Abstract

Membrane adaptor proteins are characterized by the lack of enzymatic activity and the presence of various interaction sites for other proteins and cellular membranes. They typically function as scaffolds connecting receptors or other adaptors with proximal signaling molecules at cellular membranes. Their overall effects on signaling can be activating or inhibiting depending on the nature of the effector molecules they recruit.

SCIMP is one of the membrane adaptors discussed in this thesis. It is expressed in antigen-presenting cells and it has been previously shown to enhance MHCII signaling in B cells. This thesis covers the analysis of SCIMP functions beyond B cells and describes the first analysis of SCIMP deficient mice. Although the results of this analysis did not show any alterations in immune cell populations, the novel function of SCIMP in dendritic cell signaling downstream of DECTIN-1 was uncovered. DECTIN-1 is a pattern recognition receptor involved in antifungal immunity. The data presented in this thesis describe the role of SCIMP in sustaining DECTIN-1 signaling over relatively long periods of time and the contribution of SCIMP signaling to maintaining prolonged production of pro-inflammatory cytokines.

PSTPIP2 is another interesting adaptor discussed in this thesis. It is expressed in myeloid cell lineage and is crucial for the regulation of inflammatory responses. Unlike SCIMP deficient mice, mice with mutation in PSTPIP2 are well characterized and develop autoinflammatory osteomyelitis (CMO). As a typical adaptor, PSTPIP2 can bind more interaction partners at once. We identified three novel PSTPIP2-binding proteins, including two important inhibitory phosphatases (SHIP1 and PEST family phosphatase PEP/LYP) and an inhibitory kinase CSK. In addition, we found a role for PSTPIP2 in the regulation of reactive oxygen species in primary murine granulocytes. This regulation proved to be physiologically important for the prevention of inflammatory bone damage during the course of the disease in the CMO mouse strain.