Universität Basel

Research Project

Characterization of the mechanisms of inflammasome assembly and signaling

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Inflammation is a rapid, highly coordinated response of the immune system to infection, cellular injury or irritants[1]. The inflammatory response needs to be tightly regulated and quickly terminated to prevent unnecessary damage to tissues and to the organism. Chronic inflammation is the underlying cause of many autoimmune disorders as well as atherosclerosis, ischaemic heart disease and even some types of cancer.

A major trigger of inflammation is the recognition of microbial pathogens and tissue damage by cells and receptors of the innate immune system[2,3]. A subset of these receptors controls the formation of "inflammasomes", cytosolic multi-protein signaling complexes that serve as an activation platform for the mammalian cysteine protease caspase-1[4]. Active caspase-1 promotes the induction of a lytic inflammatory cell death named pyroptosis and controls the maturation and release of pro-inflammatory cytokines interleukin-1-beta (IL-1β) and IL-18. Activation of caspase-1 requires tight control, since the dysregulation of inflammasome signaling is linked to many hereditary and acquired inflammatory disorders, commonly referred to as inflammasomopathies.

Despite its central role in immunity and auto-inflammatory diseases, numerous aspects of inflammasomes remain uncharacterized, such as the structure of the different inflammasome complexes, their regulation and the mechanism by which they induce pyroptosis and cytokine release. In addition, although caspase-1 is crucial for a successful innate immune defense, little is known about the mechanisms that regulate caspase-1 activity *in vivo*. Intriguingly, the same receptors that recognize pathogens also respond to danger signals resulting from cell injuries and can cause severe autoinflammatory disorders when dysregulated. Therefore, understanding the molecular mechanisms of inflammasome activation and downstream signaling will not only expand our knowledge on the host response to infection but also shed light on the role of the inflammasome in autoinflammatory and rheumatic diseases.

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