Abstract

Adaptive immune response plays a key role in maintaining homeostasis of the organism. T cells use an immense repertoire of T-cell receptors (TCRs) to discriminate between self and foreign antigens with very high sensitivity. Although we have many clues outlining how an ideal TCR repertoire is selected, and a good understanding of the TCR signaling machinery, there are still some key aspects of these processes that remain controversial. The objective of this thesis is to extend our knowledge of the very proximal events of TCR signaling, with special focus on interaction of TCR coreceptors with lymphocyte-specific kinase LCK.

Coreceptor-LCK interaction has been described to regulate several aspects of T-cell development and response. We observed dynamic change of this interaction in course of T-cell development. Interestingly, CD4 and CD8 coreceptors displayed differential dynamics of interaction with LCK. Our data suggest that such disparity in coreceptor-LCK interaction leads to selection of more self-reactive TCR repertoire in $CD8^+$ T cells. Moreover, when the highly self-reactive $CD8^+$ T cells get to the periphery, the homeostatic signals drive their differentiation towards a more tolerogenic memory-like phenotype.

To finally resolve the role of coreceptor-LCK interaction in the T-cell development, we established a murine genetic model with abolished coreceptor-LCK interaction. Our data clearly show that the coreceptor-LCK interaction is essential for proper T-cell development and response, especially to weaker stimuli. Yet again, CD4 and CD8 coreceptors diverge in their function. While both CD4-LCK and CD8-LCK require an enzymatic activity for response to weak stimuli, CD4-LCK seems to have additional role that does not require the LCK kinase activity.

This thesis further includes several collaborative projects. We assisted in uncovering that CD4/CD8 lineage choice precedes any changes in the coreceptor expression, and it is most likely dependent on TCR signal strength. We also helped to identify additional scaffold function of LCK, bridging two other important components of proximal TCR signalosome – kinase ZAP70 and adaptor LAT. Next, our cell line model helped to understand function of phosphatase CD45 as a gatekeeper in TCR signaling, ensuring proper TCR ligand discrimination. Finally, we assisted in identifying a single amino acid site on LAT that evolved for more efficient ligand discrimination.