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NLRP3-Inflammassome Participates in the Inflammatory Response Induced by Paracoccidioides brasiliensis

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Abstract : The inflammatory response initiates after the recognition of pathogens by receptors expressed by innate immune cells. Among these receptors, the NLRP3 was associated with the recognition of pathogenic fungi in experimental models. NLRP3 operates forming a multiproteic complex called inflammasome, which actives caspase-1, responsible for the production of the inflammatory cytokines IL-1beta and IL-18. In this study, we aimed to investigate the involvement of NLRP3 in the inflammatory response elicited in macrophages against Paracoccidioides brasiliensis (Pb), the etiologic agent of PCM. Macrophages were differentiated from THP-1 cells by treatment with phorbol-myristate-acetate. Following differentiation, macrophages were stimulated by Pb yeast cells for 24 hours, after previous treatment with specific NLRP3 (3,4-methylenedioxy-beta-nitrostyrene) and/or caspase-1 (VX-765) inhibitors, or specific inhibitors of pathways involved in NLRP3 activation such as: Reactive Oxigen Species (ROS) production (N-Acetyl-L-cysteine), K+ efflux (Glibenclamide) or phagossome acidification (Bafilomycin). Quantification of IL-1beta and IL-18 in supernatants was performed by ELISA. Our results showed that the production of IL-1beta and IL-18 by THP-1-derived-macrophages stimulated with Pb yeast cells was dependent on NLRP3 and caspase-1 activation, once the presence of their specific inhibitors diminished the production of these cytokines. Furthermore, we found that the major pathways involved in NLRP3 activation, after Pb recognition, were dependent on ROS production and K+ efflux. In conclusion, our results showed that NLRP3 participates in the recognition of Pb yeast cells by macrophages, leading to the activation of the NLRP3-inflammasome and production of IL-1beta and IL-18. Together, these cytokines can induce an inflammatory response against P. brasiliensis, essential for the establishment of the initial inflammatory response and for the development of the subsequent acquired immune response.

Keywords : inflammation, IL-1beta, IL-18, NLRP3, Paracoccidioidomycosis
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