two Signal Model for lymphocyte activation.

3 | SUPPORT FOR THE ORIGINAL TWO SIGNAL MODEL IN THE CONTEXT OF B CELLS AND CD8 T CELLS

Observations reported over some decades, following its proposal, supported the original Two Signal Model in the context of B cells and CD8 T cells. It became recognized that the activation of most B and CD8 T cells requires activated T helper cells, and that antigen can inactivate these lymphocytes in the absence of such help, as I have recently reviewed.[4] These generalizations naturally led to a recognition of the pivotal importance of what determines whether antigen activates or inactivates CD4 T cells.

4 | CURRENT MODELS FOR CD4 T-CELL ACTIVATION

The most widely accepted mechanism for what controls whether antigen activates or inactivates CD4 T cells is described by the DAMP/PAMP model.[7,8] According to this model, the activation of CD4 T cells requires the generation of a DAMP or PAMP signal; in the absence of such a signal, antigen inactivates the CD4 T cell. I have recently argued that this model is implausible and have explained why I still favour a modern formulation of our 1970 Two Signal Model of lymphocyte activation for the activation of CD4 T cells.[3,4] It is this Two Signal Model that Manjili and Manjili criticize. I argue below that addressing their criticisms brings forth central biological issues.

5 | THE REFORMULATION OF THE TWO SIGNAL MODEL IN THE FACE OF NEW FINDINGS

The 1970 model for lymphocyte activation has been challenged by new findings over the decades. New findings must either be naturally accommodated by a contemporary model or they may be problematic within its context. In the latter case, the model must be either abandoned or lead to a reformulation that is both plausible and retains the attractive features of the original. The most attractive feature of the original Two Signal Model was its ability to account for peripheral tolerance. There is also little doubt that major challenges arose from the discovery that T cells are self-MHC restricted in their recognition of antigen. One example illustrates the problem this finding posed for the original Two Signal Model and how this challenge was resolved. It was originally envisaged that the antigen-mediated interaction between B cells and activated T helper cells involved the antigen-specific receptors of both types of lymphocytes binding the same antigen molecules, thus ensuring the specificity of the short-range help delivered.[2] This model had to be abandoned once it was clear that the T-cell receptor did not bind native antigen. Lanzavecchia established the MHC-restricted model of the B cell–T helper cell collaboration.[9] According to this model, antigen is endocytosed by the B cell via its antigen-specific receptors, processed and presented by the B cell. Activated T-helper cells, specific for the nominal antigen, bind to the presented antigen and deliver signal 2. This reformulated model explains how T-cell help is delivered in an antigen-specific fashion, a critical feature of this and the original model.

The contemporary model for CD4 T-cell activation that I favour requires a target CD4 T cell to interact with an antigen-specific B cell, specific for the nominal antigen, that is or has been activated by a CD4 T cell specific for the same nominal antigen.[3,4] This reformulated Two Signal Model of lymphocyte activation explains peripheral tolerance at the level of CD4 T cells in a similar manner as the original model, as lymphocyte activation, but not inactivation, again requires lymphocyte cooperation.

This manuscript focuses on the nature of signal 1. However, one reviewer appropriately raised issues concerning signal 2 in the context of the contemporary model of CD4 T-cell activation that I favour and have outlined in the previous paragraph. If such issues are not addressed, the value of this discussion concerning the nature of signal 1 may be legitimately questioned. I therefore feel bound to at least indicate my thoughts on the issues raised. However, a full discussion would likely lead to successive rounds of spiralling interactions that would lead to a loss of focus on signal 1. I refer to papers where such issues are more fully discussed.

6 | ISSUES CONCERNING SIGNAL 2 IN THE MODEL I FAVOUR FOR CD4 T-CELL ACTIVATION

Our original 1970 model for the activation and inactivation of lymphocytes posited that antigen-mediated lymphocyte activation is required to activate all lymphocytes.[2] I further envisaged that the *optimal* activation of naive lymphocytes requires their antigen-mediated interaction with *activated* lymphocytes[10] Thus, optimal activation of naive B cells is envisaged to require activated CD4 T cells, and the optimal activation of naive CD4 T cells is envisaged to require activated B cells.[3] This scenario inevitably leads to the *priming problem*: what is the origin of the first activated lymphocytes[10]? A solution to this problem must incorporate the idea that the generation of these 'initiating' activated lymphocytes must also involve antigen-mediated lymphocyte cooperation *if* the model is still to provide an explanation of peripheral tolerance.[3,10] This is what I have proposed.[3] An alternative possibility was raised by the reviewer. He/she suggested a PAMP or DAMP signal could initiate the inductive process by facilitating the antigen-dependent activation of single lymphocytes, say a B cell. This proposal certainly provides a potential solution to the priming problem. However, given the ubiquity of PAMPs in the context of skin, gut and other flora, and of danger, when, for example, small children fall and bruise themselves, I think this possibility would likely result in the frequent activation of autoreactive lymphocytes. Indeed, if this possibility commonly obtained when there were few antigen-specific CD4 T cells and other antigen-specific lymphocytes, it would be difficult to demonstrate under diverse conditions a requirement for cooperation among CD4 T cells in their activation, as has been found.[11]

This same reviewer cites an example where the activation of CD8 T cells appears to be T helper cell independent[12] and is therefore in conflict with the model I espouse. This reference calls to mind a very interesting study in which the requirements for the in vivo activation of CD8 T cells were analysed. It was found that a certain number of CD8 T cells could be activated by antigen, but a lower number could not be activated unless CD4 T cells were additionally present.[13] These and other observations show that the activation of CD8 T cells can occur through CD8 T-cell cooperation if present in sufficient numbers.[11] I consider these findings to support our original Two Signal Model.[2]

7 | T-CELL DEVELOPMENT AND HOMEOSTASIS

A second issue arises from the nature of the specificity of T cells. It became clear that developing T cells die unless rescued when their receptors interact in some way with self-peptide/MHC complexes in the thymus, a process referred to as positive selection.[14,15] In addition, T cells can be negatively selected in the thymus when their receptors interact with nominal antigen[15,16] in a manner foretold by Lederberg.[6] Thus, TcR-mediated signals can lead developing T cells to have very different fates: their elimination or being given the 'kiss of life', an inherited property. What controls which fate occurs? Much evidence favours the idea that a stronger TcR-mediated interaction results in elimination and a weaker interaction in positive selection.[15] However, there does not appear to be a consensus on what stronger and weaker interactions means at the molecular level.[17] This is an issue I address below.

Other studies have shown that the survival of T cells in the periphery requires their TcR to competitively bind self-peptide/MHC complexes, an interaction leading to tonic signalling.[18] Tonic signalling can lead to longer survival or, if sufficiently strong, to proliferation of the T cell. Thus, mature CD4 T cells can receive a TcR-mediated signal 1 and a TcR-mediated tonic signal. How and whether these signals differ are significant questions that we address below. These issues are pertinent to those raised by the Manjili and Manjili paper,[1] as will become apparent.

8 | MODELS FOR THE 'STRENGTH' OF THE T-CELL INTERACTION WITH PRESENTED ANTIGEN

There are two kinds of model for describing TcR signal strength. Both models recognize the fact that TcRs of a T cell interact with many distinct peptide/MHC

complexes on a cell with which the T cell interacts, whether this is a target cell or an antigen-presenting cell (APC).[19,20] These two distinct models are not always explicitly described. The Avidity Model posits that the aggregate affinity of the TcRs with their ligands must achieve a threshold for signal 1 to be generated. The TcR Affinity Model posits that the affinity of the TcRs for at least *one* peptide/MHC complex on the target cell must be greater than a certain threshold affinity if the T cell is to receive signal 1.[17,21] Without such a ligand, signal 1 cannot be generated. Positive selection in the thymus, or tonic signalling in the periphery, does not need to satisfy this requirement, as discussed below.

9 | THE TcR AFFINITY MODEL

We have argued elsewhere at length for the TcR Affinity Model.[17] We briefly encapsulate the most salient considerations.

9.1 | The principle of parsimonious sensitivity

According to the Two Signal Model of lymphocyte activation, signal 1 is required for both the activation and inactivation of lymphocytes. This feature seems important in not only controlling the specificity of these processes but is likely also important in ensuring their appropriate sensitivity to antigen. Consider the minimum level of antigen required to activate and to inactivate a naive B cell, as reflected in the generation of signal 1. If the minimal level to activate a B cell was lower than the minimal level to inactivate the B cell, peripheral tolerance would be at least partially undermined; there would be levels of antigen that could activate but could not inactivate the B cell. It seems essential, to optimize the efficiency of peripheral tolerance at the B cell level, that the sensitivity of B cells for inactivation should be equal to or greater than for activation. Consider also the case where memory B cells are generated. Memory responses can usually be elicited with lower doses of antigen than primary responses. For example, the induction of a secondary antibody response can be elicited with much lower doses of antigen than those required to generate primary responses.[22] Does this mean that the level of antigen required to generate signal 1 in memory B cells is lower than that required to generate signal 1 for the activation and inactivation of the naive B cell from which the memory B cell is generated? If this were the case, memory B cells could in principle be generated by a cross-reacting foreign antigen and then be activated by a level of the peripheral self-antigen that could not have inactivated the naive B cell from which the memory B cells were generated. The mechanism of peripheral tolerance at the level of B cells would be again partially undermined. Such considerations lead to our suggestion that the sensitivity of different processes to the level of antigen, via the generation of signal 1, should be parsimonious with achieving physiological needs,[17] in this case reliable peripheral tolerance. In addition, if the sensitivity of the generation of signal 1 for inactivation was greater than that for activation, B cells would be deleted by a peripheral self-antigen that could not be activated by the peripheral self-antigen. This would reduce the diversity of the B-cell repertoire without any obvious physiological advantage. We suggest, based on these considerations, that the sensitivity for the generation of signal 1, for the activation and for the inactivation of B cells, should be the same. We discuss below how this Principle of Parsimonious Sensitivity may apply to antigen-dependent differentiation processes of T cells. We add, for clarification, that the lower antigen dose required to elicit secondary, in contrast to primary, responses likely reflects the greater frequency of lymphocytes specific for the antigen in the memory state. This greater frequency allows lower levels of antigen to mediate the lymphocyte cooperation required to generate immune responses, and not a different sensitivity of memory and naive B cells to the level of antigen required to generate signal 1.

9.2 | The sensitivity and specificity of T cells

It is well recognized that virus-specific CTL lyse appropriate virally infected target cells when only a very small fraction of the class I MHC molecules present the viral, 'agonist' peptide.[19,20] This represents impressive sensitivity. These CTL do not lyse cells genetically identical to the target cell but not infected by the virus. This represents remarkable specificity. How is this combination of sensitivity and specificity achieved?

Clues have come from studying the requirements for T cells to form synapses with targets that present the agonist peptide. Studies show that only a small fraction of the TcR involved in a synapse bind the agonist peptide/MHC restriction element; the other TcR involved bind to other peptide/MHC complexes. These peptides are, for the most part, peptides derived from self-antigens and are called 'endogenous peptides'. Mark Davis and colleagues, for example, estimated that when a CD4 T cell forms a synapse with an APC presenting the antigen, 10–24 of the TcR bind to the agonist peptide/MHC complex and about 6000 TcR bind to endogenous peptide/MHC complexes.[19,20] In addition, it is also clear that T cells interact

in a transient fashion with target cells bearing the restriction element but not presenting the agonist peptide, a process referred to as 'kinapse' formation.[23] Kinapse formation does not occur between the T cell and a target cell not bearing the MHC-restriction element. Those exposed to ideas on how crystals form cannot but be impressed by this picture of kinapse formation. It is recognized that the growth of crystals is easy to envisage, as an incoming molecule has several partners with which to interact. The initiation of crystal formation is problematical, as it would seem to require just two molecules that weakly interact in what would be a highly transient manner. Special circumstances are known to be often required to 'nucleate' crystal formation.[24] It seems kinapse formation, leading to synapse formation in the presence of agonist peptide/MHC complexes, is a nucleation event. These processes allow us to begin to understand how the sensitivity and specificity of T cells are achieved.

9.3 | A proposal for how the TcR Affinity Model might be realized at the molecular level

There are several different mechanisms by which a signal could be initiated upon the TcR binding to its ligand. We have discussed elsewhere why several of these are intrinsically implausible.[25] I further discuss below the TcR Avidity Model often implicitly assumed in the literature but usually not explicitly stated, for how the generation of signal 1 is *initiated*. I address below why the TcR Avidity Model is so significant in discussions as to how signal 1 is generated, and why I find the TcR Avidity Model implausible. Indeed, as I shall explain below, it is this possibility that Manjili and Manjili tacitly assume that leads to what I consider are their invalid criticisms of the original Two Signal Model.

A more general question arises in terms of the TcR Affinity Model. Can binding by TcRs to a few ligands, with a greater affinity than an affinity threshold, uniquely generate a signal that is not generated by multiple TcR interactions, all with an affinity for their ligands below the affinity threshold? A plausible mechanism would be able to account for the difference between kinapse and synapse formation.

McKeithan proposed almost 30 years ago a molecular mechanism by which the effects on a T cell of its TcR binding a ligand could sharply depend on the half-life of the TcR/ligand complex.[21] The paper describing this 'Kinetic Proofreading Model' is rather mathematical. I attempt to make it plausible employing only words. Suppose TcR engagement results in a series of rapidly reversible steps, until a certain number occurs, when an *irreversible event* takes place. These reversible steps could involve protein phosphorylation and be rapidly reversed by phosphatases. The requirement for multiple steps, each characterized by time constants, means the probability of the irreversible event occurring is sharply dependent on the half-life of the TcR /ligand complex. A contemporary expression of McKeithan's idea is that the mean half-life of the TcR-agonist/MHC complex is longer than that of the TcR-endogenous peptide/MHC complexes.[17] This most probably reflects a closer fit between the TcR and agonist peptide/MHC complex than with endogenous peptide/MHC complexes. This model means that the specificity of a T cell, *in generating this irreversible event*, is virtually an intrinsic property of the cell, defined by its TcR.[17,21] The model must also mean that, at the critical moment of 'nucleation', the TcRs are not greatly influencing each other's binding to their ligand. This contrasts with the Avidity Model, according to which a multitude of lower affinity TcR/ligand interactions can have the same effect as a few higher affinity interactions. The TcR affinity model is a digital, or an 'on or off' model.

9.4 | The principle of parsimonious sensitivity in the context of T cells

It seems plausible that similar reasons govern the sensitivity of peripheral T cells for the generation of signal 1, in its role in the inactivation and in the activation of the T cell, as in the inactivation and activation of B cells: sensitivity for inactivation should be equal to that for activation in order to optimize peripheral tolerance and to minimize the impact of T-cell deletion on the diversity of the T-cell repertoire. In addition, it makes sense that the antigen-dependent signal required to trigger cytotoxicity of effector CD8 T cell is equivalent to signal 1. If lower TcR affinities could trigger cytotoxicity, CD8 T cells could attack targets that could not inactivate the precursor CD8 T cell from which they were generated; if higher affinities were required, some effector CD8 CTL would not be able to attack target cells that could induce their generation.[17] This does not make physiological sense. The TcR signalling sensitivity of naive, effector and memory CD8 T cells, to antigen, as assessed by early events, appears to be indistinguishable,[26] supporting the Principle of Parsimonious Sensitivity.[17] One reviewer questioned whether the ability to elicit secondary immune responses by lower antigen levels than primary responses was solely due to the higher frequency of memory than of naive T cells. Naive and memory T cells are clearly also qualitatively different.[27] I suggest the considerations underlying the Principle of Parsimonious Sensitivity make this proposition, as to why lower levels of antigen can stimulate secondary, in contrast to

primary, responses plausible, without denying that naive and memory lymphocytes are qualitatively different. For example, naive and memory B cells are obviously different in their commitment as to what class/subclass of antibody to produce, if activated. It is important to distinguish what controls the level of antigen required to initiate the formation of signal 1 and the consequences of this initiation. As already indicated, the TcR signalling sensitivity of naive, effector and memory CD8 T cells, for early events appears to be indistinguishable.[26]

9.5 | The reality and role of agonistic and endogenous peptides

Cells from CD4 T-cell clones, raised by immunization with an antigen, can be stimulated by the antigen to proliferate in the presence of APC. The antigen can sometimes be replaced, in this assay, by a peptide derived from the antigen, in which case the peptide is referred to as an agonist peptide.

Stimulation by agonist peptides causes a very rapid influx of Ca++ into sensitized CD4 T cells in the presence of APC. Mark Davis and colleagues demonstrated that covalent *dimers* of the agonist peptide/MHC complex could also trigger a Ca++ influx *in the absence of APC*.[15,16] Previous studies had shown that agonist peptide/MHC complexes were a small minority of peptide/MHC complexes taking part in synapse formation, as discussed above. How might these findings be integrated into a model for the generation of signal 1?

The Davis group showed, using this Ca++ influx assay, that there were endogenous peptides for cells of a given CD4 T-cell clone that had four characteristics. First, their sole presence could not cause a Ca++ influx into the sensitized T cells in the presence of APC, nor, for that matter, the proliferation of these T cells. Secondly, endogenous peptide/MHC covalent dimers could *not* trigger such an influx in the absence of APC. Thirdly, a level of the agonist peptide was chosen that was somewhat below that required to cause a Ca++ influx in the presence of APC; it was shown that the additional presence of the endogenous peptide could, under such circumstances, result in an influx. Lastly, a covalent heterodimer of an agonistic peptide/MHC complex with an endogenous peptide/MHC complex *could* cause an influx in the absence of APC. I encapsulate these findings. Agonist peptide/MHC dimers can cause an influx in contrast to endogenous peptide/MHC dimers. Heterodimers of an agonist peptide/MHC complex with an endogenous peptide/MHC complex could cause an influx. These, and further observations, are the basis for the Heterodimer Model for the generation of signal 1 by T cells.[17,19,20]

9.6 | Encapsulation of a contemporary formulation of the original Two Signal Model as it pertains to the activation of CD4 T cells

The delineation of positive selection of T cells in the thymus and of tonic signalling in the periphery demonstrates that T cells can and do receive signals, via their TcR, other than 'signal 1', as originally conceived.[2] These circumstances lead to the question of whether these signals are intrinsically different in a qualitative sense, as envisaged in the TcR Affinity Model, or only in a quantitative sense, as envisaged in the Avidity Model. We have argued that physiological considerations, as encapsulated in the Principle of Parsimonious Sensitivity, favour the TcR Affinity Model.[17] The specificity of a T cell does not depend on the level of different ligands its TcR interacts with, but requires a sufficient level of a ligand with which its TcR interacts well. Specificity is intrinsic to a T cell.

9.7 | The criticism of the Quorum Model for CD4 T-cell activation put forward by Manjili and Manjili

1. Manjili and Manjili state that "The quorum model suggests that precursor T cells recognizing (peripheral) self-antigens are at a low frequency due to deletion caused by persistent antigen exposure. Conversely, those recognizing nonself-antigens accumulate because of the absence of foreign antigens, allowing them to establish a quorum for activation. However, the concept of T-cell precursor accumulation to form a quorum for nonself-antigens contradicts thymic positive selection based on which all precursor T cells not recognizing self-pMHC were deleted in the cortex, and thus, all of them in the periphery are self-reactive".[1]

These considerations expressed by Manjili and Manjili do not explicitly make a distinction between the affinity and avidity models for the generation of signal 1 by T cells, but only make sense in terms of the Avidity Model. A difficulty of the view stated is evident. The authors state that all T cells in the periphery are self-reactive, without carefully explaining what is meant by 'self-reactivity'. As I understand their description, any response against a foreign antigen would result in activated T cells with self-reactivity and, therefore, in autoreactivity and the possibility of autoimmunity. How could there be a mechanism of peripheral self-tolerance in this case? The difficulties raised by their proposal also reflect difficulties arising from other discussions in the literature. It is known that lymphopenia can predispose to

autoimmunity.[28] One explanation for this is that a decrease in lymphocyte numbers increases the level of tonic signalling due to a reduction in lymphocyte competition for such signals. The increased TcR signalling of *all* lymphocytes may lead to the generation of signal 1 for some and allow their activation.[29] This proposal is clearly cast within the context of the Avidity Model. I favour an explanation based on the TcR Affinity Model. According to this possibility, scarce lymphocytes, recent thymus emigrants, and those specific for peripheral self-antigens multiply more than usual in the lymphopenic environment, due to increased tonic signalling or decreased competition for limiting cytokines, and so some reach quorum, allowing the peripheral self-antigen to activate rather than inactivate their corresponding cells.[17] The view expressed here, favouring the TcR Affinity Model, means the specificity of T cells, as defined by the circumstances leading to the generation of signal 1, is much more restricted than in the Avidity Model. In a real sense, the specificity of T cells is an intrinsic feature of the T cell defined by its TcR. A different view is that the antigen-dependent signal, required to result in diverse processes of differentiation, can be different and indeed determines, to a large measure, which of the many different differentiation pathways occur.[30] It is not possible to reconcile such ideas with the Principle of Parsimonious Sensitivity.

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DATA AVAILABILITY STATEMENT

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