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Opinion Article

Mechanisms of Cytosolic Bacterial Detection by Inflammatory Caspases: Implications for Host Defense

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DESCRIPTION

Cytosolic bacteria pose significant threats to host organisms by subverting immune responses. In response, the host utilizes a variety of innate immune mechanisms to detect and neutralize these pathogens. Among these mechanisms, inflammatory caspases, particularly caspase-1 and caspase-11 in mice (and their human homologs, caspase-4 and caspase-5), play a major role in the detection of cytosolic bacteria. This manuscript explores the cellular and molecular processes by which inflammatory caspases recognize and respond to bacterial invasion, with an emphasis on their role in inflammasome activation, pyroptosis and immune modulation. Understanding these pathways offers insights into host defense mechanisms and potential therapeutic strategies for bacterial infections.

Cytosolic bacteria such as *Salmonella*, *Shigella* and *Listeria* are recognized by the host immune system through Pattern Recognition Receptors (PRRs) that detect Pathogen-Associated Molecular Patterns (PAMPs). Among these, inflammatory caspases serve as key sensors for bacterial detection and initiate inflammatory responses. Caspases are a family of proteases that play a critical role in regulating inflammation, cell death and immune responses. Specifically, inflammatory caspases are involved in the activation of the inflammasome, a multiprotein complex that detects pathogens and triggers immune signaling. This manuscript discusses the molecular mechanisms through which inflammatory caspases detect cytosolic bacteria and the subsequent immune responses that contribute to pathogen elimination.

Inflammatory caspases, primarily caspase-1, caspase-4 and caspase-5, are essential for the detection of cytosolic bacteria. These caspases are activated upon the recognition of bacterial components such as Lipopolysaccharides (LPS) and flagellin, which are detected by the inflammasome complex:

In mice, caspase-1 is activated through the NLRP3 inflammasome in response to a broad spectrum of cytosolic pathogens. Upon activation, caspase-1 processes pro-inflammatory cytokines such as IL-1β and IL-18, which trigger acute inflammation and recruit immune cells to the site of infection. In humans, caspase-4 and caspase-5 are homologs of murine caspase-11 and are activated by the presence of LPS in the cytosol. These caspases recognize cytosolic bacterial LPS through a direct binding mechanism, leading to inflammasome activation and pyroptosis, a form of programmed cell death that aids in pathogen clearance.

The inflammasome is a cytosolic complex formed in response to various microbial stimuli. Upon detection of cytosolic bacteria, inflammasome components such as NLR proteins (e.g., NLRP3, NLRC4) are recruited and assemble into a large multiprotein complex. This complex facilitates the activation of inflammatory caspases, including caspase-1, caspase-4 and caspase-5, which in turn cleave and activate downstream substrates.

These cytokines are potent mediators of inflammation and immune responses. Their maturation and release following inflammasome activation help to recruit immune cells and enhance the inflammatory response at the site of infection. Activated inflammatory caspases also trigger pyroptosis, a highly inflammatory form of programmed cell death. Pyroptosis results in cell membrane rupture, the release of intracellular contents and the induction of a pro-inflammatory environment that aids in pathogen clearance but can also contribute to tissue damage if uncontrolled. The detection of cytosolic bacteria by inflammatory caspases relies on several molecular mechanisms. Caspase-4 and caspase-5 are directly activated by cytosolic bacterial LPS, a major component of the outer membrane of Gram-negative bacteria. This recognition occurs when LPS is translocated into the host cytosol, where it binds to caspase-4 and caspase-5, resulting in their activation.

Pattern Recognition Receptors (PRRs) in addition to caspase-mediated detection, host cells express various PRRs such as TLRs (Toll-like receptors) and NLRs (NOD-like receptors), which initially recognize bacterial PAMPs. These receptors activate downstream signaling pathways that lead to inflammasome

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assembly and caspase activation. Some cytosolic bacteria, such as *Shigella* and *Listeria*, can directly inject bacterial effector proteins into host cells through specialized secretion systems. These effector proteins can modulate host cell functions, including the activation of inflammasomes, thereby triggering inflammatory caspase activity. Beyond their role in pathogen detection and cell death, inflammatory caspases modulate the host immune response in several ways, Caspase-1 activation leads to the secretion of pro-inflammatory cytokines such as IL-1β and IL-18, which enhance the recruitment of immune cells such as neutrophils and macrophages to the infection site.

Inflammatory caspases also interact with autophagy pathways, which are important for the degradation of intracellular pathogens. The activation of caspase-1 has been shown to enhance autophagic responses, contributing to the elimination of cytosolic bacteria. Through the release of cytokines and other pro-inflammatory mediators, inflammatory caspases help orchestrate a coordinated immune response, involving both innate and adaptive immunity to control and eliminate bacterial infections.

Understanding how inflammatory caspases detect and respond to cytosolic bacteria has important implications for therapeutic development. Caspase inhibitors or modulators could be used to regulate inflammatory responses in conditions where excessive inflammation contributes to tissue damage, such as in sepsis or inflammatory bowel disease. Conversely, enhancing caspase activation may offer potential strategies for improving host defense against bacterial infections.

CONCLUSION

Inflammatory caspases play a central role in the detection of cytosolic bacteria, initiating a cascade of immune responses that contribute to pathogen elimination. Through their involvement in inflammasome activation, cytokine release and pyroptosis, these caspases are critical for the host's defense against bacterial pathogens. Further investigation into the molecular mechanisms governing these processes will enhance our understanding of immune responses and provide new avenues for therapeutic intervention in bacterial infections.