Universität Basel

Research Project

Dynamics and molecular mechanisms of pathogen-induced inflammasome activation

Third-party funded project

Project title Dynamics and molecular mechanisms of pathogen-induced inflammasome activation
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Inflammation is a rapid, highly coordinated response of the immune system to infections, cellular injury or irritants. The inflammatory response needs to be tightly regulated and quickly terminated to prevent unnecessary damage to tissues and to the organism. Prolonged, 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 cellular damage by cells and receptors of the innate immune system. A subset of these receptors controls the activation of “inflammasomes”, cytosolic multiprotein signaling platforms that promotes the secretion of proinflammatory cytokines and induces pyroptosis, a novel form of inflammatory cell death. We have recently shown that ASC, an adaptor protein of inflammasome complexes, oligomerizes into one single, cytoplasmic structure called an ASC focus in murine macrophages infected with the intracellular pathogens *S. typhimurium* or *F. novicida*. This large structure serves as an activation platform by recruiting and processing the inactive pro-caspase-1 into proteolytically active caspase-1. We have also demonstrated that inhibition of caspase-1 activity leads to an accumulation of the caspase and its downstream targets in the ASC focus.

In this proposal we describe experiments aimed at understanding the dynamics and mechanisms that underlie the formation of the ASC focus formation in infected cells. In particular we are interested in identifying novel components and downstream signaling partners of the complex and caspase-1. To isolate the complex and identify its components, we will combine antibody- and tag-based proteomics approaches. The role of novel components in inflammasome signaling in infected macrophages will be addressed using RNA interference. The dynamics of the complex formation during infection will be studied using a novel live-cell imaging system.

Inflammasome complexes play important roles in host defense against infections, however dysregulation of inflammasome signaling has also been linked to many hereditary and acquired inflammatory disorders. Therefore, a better characterization of the signaling pathways directed by the inflammasome complex is important. We expect that this project will not only increase our knowledge of host defense mechanisms, but could also lead to a better understanding of the pathogenesis of autoinflammatory diseases. In addition, such knowledge could establish the molecular basis for the development of novel compound designed as immune modulators and/or anti■infectives.

Keywords Infection biology, Caspase-1, Inflammation, Immunology, Inflammasome complex, Pattern recognition receptors, Intracellular pathogens, Unconventional secretion, Innate Immunity, Salmonella

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