

Kinetic Proofreading Models for Immunoreceptor Signaling

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ABSTRACT

McKeithan [1] introduced a simple model, inspired by studies of kinetic proofreading in protein and DNA synthesis, and used this model to illustrate how the kinetics of ligand-receptor binding can influence T cell receptor (TCR) signaling. According to this model, a bound receptor must complete a series of modifications to generate a signal or cellular response. If the ligand dissociates before the cascade of modifications is complete, the receptor reverts to its basal state and no productive signaling occurs. The model shows that differences in the lifetime of a TCR-ligand complex produce disproportionate differences in TCR-mediated signals and cellular responses. Consistent with this prediction, Kersh *et al.* [2] found that TCR-ligands with different half-lives generate different phosphorylated forms of CD3- ζ , a signal-transducing molecule that associates with TCR. Although the model of McKeithan incorporates little molecular detail, it has provided a useful conceptual framework for investigating the relationship between TCR-ligand kinetics and T cell response.

The influence of ligand-receptor binding kinetics on signaling by Fc ϵ RI, an immunoreceptor closely related to TCR, also has been examined [3,4]. In this work, distal Fc ϵ RI-mediated signaling events and cellular responses, such as histamine release, were found to be sensitive to the time individual receptors spend in ligand-induced aggregates, consistent qualitatively with the predictions of McKeithan's model. However, Liu *et al.* [4] found that the model cannot explain several observations. The most striking example is the observation that synthesis of monocyte chemoattractant protein type 1 (MCP-1) mRNA, a relatively late cellular response to Fc ϵ RI aggregation, is insensitive to differences in ligand-receptor binding kinetics under conditions when other signaling events and responses are sensitive to these differences. Ligands that form short- and long-lived complexes with receptors were both found to stimulate expression of similar amounts of MCP-1 mRNA. This cellular response seems to escape the kinetic proofreading effect. Similar results also have been found in recent studies of TCR signaling [5].

To understand how signals and cellular responses generated by Fc ϵ RI, and related receptors, might escape kinetic proofreading, we have extended the model of McKeithan to consider cellular responses triggered by receptor-activated cytosolic messengers and by receptors in intermediate states of modification [6].

We find that the expected relationship between ligand-receptor binding kinetics and cellular response can change significantly when signal transduction involves a messenger or a receptor that has not reached the terminal state of modification. In particular, the properties of a messenger, such as a transcription factor that translocates from the membrane to the nucleus after receptor-mediated activation, can be adjusted to selectively tune the sensitivity of its targeted cellular response to the lifetime of a ligand-receptor bond.

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