Abstract

T-cell activation, an essential process for establishing adaptive immunity, occurs within a highly organized spatial platform known as the immunological synapse (IS). The formation of the IS enables the intricate interplay between membrane-associated signaling molecules, membrane morphology and the underlying cytoskeletal network, highlighting the critical role of membrane-cytoskeleton linkers that serve as bridges in this dynamic interaction.

Our previous research has revealed that early upon T-cell activation, a critical kinase Lck, in its active state, enables the formation of multiprotein complexes. Importantly, membrane-cytoskeletal linkers α-actinin-1 and α-actinin-4 were showed to be recruited to these complexes within seconds of T-cell activation, suggesting their involvement in the early stages of this process. In this study, we characterized α-actinin-4 as a negative regulator of T-cell activation at specific time points: a few seconds, 4 hours, and 24 hours post-stimulation. However, the impact of α-actinin-1 on T-cell activation was not significant, underscoring the necessity for further research.

Concurrently, we investigated the role of membrane morphology in IS formation and for the first time, to our knowledge, we identified three distinct morphological stages of early IS, during which specific membrane structures, such as microvilli and EVs, were observed. The unexpected accumulation of B-cell membrane at the IS implies that B-cell morphology may play a more complex role in T-cell activation than previously understood.

We identified α-actinin-4 as a novel regulatory molecule that negatively modulates T-cell activation, and we described the morphological stages of early IS formation demonstrating the intricate complexity of membrane morphology. Together, these insights contribute to a more comprehensive understanding of the regulatory mechanisms governing T-cell activation.

Key words: T-cell activation, α-actinin-1, α-actinin-4, membrane morphology, immunological synapse