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Activation of NLRP3-inflammasome in human monocyte-derived macrophages infected with *Mycobacterium* spp.

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Statement of the Problem: Tuberculosis (TB) is still a major public health problem worldwide, and it is estimated that 1/3 of world population could be latently infected by *Mycobacterium* spp. Active TB represents a big challenge for treatment due to the natural resistance of bacteria to common antibiotics, and to the emergence of multidrug resistant strains. The development of active disease results from the host inability to effectively counteract the bacteria. In this context, both innate and acquired immunity have been taken in account as important factors for protection against TB. Nod like receptors (NLRs) and the cytoplasmic complex known as inflammasome are responsible for caspase-1 activation and the consequent production of active form of the pro-inflammatory cytokines IL-1ß and IL-18. Experimental models have showed that *M. tuberculosis* activates NLRP3-inflammasome and IL-1ß production. Aim of this project is to evaluate the contribution of inflammasome in human TB.

Methodology & Theoretical Orientation: The distribution of 14 single polymorphisms (SNPs) in 9 selected inflammasome genes was evaluated in a case/control cohort of Amazon TB patients (allele-specific Taqman assays and qPCR). Inflammasome activation was then analyzed in human peripheral blood monocytes-derived macrophages (MDM) stimulated with *M. tuberculosis* (BCG or H37Rv) by the meaning of IL-1β and IL-18 production (ELISA), gene expression modulation (gene-specific Taqman assays and qPCR). Experiments were done in the presence of common NLRP3 inflammasome activators (ATP, LPS), or inhibitors (parthenolide).

Conclusion & Significance: Polymorphisms in inflammasome genes contributes to control (*NLRP3, CTSB*) or development (*P2X7*) of active pulmonary TB. *M. tuberculosis* induced dramatic release of IL-1β and IL-18 from MDM, and the increase of *NLRP3, IL1B* and *IL18* genes expression, suggesting that both indirect (through NF-kB) and direct (through caspase-1) activation of inflammasome are involved in the response. Preliminary data showed that this activation is significantly inhibited by parthenolide, confirming the involvement of inflammasome in response to M tuberculosis in human MDM. Associated SNPs positively correlated with IL-1ß and/or IL-18 production in MDM. Further experiments are going on to fully elucidate the contribution of inflammasome in TB.

Biography

Dhêmerson Souza de Lima has expertise in evaluation molecular biology with the emphasis on immunology, working mainly on the following topics: tuberculosis, immunogenetics of pulmonary tuberculosis, and HLA class II and inflammasome genetics and the response immune to *Mycobacterium* spp. Recently he was reported that *HLA-DRB1*04* gene and subtypes associated with pulmonary tuberculosis in Amazon Brazilian, and may be potential immunogenetic markers involved in disease. Besides, he found that NLRP3-inflammasome genetics seems to be protective against the development active pulmonary tuberculosis, however, P2X7 is associated with increased susceptibility. Currently is Ph.D. student in work with innate immune response and pathway to activation inflammasome

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