Chapter 2
A Review of Mathematical Models for T Cell Receptor Triggering and Antigen Discrimination

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Abstract Theoretical studies of T cell receptor signalling and T cell activation have become a well-known part of immunology and the models described in this chapter provide a good basis for future studies. Nonetheless it is crucial that, over the next few years, modelers seek to expand the scope of their efforts and provide a more comprehensive, predictive and multifaceted approach to T cell receptor signalling. Currently available models usually provide qualitative results and cannot be confidently parameterized. To obtain more precise and predictive models will be difficult but is plausible given improvements in quantitative experimental techniques and their quick adoption by experimentalists.

Introduction

The central event in the generation of adaptive immune responses is the binding of T cell receptors (TCR) to peptide-major-histocompatibility-complex (pMHC) molecules at the T cell-antigen-presenting-cell (APC) interface. It is important to understand how features of the molecular interaction determine the T cell response (potentially leading to a large-scale immune response in the body). This molecular recognition event is remarkably sensitive (as few as 5–10 antigenic pMHC can cause a robust cellular response) but also specific (a single amino-acid change in the presented peptide can dramatically alter the cellular response). Furthermore, the sensitivity to very small quantities of antigenic pMHC occurs in the context of a vast number of chemically similar but functionally irrelevant pMHC. These pMHC are derived from self proteins and are thought to weakly interact with TCR at the T cell-APC contact interface. Understanding the specificity and sensitivity of pMHC recognition in the presence of many self pMHC by T cells is further complicated by

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the fact that we do not understand how pMHC binding to TCR transmits a signal across the plasma membrane, a process termed TCR triggering. In this chapter we will review models that attempt to explain the interplay between sensitivity, specificity and TCR triggering.

In particular, we will focus on the organization of TCR proximal signalling events, that underlie three major classes of TCR triggering models (conformational change, aggregation, and segregation) and how the details of the TCR–pMHC interaction can affect signalling. We will begin the chapter with a very brief summary of the key experimental results that motivated these models.

Sensitivity and Specificity

T cells are challenged to detect the molecular signatures of infection, in the form of antigenic pMHC, from the background of noise, in the form of endogenous (self) pMHC. Antigen-presenting-cells express 10^5–10^6 diverse pMHC on their cell surfaces, of which relatively few are antigenic, capable of activating a T cell via its TCR. The key experiments on sensitivity, showing that very low numbers of antigenic pMHC can stimulate T cells were by Sykulev et al. (1996) [1] and Irvine et al. (2002) [2]. In the 2002 experiments, pMHC were individually labelled with a fluorescent marker, showing that CD4 and CD8 T cells will transiently respond (flux calcium) in response to a single antigenic pMHC. The level of calcium response correlated with the number of presented pMHC up to about 10. After this many pMHC are detected, a more complete response occurs. A further finding of this study was that cytotoxic T cells can kill antigen presenting cells after recognizing as few as three antigenic pMHC. This hair-trigger level of sensitivity is amazing and perhaps frightening given our knowledge of autoimmune disease. The specificity of the T cell response has been known for some time by the observation that a single amino acid substitution in the presented peptide can substantially alter the T cell response [3, 4]. Taken together, these experiments showed that T cells are able to respond to a few specific pMHC amidst a background of chemically similar endogenous pMHC, which when presented in the absence of specific pMHC do not elicit a T cell response.

Parametric Descriptions of TCR–pMHC Binding

It is natural to ask what quantitatively measurable features of the TCR–pMHC interaction determine the cellular response. The simplest model of the TCR–pMHC binding interaction treats it as a simple chemical binding with binding rate k_{on} and unbinding rate k_{off}. It is then possible to define the half-life $t_{1/2} = (\ln 2)/k_{\mathrm{off}}$ and the dissociation constant $K_{\mathrm{D}} = k_{\mathrm{off}}/k_{\mathrm{on}}$. It is important to note that k_{on} is a two-dimensional rate (units of $\mu\mathrm{m}^2\mathrm{s}^{-1}$), reflecting the fact that the pMHC and TCR are restricted to their respective cell membranes.

Commonly used methods for measuring biochemical rates, such as those using surface plasmon resonance [5, 6], yield three-dimensional rates which may or may not correlate well with the actual rates of binding and unbinding within the tight region of contact between a T cell and an APC. For example, it is possible that the bond in a physiological situation is stressed and therefore that k_{off} would be higher than a 3-d measurement would suggest [7]. On the other hand, experiments that directly measured the two-dimensional rates of CD2–CD58 and CD16–IgG Fc interactions found a 2-d off-rate that is 100-fold smaller than the 3-d measurement [8]. This observation may be due to rapid rebinding of the same ligand-receptor pair in the 2-d environment which is a consequence of diffusion-limited reactions [9,10].

In any case, 3-d measurements must be converted to two dimensions for use in mathematical models. The most commonly implemented method is to keep k_{off} the same, but modify k_{on} by dividing by an appropriate length scale (typically 5–10 nm) [11]. An additional effect was proposed by Qi et al. [12] based on the work of Krogsgaard et al. [13], who used thermodynamic methods and a cartoon model of the TCR to obtain a formula for converting experimentally measured 3-d off-rates to 2-d parameters. This method requires additional measurements of the heat capacity of the bond to be made. Both of these methods still require experimental validation or refutation.

Importance of Stable TCR–pMHC Binding

With the caveat that the parameters still need to be measured in a physiological 2-d situation, the majority of authors have focused on the stability of the TCR–pMHC interaction (presumed to be governed by k_{off} from 3-d measurements) as the key determinant of T cell activation. Experimentally, this is supported by a range of studies showing T cell activation, as measured by cytokine production, is well correlated to k_{off} (reviewed in [14, 15]) but these results were challenged by others [16, 17] who did not find such correlations. In terms of signalling, the kinetic proofreading model (discussed in detail below) gives a rationale for superior signalling by long-lived complexes in terms of a series of essential signalling steps.

In order to explain experimentally-observed deviations from this rule, more complex models have been devised that take into account additional aspects of the interaction. For instance, it appears that the TCR coreceptor CD8 stabilizes the TCR–pMHC complex by binding in a peptide-independent fashion to MHC and therefore supports TCR signalling on cytotoxic T cells [18]. An alternative approach was taken by Krogsgaard et al. [13], who measured the heat capacity of the TCR–pMHC bond and found that this could be used, along with k_{off}, to provide an improved fit of T cell activation data. This is consistent with the importance of effects of molecular reorientation during bond formation [12].

We now move on to describe models for TCR signalling following pMHC binding. In turn, we look at the following:

– Kinetic proofreading models based on a linear sequence of signalling events proximal to the TCR and dependent on pMHC binding

– Detailed biochemical models for TCR signalling, involving more complex reaction networks and feedbacks
– Conformational change of the TCR upon binding
– Models that take special account of TCR aggregation into multimeric complexes
– Segregation-based models

These models should not be viewed as contradictory. TCR signalling is a multifaceted process and each class of models takes into account only aspects of the biological situation. A full model that reconciles all experimental findings is a challenging task that will build on existing models and will only develop in tandem with appropriate experimental data.

Kinetic Proofreading Models for Antigen Discrimination

Kinetic proofreading models for TCR signalling are, at their heart, phenomenological models based on a cartoon version of biochemical signalling initiated upon TCR/pMHC binding. During signal transduction after receptor ligation, a series of biochemical events occur at the cytoplasmic tail of the receptor. These events build a signalling structure of modified components that eventually gives a complete signal. However if the ligand dissociates from the receptor, the chemical reactions are aborted and do not go to completion. The essence of the kinetic proofreading model is therefore to provide a reasonable mechanism for a time lag separating ligand binding from receptor signalling and hence allowing a receptor to discriminate between ligands with small differences in off-rate.

As a simple quantitative example, consider a receptor that signals after $\tau = 1\,\mathrm{s}$ of engagement, and two potential ligands with $k_{\mathrm{off}}^{A} = 1\,\mathrm{s}^{-1}$ and $k_{\mathrm{off}}^{B} = 5\,\mathrm{s}^{-1}$. The probability of signalling following a single engagement by ligand A is $\exp(-k_{\mathrm{off}}^{A}\tau) = e^{-1}$ while for ligand B it is $\exp(-k_{\mathrm{off}}^{B}\tau) = e^{-5}$. Ligand A is thus $\exp(4) \simeq 55$ times as likely to signal as ligand B, based on one binding event. Observe that this mechanism allows discrimination based on half-life (or equivalently, k_{off}) and that small differences in the half-life can be translated into large differences in signalling. A time-lag model of receptor signalling was considered in a more general context in [19].

Despite their simple nature, kinetic proofreading models have been extensively used in a variety of contexts. McKeithan introduced the kinetic proofreading model for TCR in his seminal paper [20], following on from earlier work in a different context [21, 22]. McKeithan's original scheme is illustrated in Fig. 2.1a. In this model, the TCR begins in an inactive state. Upon binding, it undergoes N sequential modifications, each representing an intermediary on the path to signal transduction. Upon completing N modifications, a signal is assumed to have been completely transduced. Furthermore, McKeithan supposed that if the pMHC unbinds from the TCR prior to the Nth step being reached, the TCR immediately reverts back to the inactive state. Mathematically speaking, this model essentially generates a sigmoidal response to pMHC based on their mean lifetime of binding to the TCR ($1/k_{\mathrm{off}}$). We may therefore say that the kinetic proofreading model allows

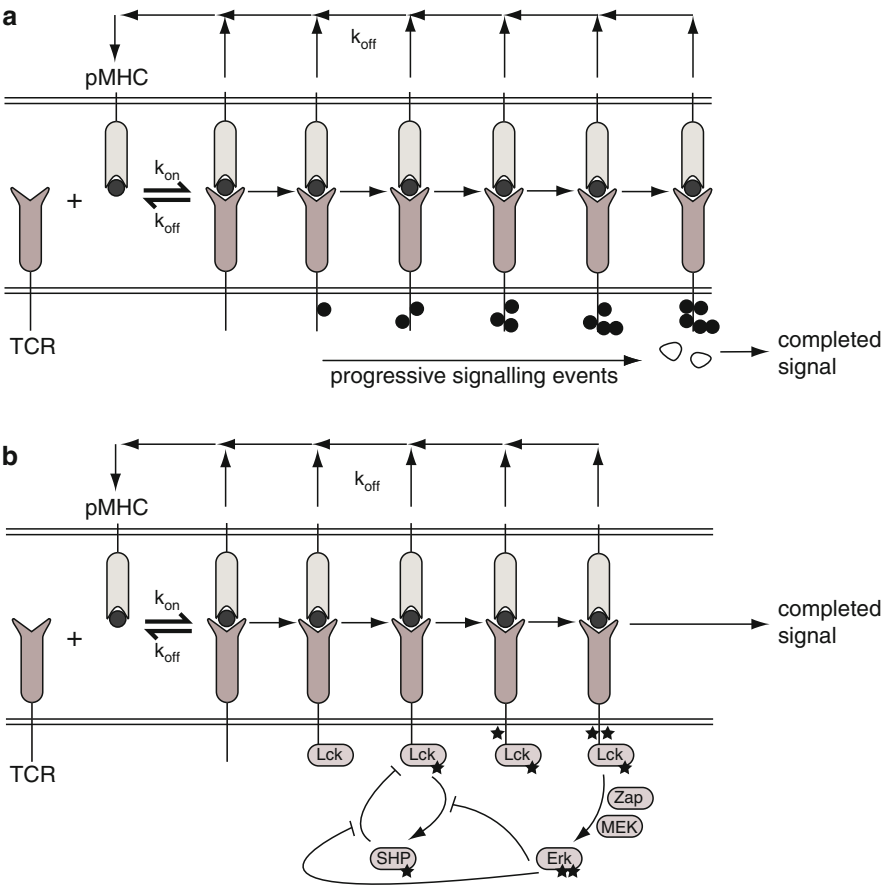

Fig. 2.1 Schematic descriptions of kinetic proofreading and feedback models. (**a**) We show the original kinetic proofreading model [20]. *Black dots* indicate unspecified signalling steps occuring at the cytosolic tail of the receptor. A full signal is transduced at the end of the signalling sequence. (**b**) A positive/negative feedback model of TCR signalling [36–38]. Schematic shown most closely resembles the feedback model by Lipniacki et al. [38]

the T cell to discriminate pMHC based on their chemical off-rate for the TCR. This model has been used by many researchers as a simple model of TCR signalling (e.g. [9, 23–27]).

One of McKeithan's observations about his model was that the specificity of discrimination grows with N, but at the expense of sensitivity (i.e. as N increases, the number of signalling events due to pMHC with high off-rates decreases, but the total number of signalling events from any pMHC also decreases). This point was examined in more detail in critical reviews of the kinetic proofreading model [25, 28], and shown to be an unavoidable feature of the basic model. It was proposed that to resolve this issue, fully activated TCR could have a decreased off-rate for the pMHC – requiring that the signalling machinery be able somehow lock the pMHC

in place at the TCR [20]. Although we note that there is no experimental evidence for this effect at present, we can speculate as to how this might be achieved. Possible non-exclusive mechanisms could include

- A direct mechanical modification of the TCR upon signalling (possibly related to the piston action or receptor deformation described below). We note that, since single amino-acid substitutions on the presented peptide can change the cellular response, it is not inconceivable that small changes in the geometry of the TCR could have an effect.
- Introduction of additional nonspecific MHC-binding coreceptors CD4 and CD8 to the signalling complex, increasing the effective affinity of the signalling complex for pMHC and fixing the pMHC in place.
- Recruitment of additional TCR to the signalling region. For this idea to make sense, nearby TCR would need to be able to act effectively to share, or integrate signals. The pMHC would then serially ligate different TCR within the signalling cluster, but the kinetic proofreading steps would take place as if via a single receptor. Experimentally, TCR are known to form clusters in response to cognate presented pMHC [29, 30].
- By modulating the local geometry of the cell membranes at the signalling receptor to optimize the intermembrane separation from the point of view of the TCR–pMHC bond, and reduce the unbinding rate. We note that TCR signalling is known to be linked to the cortical actin cytoskeleton of the T cell, that could provide a feasible mechanism for some local control. An alternative or complementary means of control would be via the removal of cell-surface molecules with large extracellular domains from the local area.

We note that mechanisms for holding pMHC fixed and bound to a single TCR contradict the serial engagement hypothesis [31] which argues that the signalling capacity of rare agonist pMHC multiplies when each pMHC binds to multiple TCR during the cellular interaction. However, serial engagement of TCR by pMHC could occur within a TCR microcluster or other localized signalling region [32].

It is also important to note that within the basic model, ligands with lower probabilities of generating a signal can compensate for this weakness by being present in larger quantities. This is critical for the TCR given the large numbers of irrelevant peptides present on the APC. This problem is partially overcome by the strong nonlinearity in response achieved if there are many proofreading steps (albeit at the expense of sensitivity) but remains a point to be addressed by more complex models.

The biological basis for the kinetic proofreading model in the case of the TCR remains unclear. We may, however, draw some inspiration from the signalling pathway of the high affinity IgE receptor FcϵRI on mast cells. This receptor, closely related to the TCR, binds IgE with high affinity and the IgE on different receptors can then be crosslinked by an appropriate ligand. The subsequent signalling cascade has been studied in great detail, allowing a detailed mathematical model to be built [33, 34]. Experimental and modelling results reflect many aspects of kinetic proofreading, but certainly do not allow us to fit the parameters of McKeithan's formulation of the model, or obtain a clear biological interpretation of the parameters (reviewed in [35]).

To summarize our discussion of kinetic proofreading, we observe that a literal interpretation of McKeithan's kinetic proofreading model is certainly not correct. The basic model is unable to reconcile specificity and sensitivity, and the intermediate steps have not been found. However, detailed modelling of the FcϵRI receptor shows that the basic idea of kinetic proofreading in terms of a set of molecular events that must happen proximal to the receptor should remain a useful paradigm for describing TCR signalling. New models can be described in terms of their deviations from the kinetic proofreading model. Additionally, the kinetic proofreading model is a useful and easily implemented component that can be incorporated into larger or more complex models of TCR signalling. A good example of this is the model of Wedagedera and Burroughs (2006) which examines the whole process of T cell activation from a queuing theory perspective [27]. The kinetic proofreading component is a simple and natural choice to capture the essence of the signalling cascade without getting bogged down in the details.

Extensions of Kinetic Proofreading

TCR–pMHC Rebinding

The reactions between many cytosolic proteins are thought to be reaction-limited because diffusion coefficients in the cytosol are relatively large. In this regime the dynamics can be accurately captured by simple ordinary-differential-equations (ODEs) which rely on the so called well-mixed assumption. In contrast, the reactions between many membrane confined proteins are thought to be diffusion-limited, whereby molecular collisions occur at much lower frequencies but often lead to a reaction owing to the reaction on-rate being larger than an appropriate measure of diffusion, see for example Lauffenburger and Linderman [39]. A consequence of diffusion-limited reactions is that a receptor-ligand complex will break and reform several times before each binding partner diffuses apart. As discussed above, the 2D reaction rates between TCR and pMHC are presently unknown but it is reasonable that their binding rate, like the binding rate for other membrane confined proteins, is diffusion-limited. Therefore it is expected that a TCR–pMHC pair will unbind and rebind many times before the TCR and pMHC move apart. Incorporating this effect into the canonical kinetic proofreading model proposed by McKeithan [20] it was found that TCR–pMHC rebinding has only a small effect on productive signalling, Fig. 2.2a. However, by supposing that the TCR signal is not lost during the brief interval between rebinding events, pMHC rebinding can have a large effect on productive signalling, Fig. 2.2b. In particular, it was found that in addition to k_{off}, the on-rate can also have a critical role in determining signalling. Therefore this simple extension to the kinetic proofreading model showed that by explicitly modelling rebinding and signal persistence at the TCR, T cells are able to discriminate pMHC based on both k_{off} and k_{on}. This theoretical work is summarized in Dushek et al. [9]. In support of this model, the potency of pMHC can be well-predicted by an effective off-rate that accounts for rebinding but not by the off-rate alone [10].

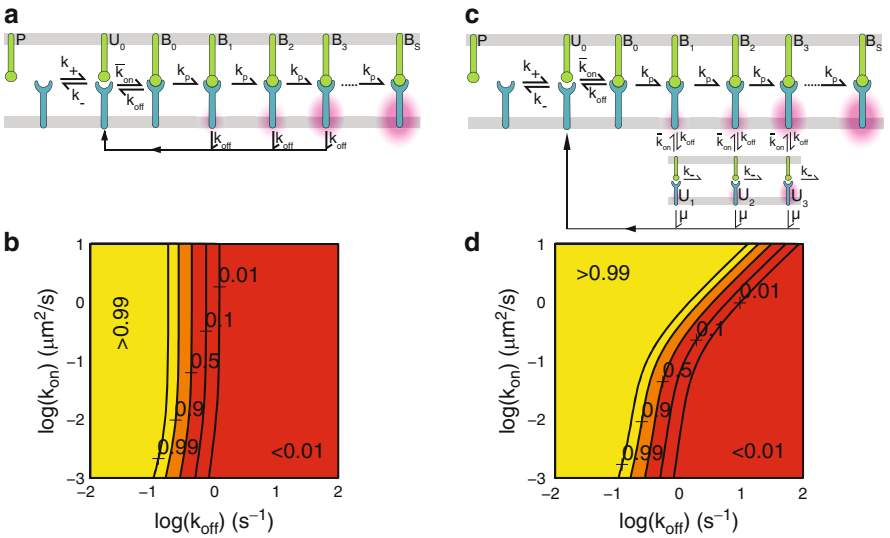

Fig. 2.2 Incorporating rebinding and signal persistence in kinetic proofreading models allows for pMHC discrimination based on both k_{off} and k_{on}. (**a**) Schematic of the canonical kinetic proofreading model modified to include the possibility of TCR–pMHC rebinding. In this model pMHC dissociation from TCR results in state U_0 which allows the two molecules to rebind or diffuse away at rate k_-. (**b**) Contours of the probability that at least 1 of 10 presented pMHC will transduce a productive signal (final step in the proofreading scheme) after $t = 30$ s as a function of k_{off} and k_{on} on a log–log plot. As expected, k_{off} is critical in determining productive signalling but increasing rebinding events, by increasing k_{on}, has little effect on productive signalling. (**c**) The scheme shown in panel (**a**) is modified to include the possibility that TCR signals persist during the brief intervals between rebinding events (states U_i). This modification is plausible given the finite time required for phosphatases to revert the phosphophorylation state of the TCR to basal levels. (**d**) In this modified scheme (shown in panel (**c**)) it is found that k_{on} may also have a critical role in determining productive signals. For further details see Dushek et al. [9]

Ligand Antagonism

Certain pMHC are known to desensitize T cells to further stimulation. These pMHC are called antagonists and we should seek to understand how they work in forming a complete theory of TCR signal transduction. A 1996 study by Rabinowitz et al. [40] used a modified kinetic proofreading model to allow for partial and incomplete signals leading to cellular desensitization. They modelled TCR as existing in three states – inactive, partially modified, and fully modified. A receptor must be fully modified to generate a positive signal. Partially modified receptors are taken to give negative signals. The existence of the intermediate state can be motivated by the observation that ZAP-70 is not activated by antagonist pMHC, indicating that pMHC discrimination occurs upstream of ZAP-70 activation and so intermediate state(s) must exist. Further experimental work shows that the membrane phosphatase SHP-1

is recruited to TCR during pMHC binding, and that this leads to the inactivation of Lck kinase, but that as binding continues, this process is inhibited by recruitment of the MAP kinase ERK-1 [36] (discussed further below).

Theoretical modelling of ligand antagonism was also performed by van den Berg, Burroughs and Rand [23]. This work proposed a method whereby careful experimentation and data analysis could be used to distinguish between passive antagonism (where antagonist pMHC successfully compete with agonists in terms of binding TCR) and active antagonism (where the signalling ability of individual TCR is reduced after antagonist binding). The strength and mode of ligand antagonism was shown to depend on the density of presented pMHC, also suggesting that T cells may control their signalling capacity by modulating surface presentation of TCR.

Spatially Extended Models of TCR Activation

The basic ideas described by Rabinowitz et al. [40] were extended in a mathematical modelling paper by Cliburn Chan et al. [41]. In this model, a spatial Monte Carlo simulation of pMHC-induced TCR activation was used to examine spatial spread of activation and inhibition from a ligated TCR to its neighbours. Individual TCR in the model were supposed to exist in different states – empty, bound, partially activated, and fully activated. Furthermore, signals were supposed to spread to neighbouring TCR. These signals could be inhibitory (prohibiting further activation) or protective (protecting the TCR against inhibition). Biologically, these effects could occur via recruitment of SHP-1 phosphatase to the signalling region (inhibiting Lck activation) and ERK-1 activation (which protects Lck from SHP-1). Inhibitory signal spreading ("receptor crosstalk") improves the specificity of signalling based on k_{off} of the TCR–pMHC bond, although it decreases sensitivity to low numbers of presented pMHC. The loss of sensitivity in the model is restored in the full model by protective signal spreading. Importantly, this model addresses a crucial shortcoming of the basic kinetic proofreading model in that it shows how a low-density, long-lived (small k_{off}) ligand can be discriminated from a very high density, but short-lived (large k_{off}) ligand.

Detailed Biochemical Models and Feedback Control of the Signalling Cascade

A development of the kinetic proofreading model based on signalling feedbacks has been advanced by Germain and coworkers [15, 36, 37]. This model contains four TCR states – unbound, bound, partially activated and completely activated. Two feedback loops are proposed: a negative feedback from the partially activated state, reducing further activation steps, and a positive feedback from the fully activated state, enhancing further signalling. The model identifies the mediator of negative feedback as SHP-1, while the positive feedback is mediated by ERK-1. The model

is described using ordinary differential equations, and broadly represents a spatially homogenized version of earlier models of Chan et al. [41, 42]. However, the focus here is on short-time (1–3 min) responses to ligand, rather than over 60 min as in Chan et al. The combination of positive and negative feedback responses in the model leads to a bistability in the T cell response. The power of this work is in the integration of modelling and detailed experimental work within a single laboratory. The model is shown to make a number of predictions, which are then tested experimentally, verifying the model. For example, the feedback model shows the response time decreases sharply as the number of pMHC is reduced. By measuring the ERK-1 response at different ligand densities, Altan-Bonnet and Germain were able to verify this behaviour [37]. Wylie et al. (2007) incorporated the same feedback mechanisms in another model for the role of CD4 coreceptors (constitutively associated with Lck) and nonagonist ligands in T cell activation [43]. This latter paper also emphasizes the importance of considering stochastic fluctuations when analyzing receptor signalling models.

The basic idea of combining kinetic proofreading with positive and negative feedbacks received further attention in a modelling paper by Lipniacki et al. [38]. In this model, TCR can exist in six states: (1) unbound; (2) bound; (3) associated with unphosphorylated Lck; (4) associated with phosphorylated Lck; (5) with phosphorylated Lck and TCR-ζ chain singly phosphorylated; (6) with phosphorylated Lck and TCR-ζ chain doubly phosphorylated, leading to cellular activation. The model also incorporates negative feedback via phosphorylated SHP from state (4) onto itself, and positive feedback from state (6) via a pathway from the receptor to ZAP-70, MEK and ultimately doubly phosphorylated ERK onto the negative feedback. The model, which explicitly contains SHP and ERK, is expressed as a set of ordinary differential equations which are solved deterministically and also in a stochastic framework. The results indicate that the T cell will respond, most of the time, to 5–10 agonist pMHC, but that the sensitivity is substantially reduced in the presence of antagonist pMHC. The modelling indicates a bistability in response (activation or nonactivation with no intermediate) but that the barrier between the basins of attraction is low enough that small fluctuations can change the response. It is shown that the deterministic solution of the system is therefore a poor descriptor of the actual behaviour in the presence of noise.

To summarize, models based on known biochemical events, and particularly the SHP-1 / ERK-1 feedback loops, allow experimentally testable predictions to be made (and tested), and surely represent the future of TCR signalling models. However, substantial challenges remain:

– The accurate parameterization of the models remains a thorny issue, especially given the multitude of interacting chemical species. This means that sensitivity analysis becomes extremely important (discussed in [43]). However, the fact that we can speak of measuring identifiable parameters at all is a major step forward.
– The models must handle the presence of two kinds of stochastic effects. First, the obviously stochastic nature of any biochemical reaction network with small numbers of players. Second, there is substantial variation in expression levels of signalling components between cells. This second point was examined in detail in a theoretical-computational study of Feinerman et al. [44].

– The role of spatial effects such as TCR clustering and segregation of signalling molecules must be carefully addressed. This requires the intelligent use of models defined by partial differential equations or (more likely) spatial Monte Carlo simulations. The development of efficient algorithms is an important ongoing concern [45–47].

The authors of competing feedback models are sometimes at pains to distinguish their work from kinetic proofreading. We find this, to some extent, to be a false dichotomy since in every model we have described, a core pathway can be distinguished, which is essentially determining a kinetic proofreading process. This scheme is modified by the presence of feedback loops, of course. As stated above, the paradigm of kinetic proofreading remains useful in describing the basic features of these models.

Models of TCR Triggering

The mathematical models described above have assumed that TCR proximal signalling is initiated upon pMHC binding to the TCR. For example, kinetic proofreading models assume that proofreading initiates when pMHC binds TCR and is terminated when pMHC unbinds. However, the exact mechanism by which the pMHC signal is communicated across the plasma membrane and initiates signalling is presently unknown. We now review three broad classes of TCR triggering models and discuss how kinetic proofreading is modified in these systems.

Models Relying on a Conformational Change

Conformational change models postulate that TCR binding to pMHC somehow results in a conformational change in the CD3 cytoplasmic portions. Early conformational change models postulated that a conformational change was transmitted allosterically through the TCR$\alpha\beta$ subunits. However this is implausible given the huge semi-random structural diversity of TCR/pMHC interfaces, and structural studies of the TCR/pMHC complexes have failed to identify any such long-range conformational change which is common to many TCR upon pMHC binding. More recent models have postulated that the TCR binding leads to a conformational change of two TCR/CD3 complexes with respect to each other, the TCR$\alpha\beta$ module with respect to the CD3 chains or a ‘piston-like’ change in the TCR/CD3 complex with respect to the plasma membrane. How could pMHC binding lead to such changes? We have noted that pMHC binding will automatically subject the TCR to a mechanical pulling force [7] and proposed that this pulling could be responsible for such conformational changes [48, 49]. A very similar ‘receptor-deformation’ model has been proposed more recently by others [50].

Support for conformational change models has come from the demonstration that the cytoplasmic portions of the CD3 chains undergo conformational change [51–53]. In one case the conformational change in a proline-rich motif of the CD3ϵ was shown to be induced by TCR binding to pMHC [54], although subsequent functional studies indicated that this motif is not required for TCR signalling but is instead involved in regulation of TCR/CD3 surface density in thymocytes [55]. The recent evidence that the CD3ϵ chain binds to the membrane, with the two ITAM tyrosine residues sequestered deep therein, suggests how conformational change might regulate tyrosine phosphorylation [53]. It is possible, however that phosphorylation of CD3ϵ regulates membrane association rather than vice versa, and it remains to be shown that TCR binding to pMHC can influence this CD3ϵ binding to the membrane.

In this model of TCR triggering, the basic kinetic proofreading scheme does not need any modification. The binding of pMHC to TCR transduces a conformational change at the TCR which initiates kinetic proofreading (signalling) while pMHC unbinding reverses the TCR conformational change which terminates kinetic proofreading (signalling). In this way, TCR triggering by a conformational change is the simplest kinetic proofreading mechanism.

Molecular Aggregation Models

A common mechanism of signal transduction across the plasma membrane is the dimerization (or oligomerization) of cell surface proteins [56]. For example, receptor tyrosine kinases (RTKs) are transmembrane receptors composed of an extracellular ligand binding site and an intracellular tyrosine residue which can become phosphorylated by a specific kinase domain also located on the RTK. Typically, a single RTK cannot phosphorylate itself because these intracellular domains are physically separated. Ligand binding induces RTK dimerization which brings these domains into close proximity and allows each receptor to phosphorylate the other, a process known as trans-autophosphorylation. Unlike RTKs, the TCR does not have intrinsic kinase domains that allow for autophosphorylation. However, tyrosine kinases of the Src family (SFKs) (e.g. Lck, Fyn) may associate with the TCR/CD3 complex even in the basal state such that subsequent dimerization of TCRs bring SFKs into close proximity of tyrosine residues on the other TCR. Therefore it is possible that signal transduction is initiated by TCR aggregation.

Several experimental studies have demonstrated that TCR aggregation is sufficient for TCR triggering. Stern and colleagues [57] have used *soluble* pMHC oligomers to demonstrate that homo-dimers, -trimers, and -tetramers are able to induce T cell activation (by crosslinking TCR) but monomeric pMHC cannot. However, in a physiological setting agonist pMHC are present at low concentrations making it improbable to find agonist pMHC homodimers. To address this, a subsequent study revealed that even agonist-endogenous pMHC heterodimers can drive

T cell activation [58]. These studies have convincingly demonstrated that TCR aggregation via pMHC oligomers can drive TCR triggering.

A key drawback to a model where pMHC oligomers drive TCR triggering by aggregation is that, to date, there is little evidence that pMHC form oligomers when presented to T cells on the APC membrane [49]. However, quantitative analysis of the dependence of TCR internalization rates on TCR surface density suggests that TCR internalization following exposure to pMHC pulsed APCs is preceded by TCR dimerization [59,60]. Since only triggered TCR are marked for internalization, these result imply that TCR triggering is accompanied by TCR dimerization. Although suggestive, it does not follow that TCR triggering is the result of and follows dimerization/aggregation. Moreover, it is possible that TCR dimerization/aggregation follows and is the result of TCR triggering.

Assuming that TCR aggregation via pMHC binding is required for TCR triggering, it is natural to ask what are the effects of TCR aggregation on pMHC discrimination. This question was investigated using a mathematical model by Salzmann and Bachmann [61] (reviewed by Bachmann and Ohashi [62]). The model assumes that two pMHC species, denoted with superscript plus and minus, undergo reversible reactions with TCR,

$$C^+ = K^+ P^+ T$$
$$C^- = K^- P^- T$$

where T, P, and C represent the free TCR, free pMHC, and bound TCR–pMHC concentrations. Assuming that all TCR–pMHC complexes rapidly partition into dimers they approximate the dimer concentrations as

$$D_{+/+} = \beta (C^+)^2 / C_{\text{tot}}$$
$$D_{+/-} = 2\beta C^+ C^- / C_{\text{tot}}$$
$$D_{-/-} = \beta (C^-)^2 / C_{\text{tot}}.$$

where $C_{\text{tot}} = C^+ + C^-$, β is a dimensionless proportionality constant, and the subscripts indicate the dimer composition. The model next assumes that both TCR in the newly formed dimer undergo basic kinetic proofreading and that a productive signal is transduced only if both TCR remain bound to pMHC. They do not model kinetic proofreading explicitly, but instead assume a simple lag time (τ) between TCR/pMHC binding and full TCR activation. The probability that both TCR in an agonist homodimer remain bound after time t is simply $\mathrm{e}^{-k_{\text{off}}^+ t} \mathrm{e}^{-k_{\text{off}}^+ t}$. Signals generated by each pMHC can be computed as

$$A_{+/+} = \beta \frac{(C^+)^2}{C_{\text{tot}}} \exp^{-2k_{\text{off}}^+ t}$$
$$A_{-/-} = \beta \frac{(C^-)^2}{C_{\text{tot}}} \exp^{-2k_{\text{off}}^- t}.$$

Extending the analysis for an oligomer consisting of n TCR–pMHC complexes the relative signal obtained from the two pMHC species is then

$$\frac{A_{n+}}{A_{n-}} = \left[\frac{C^+}{C^-}\right]^n \exp^{-n(k_{\text{off}}^+ - k_{\text{off}}^-)\tau} \tag{2.1}$$

where τ is the lag phase required for signalling. The equation is further simplified by assuming 1) both pMHC are present at concentrations that exceed the TCR concentration and 2) both pMHC are present at equal concentrations. The ratio of signals generated becomes

$$\frac{A_{n+}}{A_{n-}} = \left[\frac{k_{\text{on}}^+ / k_{\text{off}}^+}{k_{\text{on}}^- / k_{\text{off}}^-}\right]^n \exp^{-n(k_{\text{off}}^+ - k_{\text{off}}^-)\tau}.$$

Note that molecular concentrations do not appear in the equation. Based on the form of this equation the authors argue that the discriminatory capacity of T cells increases more rapidly with the oligomer size n (appearing in both exponents) than the proofreading lag τ. This result is important because increasing τ will, in general, reduce the total signals obtained by the T cells (equivalent to reducing sensitivity by additional proofreading steps). By requiring both TCR in a dimer to be bound to pMHC, they propose that a further increase in specificity can be achieved.

There are several shortcomings to the model. The most critical shortcoming is the omission of kinetic processes, mainly serial binding. We expect that pMHC with large off-rates will be less likely to transduce productive signals (as predicted by the model) but in addition, these pMHC will be able to rapidly form and reform many dimers effectively increasing the probability of transducing productive signals. We suspect that including this effect will remove the n dependence in the first fraction above, reducing specificity obtained by oligomers. Additionally, it is unclear how these results will be altered if the two pMHC species are present in unequal numbers (e.g. $[P^+] \ll [P^-]$). In the future, it will be important to extend the model to the physiological scenario where the agonist pMHC is expressed at low numbers, possibly revealing the importance of agonist-endogenous pMHC heterodimers. In addition, any future model should account for the process of aggregation as a kinetic process that allows for the formation and also disassembly of TCR oligomers.

We briefly mention that models have been proposed based on the aggregation of T cell coreceptors (CD4/CD8) and TCR [49]. T cell coreceptors are able to bind pMHC directly at a site that is independent of the TCR binding site and therefore complexes composed of TCR–pMHC–coreceptor are expected to form. This coreceptor heterodimerization model posits that only once this complex forms can a productive signal be transduced. This mechanism is possible because Lck, an important kinase that can phosphorylate the TCR signalling modules, is constitutively associated with T cell coreceptors. However, many studies have shown that TCR triggering is possible in the complete absence of the T cell coreceptors, suggesting that coreceptors may enhance triggering by recruiting additional Lck to the

TCR–pMHC complex [16] or stabilizing the TCR/pMHC interaction [63]. A model incorporating the effects of agonist-endogenous pMHC heterodimers and coreceptors has also been proposed [58]. This pseudodimer model, although plausible in principle, cannot account for TCR triggering in the complete absence of coreceptors.

In summary, studies have shown that TCR aggregation, by TCR crosslinking with soluble pMHC oligomers, can activate T cells and therefore trigger TCR. However, the mechanism of TCR crosslinking at the T cell–APC interface remains elusive because pMHC do not form oligomers. Under the assumption that TCR–pMHC complexes aggregate, mathematical modelling has attempted to determine the effects of oligomerization on T cell specificity. Future experiments and modelling is required to determine the physiological mechanism of TCR aggregation and the effects that aggregation may have on pMHC detection and discrimination.

In recent years, experiments have demonstrated that TCR rapidly aggregate into sub-micron scale clusters when stimulated by pMHC on a supported planar bilayer [29,30,64]. These studies demonstrated the importance of TCR clusters by showing that signalling molecules localize to them. However, it is unclear if TCR cluster formation is required for TCR triggering (via aggregation) or if TCR clusters form once triggering has already taken place, possibly allowing for signal amplification. In addition to the aggregation of TCR (and signalling molecules) in clusters, studies have also revealed that certain molecules (e.g. the membrane phosphatase CD45) are excluded from clusters [30]. This raises the possibility that TCR clusters may be important for molecular segregation. The role of molecular segregation in TCR triggering and pMHC discrimination is the topic of the next section.

Segregation

Given the inability of the conformational change and aggregation mechanisms to fully account for TCR triggering, a third type of mechanism has been proposed, namely that triggering is the result of segregation of the engaged TCR/CD3 complex from inhibitory molecules [65–67]. This kinetic-segregation model of TCR triggering was inspired by two observation. Firstly, exposure of T cells to tyrosine phosphatase inhibitors stimulates a dramatic increase in tyrosine phosphorylation on the TCR/CD3 complex and results in full T cell activation. This observation indicates that there is constitutive tyrosine phosphorylation of the TCR/CD3 complex which is normally balanced by tyrosine phosphatases (reviewed in [66]). Secondly, the most abundant receptor tyrosine phosphatase, CD45, has a much larger ectodomain than the TCR and would therefore be expected to segregate from the engaged TCR at the T cell/APC contact interface [68]. As a result of this local segregation, the kinase/phosphatase balance is shifted decisively towards phosphorylation which triggers a signal cascade.

This model of TCR triggering was explored using stochastic simulations by Burroughs et al. [69]. The simulation domain was taken to be a square of area of $1\,\mu m^2$ with periodic boundary condition. In the absence of agonist pMHC,

TCR randomly diffuse on a lattice and are continually phosphorylated (kinases) and dephosphorylated (phosphatases). Since there are multiple phosphorylation sites on the TCR they use kinetic proofreading to represent each phosphorylated state of the TCR but unlike previous schemes, they account for the ability of phosphatases to reverse individual kinetic proofreading steps. In the basal state, an individual TCR cannot reach the final step in the kinetic proofreading scheme because phosphatases rapidly reverse each step. Therefore this study accounts for phosphatase activity by implementing a dual-track (reversible) kinetic proofreading mechanism.

In the presence of agonist pMHC, TCR/pMHC complexes will form which will segregate membrane proteins with large ectodomains, such as the membrane phosphatase CD45. For simplicity the model does not account for the formation of areas depleted of CD45, herein referred to as kinase rich domains (KRD), and instead models nine identical and static KRDs within the simulation domain, Fig. 2.3a. KRDs have two major effects that collectively allow for TCR triggering. First, the rate to traverse forward steps in the reversible kinetic proofreading scheme is increased while the backward rate decreases, due to the depletion and enrichment of phosphatases and kinases, respectively. Secondly, TCR that bind pMHC within KRDs are expected to become trapped for longer periods of time due to membrane deformation. This effect is modelled by assuming that the TCR/pMHC bond is spring-like, favoring an optimal intermembrane separation. Departing a close-contact zone will stress the bond and therefore effectively confines complexes to KRDs. Longer durations in KRDs will increase the probability of TCR triggering.

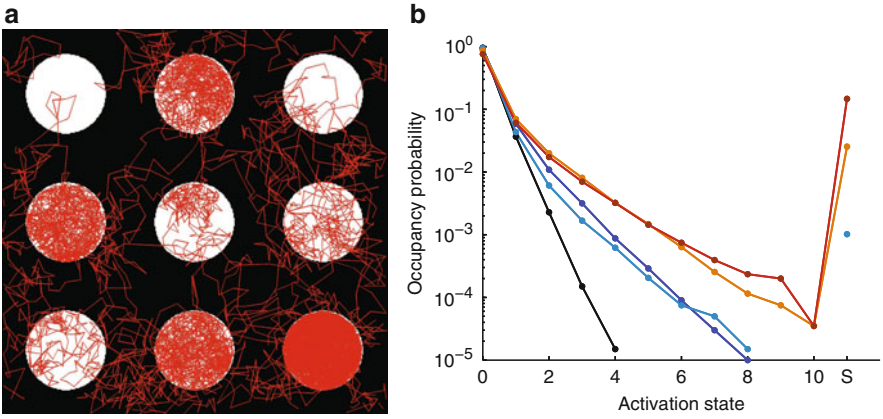

Fig. 2.3 T cell receptor triggering via kinetic segregation. (**a**) Stochastic spatial simulations of diffusing TCRs (*red traces*) are performed on a periodic boundary consisting of nine kinase rich domains (KRDs). (**b**) The probability of the TCR being in the ith proofreading step is shown without any pMHC (*black line*), low activity self pMHC with $k_{\text{off}} = 5\text{s}^{-1}$ and [pMHC]=$300\,\mu\text{m}^{-2}$ (*dark blue*), self pMHC with $k_{\text{off}} = 3\text{s}^{-1}$ and [pMHC] = $50\,\mu\text{m}^{-2}$ (*light blue*), high density self pMHC with $k_{\text{off}} = 3\text{s}^{-1}$ and [pMHC]=$300\,\mu\text{m}^{-2}$ (*orange*), and high density self pMHC with agonist pMHC having $k_{\text{off}} = 0.1\text{s}^{-1}$ and [pMHC]=$1\,\mu\text{m}^{-2}$ (*red*). The physiologically relevant comparisons are the *light blue curve* (little productive signalling) and *red curve*, showing substantial productive signalling only when agonist pMHC are present. For further details see Burroughs et al. [69]

The critical results from the model are shown in Fig. 2.3b, where the kinetic proofreading steps are plotted against the occupancy probability. First, we see that TCR are able to reach the final activation state (S) and hence become triggered by remaining in KRDs for sufficiently long. Second, TCR triggering by self pMHC is minimal and therefore kinetic-segregation is also able to minimize noise from a high density of such pMHC. Lastly, small changes in the off-rate of agonist pMHC alters the number of triggered TCR and therefore allow for pMHC discrimination (not shown).

The model itself has several shortcomings. For simplicity, forward and reverse kinetic proofreading steps are assumed to be first order. However, these kinase/phosphatase enzymatic interactions are bimolecular two-step reactions. In the future it will be important to investigate the role of these nonlinearities in pMHC detection. The model is also sensitive to the size of KRDs, whereby KRDs with a radius of over 300 nm lead to TCR triggering from self pMHC. It will be important to determine which factors determine the size of KRDs and whether they reach this critical size on the T cell surface.

In addition to kinetic-segregation, another class of TCR triggering model based on segregation invokes lipid rafts, which are lipid microdomains thought to be enriched tyrosine kinases such as Lck and deficient in tyrosine phosphatases such as CD45. These models postulate that TCR engagement of pMHC results in association of the TCR/CD3 complex with lipid rafts, resulting in enhances phosphorylation because of the altered kinase/phosphatase balance within rafts. The main drawback of lipid raft models is that they do not provide a plausible molecular mechanism by which TCR engagement of pMHC drives association with rafts.

Concluding Remarks

Experiments have shown that T cells respond to very few and very specific pMHC presented on antigen presenting cells. In order to understand these observations various mathematical models have been formulated based on the known biophysics and biochemistry of TCR/pMHC interactions and the signalling events that are triggered within the T cell upon pMHC binding to TCR. The backbone of all mathematical models to date is the kinetic proofreading model which is able to explain pMHC discrimination based on the TCR/pMHC bond off-rate. Over the past decade, this simple model has been extended and modified to explain various experimental observations. In parallel to this research aimed at understanding antigen discrimination, molecular immunologists have been investigating the mechanism by which pMHC binding to TCR transduces a signal across the plasma membrane that initiates the very first steps intracellular signalling. This process of TCR triggering is intricately linked to antigen discrimination and we believe that additional insights can be made by future mathematical modelling that couples the two processes.

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References

1. Sykulev Y, Joo M, Vturina I, Tsomides TJ, Eisen HN (1996) Evidence that a single peptide-MHC complex on a target cell can elicit a cytolytic T cell response. Immunity 4:565–571
2. Irvine DJ, Purbhoo MA, Krogsgaard M, Davis MM (2002) Direct observation of ligand recognition by T cells. Nature 419:845–849
3. Sloan-Lancaster J, Shaw AS, Rothbard JB, Allen PM (1994) Partial T cell signaling: Altered phospho-ζ and lack of ZAP-70 recruitment in APL-induced T cell anergy. Cell 79:913–922
4. Kersh GJ, Miley MJ, Nelson CA, Grakoui A, Horvath S, Donermeyer DL, Kappler J, Allen PM, Fremont DH (2001) Structural and functional consequences of altering a peptide MHC anchor residue. J Immunol 166:3345–3354
5. Jönsson U, Fägerstam L, Ivarsson B, Johnsson B, Karlsson R, Lundh K, Löfás S, Persson B, Roos H, Rönnberg I (1991) Real-time biospecific interaction analysis using surface plasmon resonance and a sensor chip technology. BioTechniques 11:620–627
6. Malmqvist M (1993) Biospecific interaction analysis using biosensor technology. Nature 361:186–187
7. van der Merwe PA (2001) The TCR triggering puzzle. Immunity 14:665–668
8. Tolentino TP, Wu J, Zarnitsyana VI, Fang Y, Dustin ML, Zhu C (2008) Measuring diffusion and binding kinetics by contact area FRAP. Biophys J 95:920–930
9. Dushek O, Das R, Coombs D (2009) A role for rebinding in rapid and reliable T cell responses to antigen. PLoS Comput Biol 5:e1000578
10. Aleksic M, Dushek O, Zhang H, Shenderov E, Chen JL, Cerundolo V, Coombs D, van der Merwe PA (2010) Dependence of T cell antigen recognition on T cell receptor-peptide MHC confinement time. Immunity 32:1–12
11. Wofsy C, Coombs D, Goldstein B (2001) Calculations show substantial serial engagement of T cell receptors. Biophys J 80:606–612
12. Qi S, Krogsgaard M, Davis MM, Chakraborty AK (2006) Molecular flexibility can influence the stimulatory ability of receptor-ligand interactions at cell-cell junctions. Proc Natl Acad Sci USA 103:4416–4421
13. Krogsgaard M, Prado N, Adams EJ, He XL, Chow DC, Wilson DB, Garcia KC, Davis MM (2003) Evidence that structural rearrangements and/or flexibility during TCR binding can contribute to T cell activation. Mol Cells 12:1367–1378
14. van der Merwe PA, Davis SJ (2003) Molecular interactions mediating T cell antigen recognition. Annu Rev Immunol 21:659–684
15. Feinerman O, Germain RN, Altan-Bonnet G (2008) Quantitative challenges in understanding ligand discrimination by alphabeta T cells. Mol Immunol 45:619–631
16. Holler PD, Kranz DM (2003) Quantitative analysis of the contribution of TCR/pepMHC affinity and CD8 to T cell activation. Immunity 18:255–264
17. Tian S, Maile R, Collins EJ, Frelinger JA (2007) CD8+ T cell activation is governed by TCR-peptide/MHC affinity, not dissociation rate. J Immunol 179:2952–2960
18. Wooldridge L, van den Berg HA, Glick M, Gostick E, Laugel B, Hutchinson SL, Milicic A, Brenchley JM, Douek DC, Price DA, Sewell AK (2005) Interaction between the CD8 coreceptor and major histocompatibility complex class I stabilizes T cell receptor-antigen complexes at the cell surface. J Biol Chem 280:27491–27501
19. van den Berg HA, Rand DA, Burroughs NJ (2001) A reliable and safe T cell repertoire based on low-affinity T cell receptors. J Theor Biol 209:465–486

20. McKeithan K (1995) Kinetic proofreading in T-cell receptor signal transduction. Proc Natl Acad Sci USA 92:5042–5046
21. Hopfield JJ (1974) Kinetic proofreading: A new mechanism for reducing errors in biosynthetic processes requiring high specificity. Proc Natl Acad Sci USA 71:4135–4139
22. Ninio J (1975) Kinetic amplification of enzyme discrimination. Biochimie 57:587–595
23. van den Berg HA, Burroughs NJ, Rand DA (2002) Quantifying the strength of ligand antagonism in TCR triggering. Bull Math Biol 64:781–808
24. Coombs D, Kalergis AM, Nathenson SG, Wofsy C, Goldstein B (2002) Activated TCRs remain marked for internalization after dissociation from pMHC. Nat Immunol 3:926–931
25. Chan C, George AJT, Stark J (2003) T cell sensitivity and specificity - kinetic proofreading revisited. Discrete Continuous Dyn Syst - Series B 3:343–360
26. Gonzalez PA, Carreno LJ, Coombs D, Mora JE, Palmieri E, Goldstein B, Nathenson SG, Kalergis AM (2005) T cell receptor binding kinetics required for T cell activation depend on the density of cognate ligand on the antigen-presenting cell. Proc Natl Acad Sci USA 102: 4824–4829
27. Wedagedera JR, Burroughs NJ (2006) T-cell activation: A queuing theory analysis at low agonist density. Biophys J 91:1604–1618
28. George AJT, Stark J, Chan C (2005) Understanding specificity and sensitivity of T-cell recognition. Trends Immunol 26:653–659
29. Campi G, Varma R, Dustin ML (2005) Actin and agonist MHC-peptide complex-dependent T cell receptor microclusters as scaffolds for signaling. J Exp Med 202:1031–1036
30. Varma R, Campi G, Yokosuka T, Saito T, Dustin ML (2006) T cell receptor-proximal signals are sustained in peripheral microclusters and terminated in the central supramolecular activation cluster. Immunity 25:117–127
31. Valitutti S, Muller S, Cella M, Padovan E, Lanzavecchia A (1995) Serial triggering of many T-cell receptors by a few peptide-MHC complexes. Nature 375:148–151
32. Dushek O, Coombs D (2008) Analysis of serial engagement and peptide-MHC transport in T cell receptor microclusters. Biophys J 94:3447–3460
33. Torigoe C, Inman JK, Metzger H (1998) An unusual mechanism for ligand antagonism. Science 281:568–572
34. Faeder JR, Hlavacek WS, Reischl I, Blinov ML, Metzger H, Redondo A, Wofsy C, Goldstein B (2003) Investigation of early events in FceRI-mediated signaling using a detailed mathematical model. J Immunol 170:3769–3781
35. Goldstein B, Coombs D, Faeder JR, Hlavacek WS (2008) Kinetic proofreading model. Adv Exp Med Biol 640:82–94
36. Stefanová I, Hemmer B, Vergelli M, Martin R, Biddison WE, Germain RN (2003) TCR ligand discrimination is enforced by competing ERK positive and SHP-1 negative feedback pathways. Nat Immunol 4:248–254
37. Altan-Bonnet G, Germain RN (2005) Modeling T cell antigen discrimination based on feedback control of digital ERK responses. PLoS Biol 3:e356
38. Lipniacki T, Hat B, Faeder JR, Hlavacek WS (2008) Stochastic effects and bistability in T cell receptor signaling. J Theor Biol 254:110–122
39. Lauffenburger D, Linderman J (1993) Receptors: Models for binding, trafficking, and signaling. Oxford University Press, Oxford
40. Rabinowitz JD, Beeson C, Lyons DS, Davis MM, McConnell HM (1996) Kinetic discrimination in T-cell activation. Proc Natl Acad Sci USA 93:1401
41. Chan C, George AJT, Stark J (2001) Cooperative enhancement of specificity in a lattice of T cell receptors. Proc Natl Acad Sci USA 98:5758–5763
42. Chan C, Stark J, George AJT (2004) Feedback control of T-cell receptor activation. Proc R Soc B: Biol Sci 271:931–939
43. Wylie DC, Das J, Chakraborty AK (2007) Sensitivity of T cells to antigen and antagonism emerges from differential regulation of the same molecular signaling module. Proc Natl Acad Sci USA 104:5533–5538

44. Feinerman O, Veiga J, Dorfman JR, Germain RN, Altan-Bonnet G (2008) Variability and robustness in T cell activation from regulated heterogeneity in protein levels. Science 321:1081–1084
45. Casal A, Sumen C, Reddy TE, Alber MS, Lee PP (2005) Agent-based modeling of the context dependency in T cell recognition. J Theor Biol 236:376–391
46. Wylie DC, Hori Y, Dinner AR, Chakraborty AK (2006) A hybrid deterministic-stochastic algorithm for modeling cell signaling dynamics in spatially inhomogeneous environments and under the influence of external fields. J Phys Chem B 110:12749–12765
47. Dushek O (2008) Mathematical modeling in cellular immunology: T cell activation and parameter estimation. PhD thesis, University of British Columbia
48. Choudhuri K, Kearney A, Bakker TR, van der Merwe PA (2005) Immunology: How do T cells recognize antigen? Curr Opin Biol 15:R382–R385
49. Choudhuri K, van der Merwe PA (2007) Molecular mechanisms involved in T cell receptor triggering. Semin Immunol 19:255–261
50. Ma Z, Janmey PA, Finkel TH (2008) The receptor deformation model of TCR triggering. FASEB J 22:1002–1008
51. Aivazian D, Stern LJ (2000) Phosphorylation of T cell receptor zeta is regulated by a lipid dependent folding transition. Nature 7:1023–1026
52. Gil D, Schamel WWA, Montoya M, Sánchez-Madrid F, Alarcón B (2002) Recruitment of Nck by CD3ϵ reveals a ligand-induced conformational change essential for T cell receptor signaling and synapse formation. Cell 109:901–912
53. Xu C, Gagnon E, Call ME, Schnell JR, Schwieters CD, Carman CV, Chou JJ, Wucherpfennig KW (2008) Regulation of T cell receptor activation by dynamic membrane binding of the CD3epsilon cytoplasmic tyrosine-based motif. Cell 135:702–713
54. Gil D, Schrum AG, Alarcon B, Palmer E (2005) T cell receptor engagement by peptide-MHC ligands induces a conformational change in the CD3 complex of thymocytes. J Exp Med 201:517–522
55. Mingueneau M, Sansoni A, Grégoire C, Roncagalli R, Aguado E, Weiss A, Malissen M, Malissen B (2008) The proline-rich sequence of CD3epsilon controls T cell antigen receptor expression on and signaling potency in preselection $CD4^+CD8^+$ thymocytes. Nat Immunol 9:522–532
56. Heldin CH (1995) Dimerization of cell surface receptors in signal transduction. Cell 80: 213–223
57. Cochran JR, Cameron TO, Stern LJ (2000) The relationship of MHC-peptide binding and T cell activation probed using chemically defined MHC class II oligomers. Immunity 12:241–250
58. Krogsgaard M, Li QJ, Sumen C, Huppa JB, Huse M, Davis MM (2005) Agonist/endogenous peptide-MHC heterodimers drive T cell activation and sensitivity. Nature 434:238–243
59. Bachmann MF, Salzmann M, Oxenius A, Ohashi PS (1998) Formation of TCR dimers/trimers as a crucial step for T cell activation. Eur J Immunol 28:2571–2579
60. Utzny C, Coombs D, Müller S, Valitutti S (2006) Analysis of peptide/MHC-induced TCR downregulation: Deciphering the triggering kinetics. Cell Biochem Biophys 46:101–111
61. Salzmann M, Bachmann MF (1998) The role of T cell receptor dimerization for T cell antagonism and T cell specificity. Mol Immunol 35:271–277
62. Bachmann MF, Ohashi PS (1999) The role of T-cell receptor dimerization in T-cell activation. Immunol Today 20:568–576
63. Wyer J, Willcox B, Gao G, Gerth U, Davis S, Bell J, van der Merwe P, Jakobsen B (1999) T cell receptor and coreceptor CD8 alphaalpha bind peptide-MHC independently and with distinct kinetics. Immunity 10:219–225
64. Yokosuka T, Sakata-Sogawa K, Kobayashi W, Hiroshima M, Hashimoto-Tane A, Tokunaga M, Dustin ML, Saito T (2005) Newly generated T cell receptor microclusters initiate and sustain T cell activation by recruitment of Zap70 and SLP-76. Nat Immunol 6:1253–1262
65. Davis SJ, van der Merwe PA (1996) The structure and ligand interactions of CD2: Implications for T-cell function. Immunol Today 17:177–187
66. van der Merwe PA, Davis SJ, Shaw AS, Dustin ML (2000) Cytoskeletal polarization and redistribution of cell-surface molecules during T cell antigen recognition. Semin Immunol 12:5–21

67. Davis SJ, van der Merwe PA (2006) The kinetic-segregation model: TCR triggering and beyond. Nat Immunol 7:803–809
68. Springer TA (1990) Adhesion receptors of the immune system. Nature 346:425–434
69. Burroughs NJ, Lazic Z, van der Merwe PA (2006) Ligand detection and discrimination by spatial relocalization: A kinase-phosphatase segregation model of TCR activation. Biophys J 91:1619–1629

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