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Negative costimulatory microclusters inhibiting T cell-mediated inflammation

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Abstract

T cells play a pivotal role in the regulation of inflammation by orchestrating immune systems. The regulation of T cell activation is a key for the maintenance of the balance between immunity and inflammation, and is mediated by T cell receptors (TCRs) and various costimulatory molecules by an interrelated manner. Programmed cell death-1 (PD-1) is a negative costimulatory receptor critical for the suppression of T cell activation in vitro and in vivo and recently identified functional in chronic inflammation such as hepatitis C virus and HIV infections. Using single cell imaging, we identified a dynamic molecular mechanism of PD-1-mediated suppression through formation of a novel costimulatory signalosome. PD-1 becomes clustered with TCRs in a ligand-dependent manner and is transiently associated with the phosphatase SHP2, forming “negative costimulatory microclusters” that induce the dephosphorylation of the proximal TCR signaling molecules. This results in the suppression of T cell activation and blockade of the TCR-induced stop signal. Furthermore, in addition to PD-1 clustering, the PD-1-TCR colocalization in the microclusters is required for PD-1-mediated suppression. This inhibitory mechanism also functions in PD-1hi T cells generated in vivo, and can be abolished by a neutralizing anti-PD-L1 antibody. Therefore, PD-1 microcluster formation is important for regulation of T cell activation and possibly for therapeutic purposes.