INFLAMMASOME BIOLOGY

FUNDAMENTALS, ROLE IN DISEASE STATES, AND THERAPEUTIC OPPORTUNITIES

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CHAPTER

Cellular signaling, molecular activation, and regulation of the noncanonical inflammasome

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1. Introduction

The innate immune system employs extracellular membrane bound and intracellular pattern recognition receptors (PRRs) to detect a diverse repertoire of conserved microbial- or pathogen-associated molecular patterns (MAMPs and PAMPs, respectively) as well as host-derived danger associated molecular patterns (DAMPs), and PRR activation elicits a concerted and controlled inflammatory response. Lipopolysaccharide (LPS) is the major component of the outer membrane of Gram-negative bacteria and a very potent proinflammatory PAMP. The Toll-like receptor 4 (TLR4) complex has been recognized as the major cellular LPS recognition system until caspase-4/-5 and -11 were identified as intracellular LPS receptors that are forming the noncanonical inflammasome [1–3]. LPS-meditated TLR4 activation engages nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and interferon regulatory factors (IRFs) downstream of Myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adapter-inducing interferon-β (TRIF), which induces transcription of inflammatory cytokines, chemokines, adhesion molecules, interferons, and other proinflammatory and antimicrobial factors [4]. In contrast, canonical and noncanonical inflammasome activation culminates in the activation of inflammatory caspases, which are described in other chapters of this book, leading to proteolytical maturation and release of the cytokine substrates interleukin (IL)-1β and IL-18 and induction of pyroptosis. Pyroptosis is an inflammatory cell death in response to caspase-mediated proteolytic cleavage of gasdermin D (GSDMD), which removes the inhibitory C-terminal domain and allows polymerization and insertion of the N-terminal fragment into membranes, thereby forming a lytic pore [5]. Subsequently, a multitude of proinflammatory cellular danger signals, including HMGB1, IL-1α, and polymerized inflammasome particles, are released through the GSDMD pore. Canonical inflammasomes assemble upon activation of NLRs, AIM2, Pyrin, or CARD8, and mediate caspase-1 activation and detailed mechanisms of canonical inflammasome activation are described in the different chapters of this book. Active caspase-1 cleaves cytokine substrates as well as GSDMD and promotes cytokine release as well as pyroptosis, but activation of human caspases-4 and -5 and mouse caspase-11 in the noncanonical inflammasome only results in the

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