Dissertation summary

The role of membrane microdomains and transmembrane adaptor proteins PRR7 and SCIMP in the regulation of immunoreceptor signaling

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How do the plasma membrane microdomains and transmembrane adaptor proteins (TRAPs) influence the outcome of immunoreceptor signaling? These have been the important questions of molecular immunology. In spite of the years of intensive research, these problems remain incompletely understood. The plasma membrane is a highly dynamic heterogeneous bilayer spontaneously organized into microdomains of various size, composition, and lifetime. The lipid rafts are one example of such microdomains and have been implicated in many biological processes, including immunoreceptor signaling. Because rafts are enriched in many signaling proteins, they are believed to function as platforms for signal initiation and propagation. The TRAPs are important organizers and regulators of immunoreceptor signaling. For example, LAT is indispensable in T cell receptor (TCR) signaling and T cell development, PAG for the regulation of Src family tyrosine kinases (SFKs), and NTAL is a multifunctional negative and positive regulator. The presence of these TRAPs in lipid rafts seems to be crucial for their functions, however, is still a matter of debate. Moreover, other so far unidentified TRAPs could exist and play important roles in signal transduction pathways.

Here, we studied how the membrane environment influences the signaling capacity of LAT. According to our results, LAT targeted outside lipid rafts is less functional than wild-type LAT. Surprisingly, we found that LAX, a TRAP which was originally described as a typical non-raft TRAP, is targeted to a novel biochemically distinct type of membrane microdomains that can be isolated as heavy detergent resistant membranes (DRMs). We also discovered two novel leukocyte TRAPs, PRR7 (proline rich 7) and SCIMP (SLP65/SLP76 and Csk interacting membrane protein). PRR7 is up-regulated in activated T cells. When overexpressed in Jurkat T cells, the majority of cells undergo a programmed cell death. During this process, PRR7 is removed from the plasma membrane and accumulates in perinuclear vesicular compartments. A so far unidentified WW domain-containing protein probably mediates these effects. PRR7 interact with Src and selectively stimulates the transcription factor c-Jun, while all other TCR signaling pathways are suppressed in the presence of PRR7. In contrast, SCIMP expression is restricted to professional antigen presenting cells (APCs) where it associates with tetraspanin-enriched domains (TEMs). SCIMP is recruited to immunological synapse, and regulates signaling elicited from engaged MHCII molecules. In B cells tyrosine phosphorylated SCIMP organizes a protein complex composed of Lyn, Csk, BLNK, and Grb2. Overexpression and knock-down experiment revealed that SCIMP positively regulates the Erk MAP kinase pathway. Collectively, our results highlight the importance of membrane microdomains and TRAPs in many aspects of immunoreceptor signaling.