Dynamic regulation of T cell activation by TCR microclusters and a c-SMAC.

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The interaction between a T cell and an antigen-presenting cell (APC) results in the formation of the immunological synapse, which had been considered to be responsible for T cell antigen recognition and its activation. Recent advances in imaging analysis have provided us new insights into T cell activation. The T cell receptor (TCR) microclusters, which contain TCRs and their downstream kinases and adaptors, are generated at the interface between a T cell and an APC or an antigen-resenting lipid bilayer and serve as a fundamental signaling unit for T cell activation. Furthermore, each costimulatory receptors forms their characteristic signaling domains and regulates T cell activation cooperatively or antagonistically with TCR microclusters. The positive costimulatory receptor CD28 generates a novel activation cluster at the central-supramolecular activation cluster (c-SMAC) with an atypical kinase PKCθ and a scaffold protein Carma1, that are pivotal molecules in the NF-κB pathway, and the negative receptor CTLA-4 breaks the CD28–PKCθ–Carma1 signaling complex there competing with CD28 for the ligand CD80/CD86-binding. In contrast, another negative costimulatory receptor PD-1 forms clusters specifically recruiting the phosphatase SHP-2 and dephosphorylates the most of the kinases and adaptors in the TCR proximal downstream. Further analyses propose us the other signaling clusters in the different signaling pathways. I will present and discuss the mechanisms of T cell activation regulation by TCR microclusters in a spatiotemporal manner.

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