Abstract

The immune system possesses multiple mechanisms to protect the human body against pathogens. One of the key tools in eliminating the threat is the induction of inflammatory response. Inflammation aims to contain the infection and thus shield the tissue from further damage. Weak inflammatory process allows pathogens to harm the infected tissue. On the other hand, chronic inflammation is the cause of numerous diseases, such as psoriasis or multiple sclerosis. Therefore, it is crucial for the body to regulate the inflammatory process properly. The precise control of the mounted immune response is exerted by cytokines, small proteins secreted into the intercellular space. Cytokines influence various cells throughout the body and spread information about invading pathogens. Among the most important proinflammatory cytokines, interleukin 17 (IL-17) and tumor necrosis factor (TNF) play a crucial role. The presented work discusses the current state of knowledge of these cytokines and the signaling pathways they trigger.

The first part of this doctoral thesis deals with the signaling pathway triggered by IL-17. In our two published studies, we employed a new mass spectrometry-based methodology to study the composition of the IL-17 receptor signaling complex. We provided compelling evidence that IL-17-provoked signaling was negatively regulated by two kinases TBK1 and IKKε via a robust feedback loop. Moreover, we identified a new component of the IL-17 receptor signaling complex – a transmembrane protein CMTM4. We revealed, that this protein was crucial for the mediation of the IL-17 signal in IL-17-dependent autoimmune diseases.

The second part of this doctoral thesis focuses on the signaling pathway triggered by TNF. Although TNF proinflammatory and cell death-inducing signaling has been deeply studied over the past years, some aspects remain elusive. In our study, shich is currently under revisions, we described the role of adaptor proteins TANK and AZI2 in the protection against TNF-induced cell death. We revealed that although these proteins have a redundant role within the TNF signaling, their presence is indispensable for the protection against TNF-induced cell death.

Overall, our studies provide a deeper insight into the regulation of crucial proinflammatory signaling pathways and their role in health and disease