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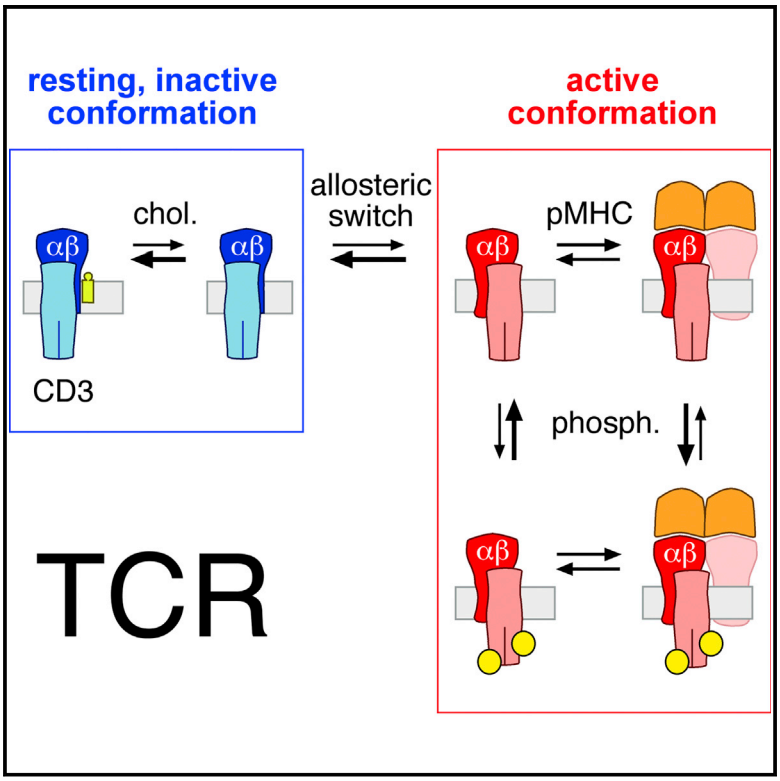
Immunity

A Cholesterol-Based Allostery Model of T Cell Receptor Phosphorylation

Graphical Abstract



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In Brief

The TCR can adopt an inactive, resting or an active, primed state. Schamel and colleagues show that the TCR is in equilibrium between these states. Peptide-MHC binding stabilizes the primed state that can be phosphorylated. Cholesterol binding stabilizes the resting state and thereby tunes the TCR activation threshold.

Highlights

- TCRs can spontaneously switch from the resting to the active conformation.
- Cholesterol binding to TCRβ prevents the switching to the active conformation.
- Only in the active conformation can TCRs be phosphorylated.
- The active conformation can signal without antigen.

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A Cholesterol-Based Allostery Model of T Cell Receptor Phosphorylation

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SUMMARY

Signaling through the T cell receptor (TCR) controls adaptive immune responses. Antigen binding to TCRαβ transmits signals through the plasma membrane to induce phosphorylation of the CD3 cytoplasmic tails by incompletely understood mechanisms. Here we show that cholesterol bound to the TCRβ transmembrane region keeps the TCR in a resting, inactive conformation that cannot be phosphorylated by active kinases. Only TCRs that spontaneously detached from cholesterol could switch to the active conformation (termed primed TCRs) and then be phosphorylated. Indeed, by modulating cholesterol binding genetically or enzymatically, we could switch the TCR between the resting and primed states. The active conformation was stabilized by binding to peptide-MHC, which thus controlled TCR signaling. These data are explained by a model of reciprocal allosteric regulation of TCR phosphorylation by cholesterol and ligand binding. Our results provide both a molecular mechanism and a conceptual framework for how lipid-receptor interactions regulate signal transduction.

INTRODUCTION

Membrane lipids are thought to play a passive role in the function of transmembrane (TM) proteins by embedding and organizing them into lipid microdomains (Coskun and Simons, 2011). In a few cases it has been shown that TM regions and certain lipids interact in a specific manner (Cherezov et al., 2007; Contreras et al., 2012; Coskun and Simons, 2011; Hanson et al., 2008) with mostly unknown functional implications. We have previously found that the T cell receptor (TCR) specifically binds to cholesterol in resting T cells to aid formation of TCR nanoclusters (Molnar et al., 2012). Here, we investigated whether this binding also regulated TCR signaling.

The TCR consists of eight TM proteins organized in dimers: TCRαβ, CD3εγ, CD3εδ, and CD3ζζ. TCRαβ binds to peptides presented on major histocompatibility complex (pMHC) molecules (Davis et al., 1998). The information provided through pMHC binding is transferred to the CD3 subunits, which are subsequently phosphorylated on immunoreceptor tyrosine-based activation motifs (ITAMs) by the SRC-family tyrosine kinase LCK (Iwashima et al., 1994). Phospho-CD3s serve as docking sites for the kinase ZAP70, which becomes active at the TCR and transmits downstream signals.

The mechanism of signal transduction from the extracellular domains of TCRαβ through the membrane, resulting in phosphorylation of the CD3 cytoplasmic tails, is poorly understood (Davis and van der Merwe, 2006). Any mechanistic model needs to take into account that in resting T cells a large proportion of LCK is active (Nika et al., 2010), yet CD3s are not phosphorylated. Accordingly, several models, including spatial segregation of phosphatases and sequestration of the CD3 chains, have been proposed (Kuhns and Davis, 2012; Shi et al., 2013; van der Merwe and Dushek, 2011; Xu et al., 2008).

Using protease resistance, fluorescence resonance energy transfer (FRET), and biochemical approaches, researchers have shown that the quaternary structure of the TCR changes upon ligand binding and that this alteration results in a reversible conformational change in the cytoplasmic tails of the CD3 subunits (Gil et al., 2002; Lee et al., 2015; Risueno et al., 2005; Risueno et al., 2008). These studies have led to the permissive-geometry model of TCR activation (Minguet and Schamel, 2008; Minguet et al., 2007). One hallmark of this structural change is the regulation of the accessibility of a proline-rich sequence (PRS) in the CD3ε cytosolic tail. In the non-ligand-bound TCR, the PRS cannot