[PS1.12]

Mycobacterium tuberculosis Protein ESAT-6 is a Potent Activator of the NLRP3/ASC Inflammasome

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Interleukin-1b (IL-1b) represents one of the most important mediators of inflammation and host responses to infection. Increased production of IL-1b has been linked to a wide variety of diseases. *Mycobacterium tuberculosis (Mtb)*, the causative agent of human tuberculosis, induces IL-1b secretion at the site of infection, but the underlying mechanism(s) are poorly understood. In this work we show that *Mtb* infection of macrophages stimulates caspase-1 activity and promotes the secretion of IL-1b. This stimulation needs the active contribution of the bacterium, as live intracellular bacteria expressing a functional ESX-1 secretion system are required. ESAT-6, an ESX-1 substrate implicated in membrane damage, is both necessary and sufficient for caspase-1 activation and IL-1b secretion. ESAT-6 promotes the access of other immunostimulatory agents such as AG85 to the macrophage cytosol, indicating that ESX-1 may contribute to this process largely by damaging host cell membranes. Using a high-throughput shRNA-based screen we found that numerous NOD-like receptors (NLRs) and CARD-domain containing proteins (CARDs) were important for IL-1b secretion upon *Mtb* infection. Most importantly, NLRP3, ASC, and caspase-1 form an infection-inducible inflammasome complex that is essential for IL-1b secretion. In summary, this work demonstrates that the ESAT-6 promotes the translocation of mycobacterial PAMPs into the host cell cytosol. This event is primarily sensed by NLRP3-inflammasome, but is regulated by a number of other NLR/CARD proteins as well.

(financial support of FCT project PIC/82859/2007)

Keywords: Mycobacterium tuberculosis, inflammasome, PAMPS, ESAT6