免疫-受体信号传送的数学和计算机模型

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概述

- 获得性免疫系统的细胞使用B-cell receptors(BCRs)，T-cell receptors(TCRs)，Fc receptors来分别识别抗原，与MHC分子结合的抗原，抗原抗体复合物。

- 这些受体属于multichain immune-recognition receptor(MIRR)家族，它们分为参与抗原识别的胞外部分和参与细胞内信号转导的部分。

- 负责胞内信号转导的部分至少有一份immunoreceptor tyrosine-based activation motif(ITAM)。

概述

- 配体通过多价化（多个配体相连，形成的整体可以同时结合多个受体）来诱导MIRR聚集。
- SRC蛋白家族（一类膜相关蛋白）以其SRC homology 2(SH2) domains磷酸化ITAM中的tyrosine。
- SYK蛋白（B cells和mast cells中）或ZAP70（T cells中）与被双磷酸化的ITAMs结合。

概述

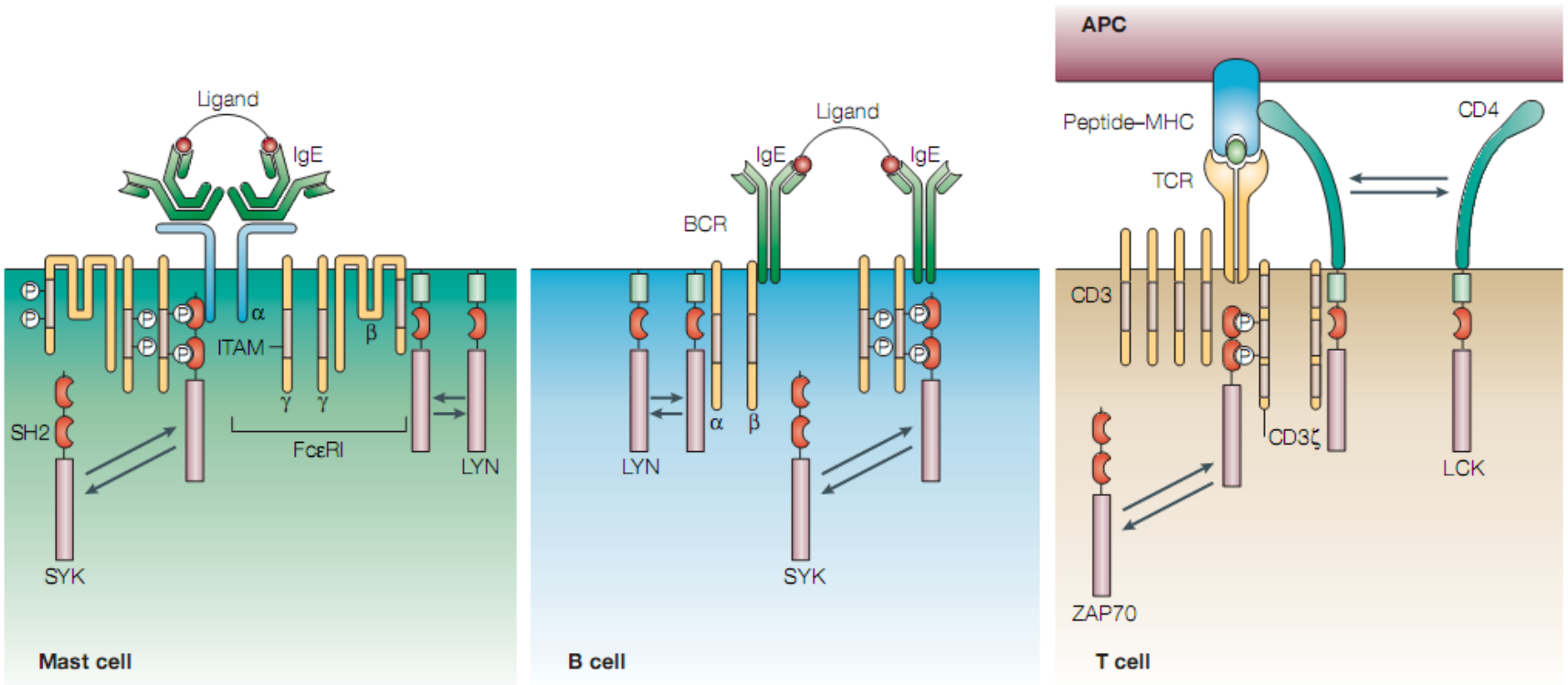
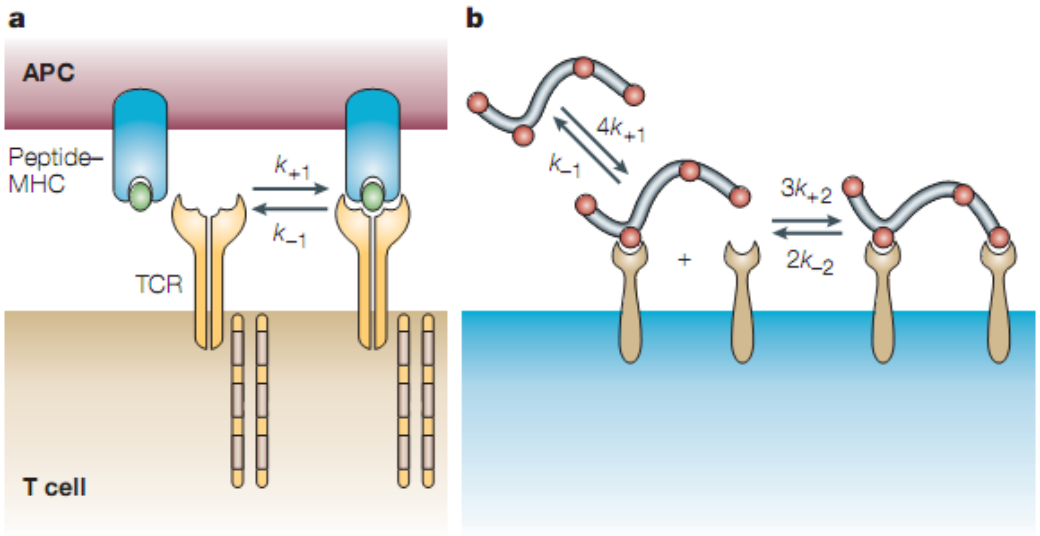


Figure 1 | **Initiation of immune-receptor signalling.** After B-cell receptor (BCR) or Fc receptor aggregation, or after the binding of a peptide–MHC complex to a T-cell receptor (TCR) (which occurs in the contact region between the T cell and an antigen-presenting cell, APC), a SRC-family kinase phosphorylates tyrosine residues within the immunoreceptor tyrosine-based activation motifs (ITAMs). The SRC kinase LYN associates with the unphosphorylated α-chain (CD79a) of the BCR[83] and the unphosphorylated β-chain of the high-affinity IgE receptor (FcεRI)[84]. In T cells, the SRC kinase LCK associates with CD4 (or CD8); CD4 also interacts with MHC class II molecules, and LCK also interacts with phosphorylated CD3ζ, through its SRC homology 2 (SH2) domain. LYN and LCK can also bind with higher affinity to phosphorylated ITAMs (not shown). SYK (spleen tyrosine kinase) is recruited to the α- and β-chains of the BCR and the γ-chains of FcεRI when their ITAMs are doubly phosphorylated. Similarly, ZAP70 (ζ-chain-associated protein kinase 70 kDa isoform) is recruited to doubly phosphorylated ITAMs on the ζ-chains of the TCR–CD3 complex. All the binding reactions are reversible with relatively short half-lives (tens of seconds). There are also phosphatases present that can rapidly dephosphorylate phosphotyrosines that are not protected from dephosphorylation by being bound to SH2 domains (not shown). For a more detailed description of these early signalling events see REFS 85–88.

Box 2 | **Rate of serial engagement**



For the reaction shown in part **a**, the rate of encounters (also known as the hitting rate) between a peptide–MHC complex on an antigen-presenting cell (APC) and a T-cell receptor (TCR) in an immunological synapse can be described using equation 1 (REF. 33).

$$\text{hits per second} = k_{-1}\left[\frac{KR}{1+KR}\right] \quad (1)$$

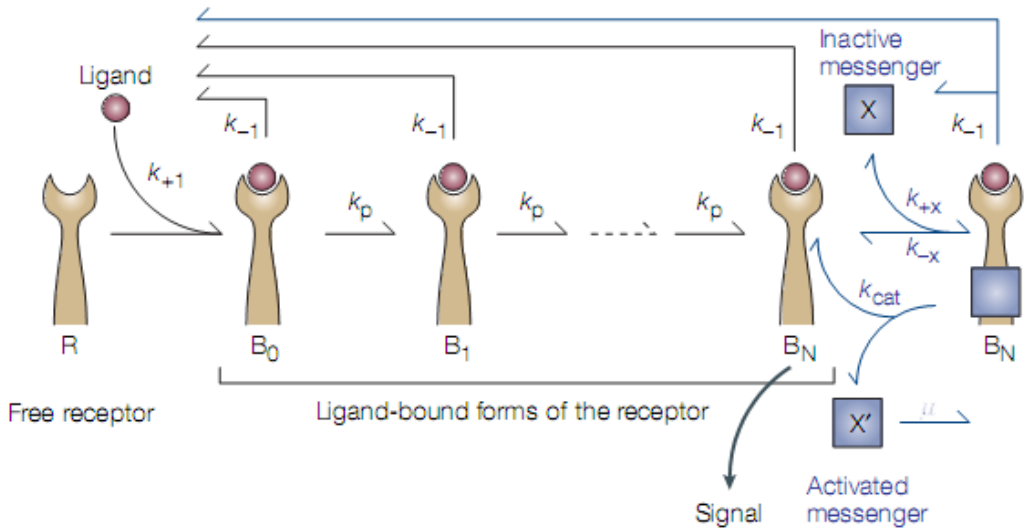
where K is the two-dimensional equilibrium binding constant, R is the surface concentration of free TCRs and k_{-1} is the dissociation rate constant. When receptors are in large excess ($KR>>1$) — so that a peptide–MHC complex spends most of its time bound to TCR — the hitting rate becomes k_{-1}. Equation 1 assumes that receptor internalization does not influence the dissociation of the peptide–MHC–TCR complex. If internalization acts on TCRs that are bound to peptide–MHC by breaking the peptide–MHC–TCR bond and freeing the peptide–MHC, this will enhance the rate of serial engagement by providing an additional way for peptide–MHC to dissociate from the TCR. The form of the hitting rate depends on the model for internalization[27].

Replacing K with K_2 (where $K_2 = k_{+2}/k_{-2}$) and k_{-1} with k_{-2} in equation 1 gives the rate at which a binding site on a multivalent ligand (with a total of four binding sites, in this example) serially engages receptors (as shown in part **b**).

连续结合
(serial engagement)
&连续引发
(serial triggering)

可以解释低密度的
peptide-MHC复合体或
抗原怎样引发激活信号

Box 3 | **Kinetic proofreading extended to include a messenger**



The figure shows McKeithan's[35] original model (black). Elements have also been added to consider a cytosolic second messenger (blue), as in the studies of Hlavacek *et al.*[52] Ligand–receptor binding is monovalent and characterized by the on-rate k_{+1}, and the off-rate k_{-1}. A bound receptor can undergo a series of N sequential modifications, each step of which is energy driven and is characterized by the rate constant k_p. R is the number of unbound receptors; B_0 is the number of bound unmodified receptors; B_1 is the number of bound receptors modified once; B_N is the number of bound receptors modified N times. A fully modified receptor generates a signal (as in the original model) and/or catalyses the activation of a cytosolic messenger through a Michaelis–Menten mechanism, in which the enzyme is a fully modified receptor, the substrate is an inactive messenger and the product is an activated messenger. The parameters of messenger activation are the rate constants k_{+x} and k_{-x}, which describe enzyme–substrate binding, and k_{cat}, which describes the catalytic conversion of substrate to product. The activated form of the messenger (X′) returns to the inactive form (X) with rate constant μ. If the ligand and receptor dissociate, it is assumed that receptor modifications are immediately reversed. Similarly, if the ligand dissociates from a messenger-associated receptor, it is assumed that the messenger dissociates simultaneously.

动力学校对 (kinetic proofreading)

基于配体-受体结合在一起的时间可以解释T cell，B cell及mast cell等怎样高度专一性地区分配体。

专一性versus敏感性

Escape:
从动力学校对中逃脱

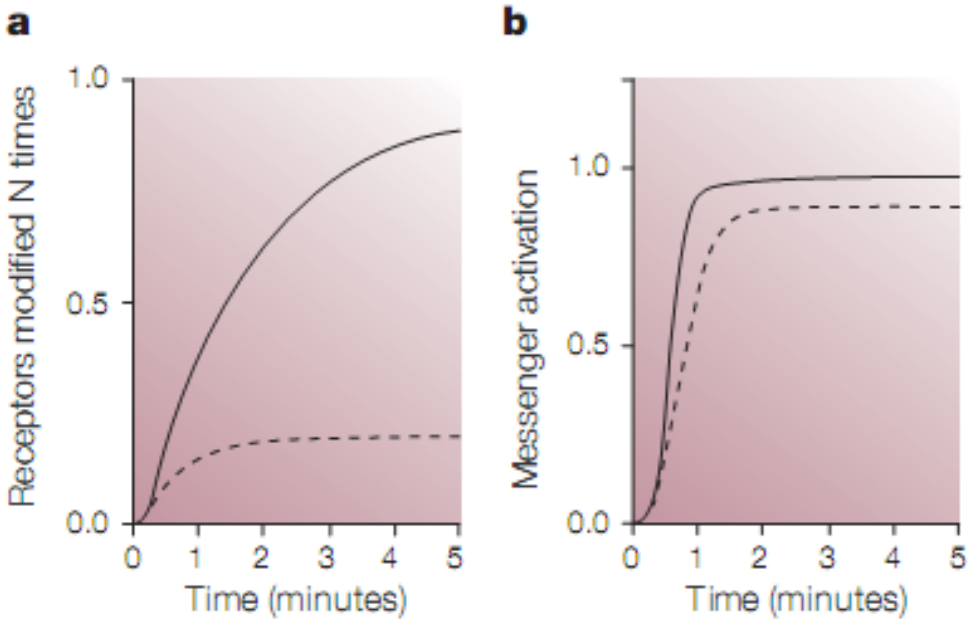


Figure 2 | **Escape from kinetic proofreading.** Cellular responses controlled by a cytosolic messenger can be insensitive to the kinetic quality of ligand-induced activation, even if other responses (such as those controlled by receptor modification) depend on the kinetics of ligand–receptor binding. **a** | The number of fully activated receptors stimulated by a slowly dissociating ligand (solid line) and a rapidly dissociating ligand (dashed line) is plotted as a function of time after ligand activation. **b** | The number of activated messengers activated by the same two ligands is plotted as a function of time. Calculations are based on the model of Hlavacek *et al.*[53], in the form of a system of ordinary differential equations, which is similar to that shown in BOX 3. These images are reproduced with permission from REF. 53 © (2002) Elsevier.

Escape

时间加和(temporal summation)

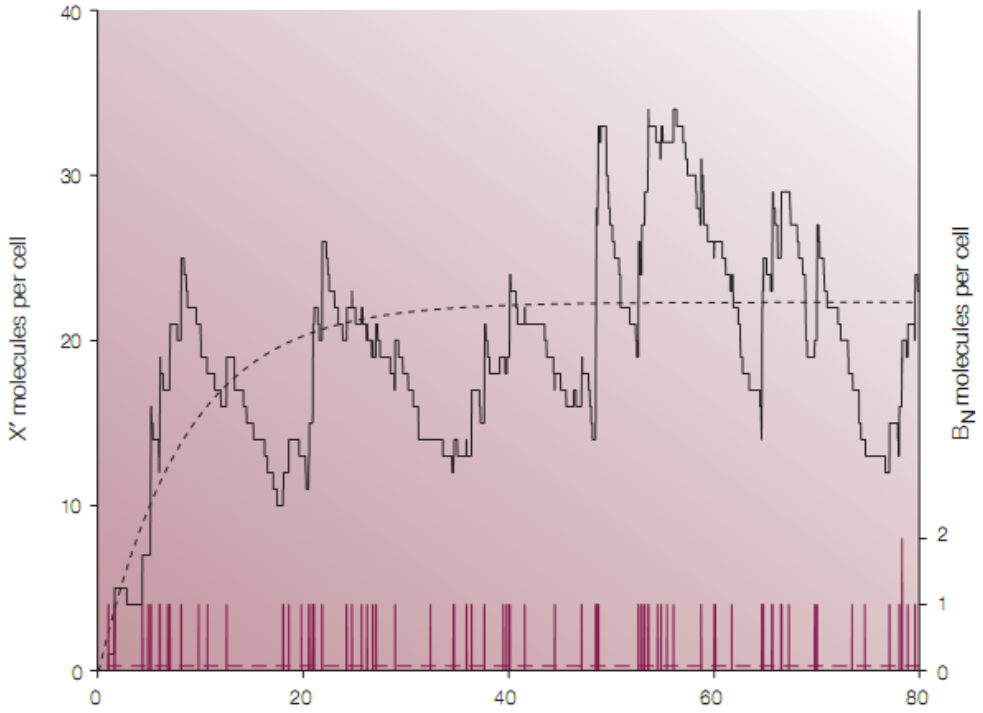


Figure 3 | **Production of activated messengers and fully modified receptors in a single T cell, as a function of time after ligand stimulation.** Over the time course shown, the fully modified receptor (B_N) state (red) is occupied intermittently by a single T-cell receptor (TCR) or in one instance two TCRs. While a TCR is in this state, the receptor catalyses messenger activation. As illustrated, the number of activated messengers (X') fluctuates. Calculations are based on the model illustrated in BOX 2. The jagged solid curve and the pulses (red) represent the results of a single stochastic simulation using the Gillespie algorithm[80,81] (BOX 1) and predict the response of a single cell. The dashed curve, calculated using ordinary differential equations, predicts the average number of activated messengers per cell for a population of cells. Parameter values for ligand–receptor binding correspond to the case of an interaction between an antigen-presenting cell (APC) and a T cell (through a single cell–cell contact region) and are based in part on estimates by Coombs *et al.*[27] See BOXES 2,3 for definitions of model parameters and rate constants. Red pulses represent the number of B_N molecules per cell.

连续结合(serial engagement) versus动力学校对(kinetic proofreading)

- 矛盾
- 最优结合时间
- 这些免疫受体被“标记”了吗？

更详细的模型 组合复杂性

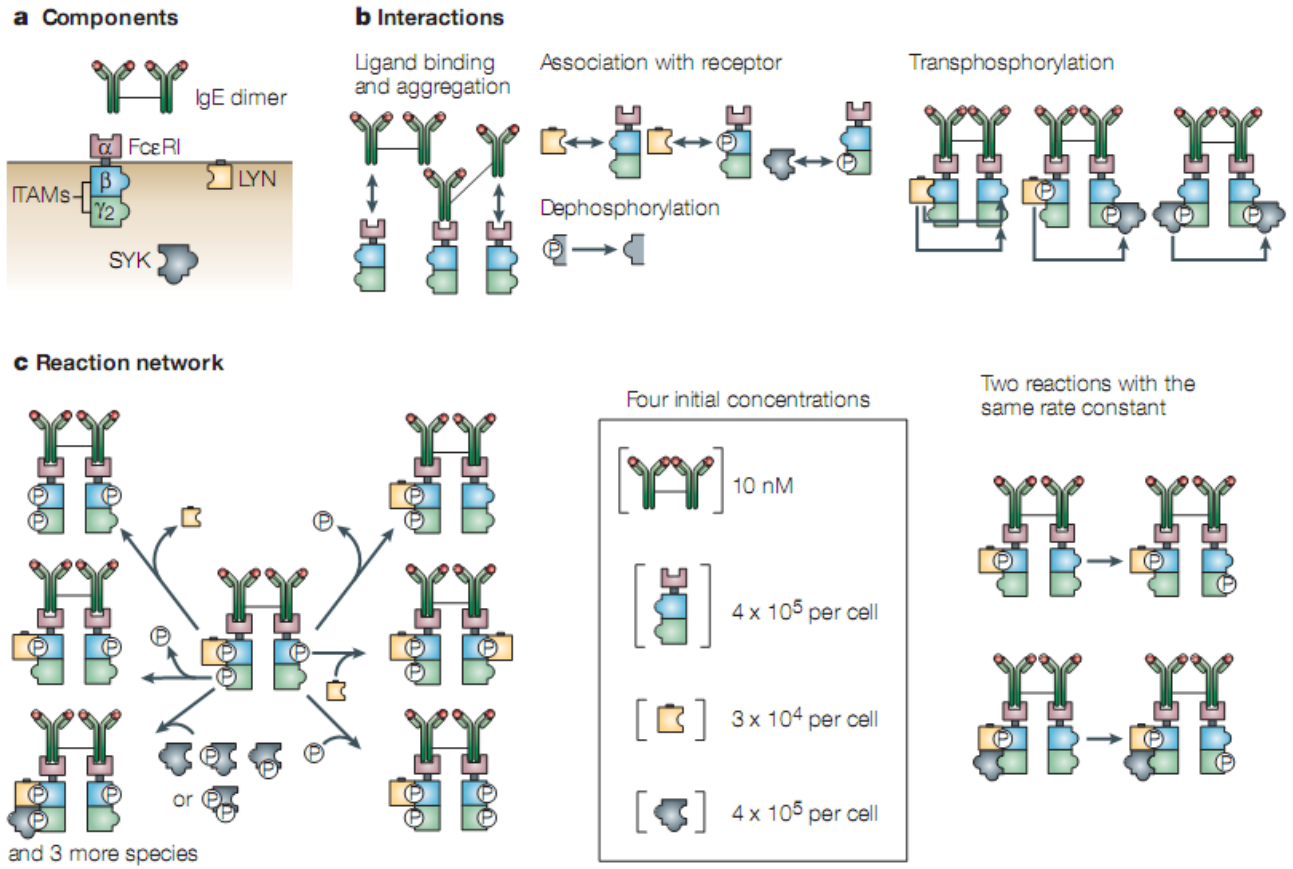
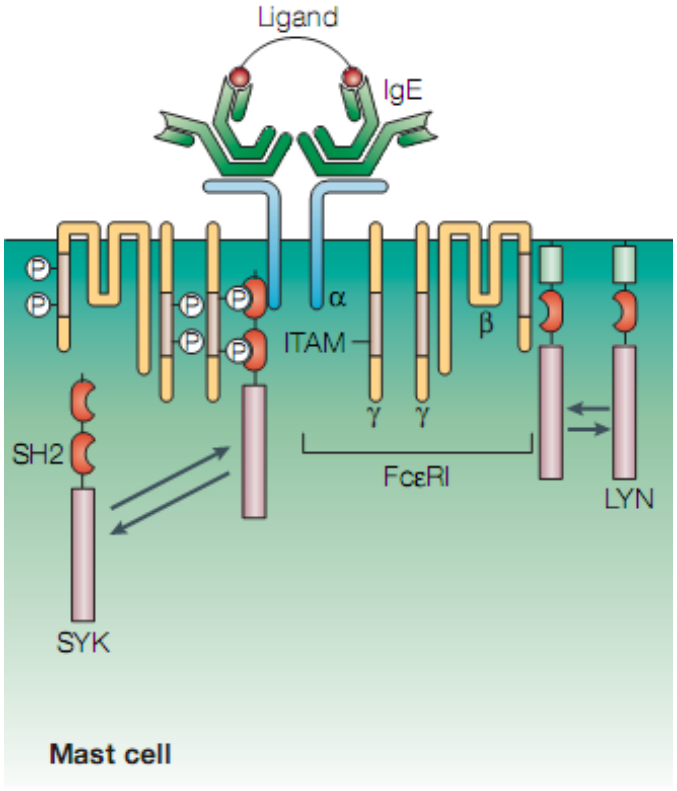


Figure 4 | **Detailed model of early events in FcεRI signalling. a** | The four components in the model are the ligand (IgE dimer), the receptor (FcεRI) and the two kinases LYN and SYK (spleen tyrosine kinase). The receptor is represented as an extracellular domain that binds the ligand and two cytoplasmic domains each containing an immunoreceptor tyrosine-based activation motif (ITAM). SYK also contains two regions that can be phosphorylated. **b** | Nine basic interactions are included: five for association or dissociation of molecular components, three for catalysis of phosphorylation and one for dephosphorylation, which can occur at any phosphorylated site that is not protected by binding another protein. **c** | The interactions give rise to a large number of complexes and phosphorylation states (354 states), each of which is tracked as a separate species. One typical species is illustrated along with the nine different reactions it can undergo. The species are connected by a large biochemical reaction network (composed of 3,680 reactions). A small number of parameters define this network — the initial concentrations of the 4 proteins and 21 rate constants — because the same rate constant can be used for many similar reactions. The figure depicts 2 of the 24 reactions in which LYN transphosphorylates the γ-ITAM (subsequent to its activation through binding the phosphorylated β-ITAM).

Fc receptor介导的信号转导

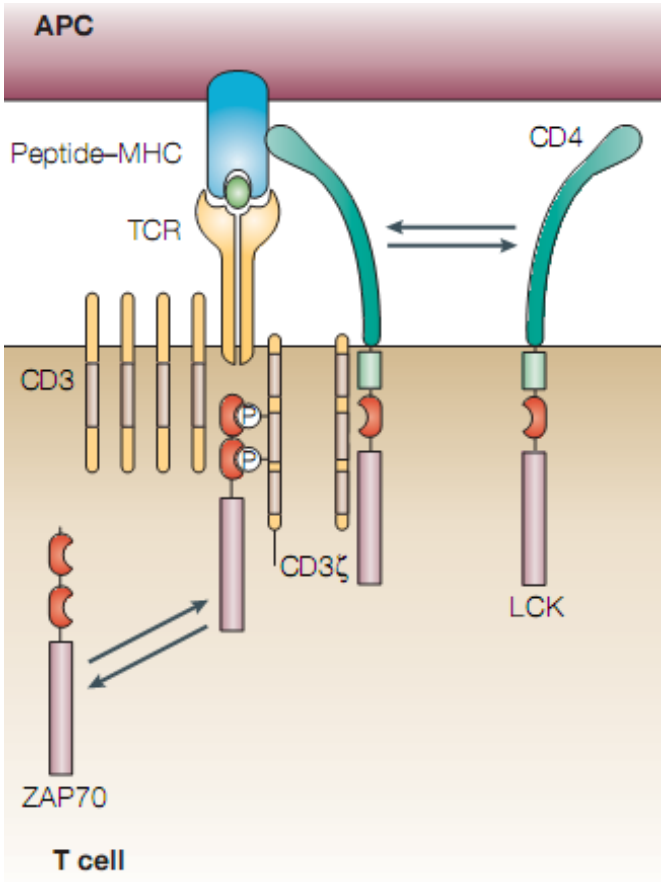


LYN是受体磷酸化的限制因素

低浓度LYN时，受体磷酸化水平与LYN浓度成线性关系

surprise：总LYN 浓度很高

TCR信号转导



central supramolecular activation cluster(cSMAC)

NOT surprising：
cSMAC加速受体磷酸化

surprising：
CD2AP缺陷小鼠（不能形成cSMAC）受体磷酸化被推迟但持久

动力学校对&连续结合

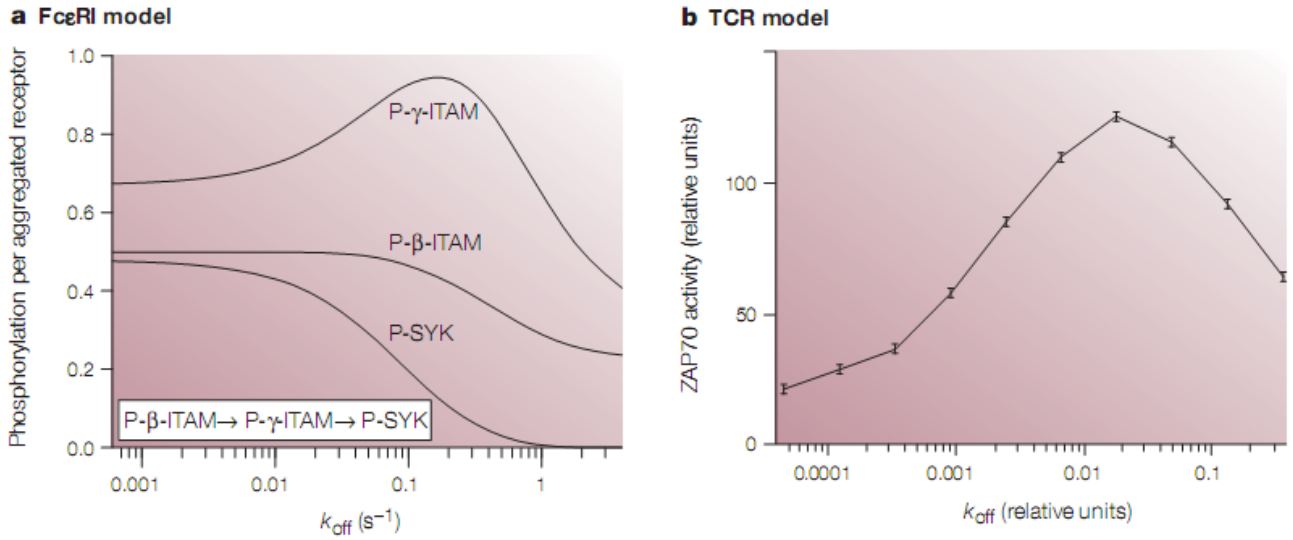


Figure 5 | **Effect on signalling events of varying the ligand–receptor off-rate in two detailed models. a** | The model depicted is that reported in REF. 22 for signalling through the high-affinity IgE receptor (FcεRI). The curves show the level of phosphorylated β-immunoreceptor tyrosine-based activation motif (P-β-ITAM), phosphorylated γ-ITAM (P-γ-ITAM) and phosphorylated SYK (P-SYK) per aggregated receptor, under steady-state conditions, at ligand concentrations in which fewer than 1% of receptors are aggregated. Phosphorylation levels are normalized in terms of the total number of receptors in aggregates, to control for the decrease in ligand affinity as the off-rate (k_{off}) is increased. The inset box shows the order of phosphorylation events in the model; this is only approximate because LYN can associate with the unphosphorylated receptor, and therefore β-ITAM phosphorylation is not absolutely required to precede γ-ITAM phosphorylation[22]. SYK phosphorylation shows strong kinetic proofreading, decreasing to nearly zero at higher off-rates. Phosphorylation of the β-ITAM, which is upstream of SYK phosphorylation, decreases more slowly (as predicted by the kinetic proofreading model) but does not decrease to zero (in contrast to the kinetic proofreading model)[53]. Intermediate between these two, γ-ITAM phosphorylation increases with increasing off-rate (a signature of serial engagement) and passes through a maximum before declining at higher off-rates (kinetic proofreading). **b** | The model depicted is the full network model reported in REF. 28 for signalling through the T-cell receptor (TCR). The curve shows the relative level of ZAP70 (ζ-chain-associated protein kinase 70 kDa isoform) activity at a fixed number of steps after the stimulation of 120 TCRs with 12 peptide–MHC complexes. The error bars represent the standard error of the mean for 10 trials. Up to an off-rate of approximately 0.01, ZAP70 activation increases with an increasing off-rate, which demonstrates serial engagement and triggering of TCRs. Although serial engagement continues to increase at higher off-rates, kinetic proofreading makes ligand–receptor encounters ineffective at generating a downstream signal, which leads to an overall reduction in ZAP70 activation. Normalization of ZAP70 activation (as shown in part **a**) is not required, because even at the highest off-rates, essentially all peptide–MHC complexes are bound as a result of the effectively high concentration of TCRs. This image is reproduced with permission from REF. 28 © (2003) American Association for the Advancement of Science.

评论

- 数学和计算机模型可以解释和预测一些现象
- 建模所需数据和建模方法限制了模型
- 同志们还需努力

Thanks a ton !