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Translocation To The Cytosol Determines Mycobacterial Pathogenicity

N van der Wel*[1], D Houben[1], R Brosch[2], J van Ingen[3], D van Soolingen[3], P Peters[1,4] et al
[1]NKI-AvL, Netherlands, [2]Institut Pasteur, France, [3]RIVM, Netherlands, [4]Delft University of Technology, Netherlands

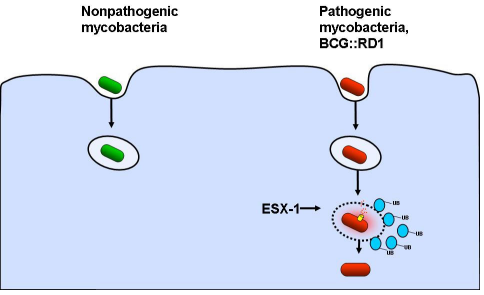
Introduction *Mycobacterium tuberculosis* has evolved to be among the most important human pathogens. The paradigm of the exclusive phagosomal localization in the human system was recently challenged by the identification of cytosolic *M. tuberculosis* and *M. leprae*. It is not known which system is responsible for translocation and whether translocation is important for pathogenicity of mycobacteria.

Methods Here we investigated a wide range of patient derived pathogenic and non-pathogenic *Mycobacterium* species for their ability to translocate to the cytosol of human phagocytic cells. Bacteria of these different species were cultured to OD 0.5, used for infection of THP-1 cells and processed for cryo-immunogold electron microscopy.

Results We have analyzed the localization of 18 isolates; covering 11 important pathogenic species. Multiple patient derived mycobacteria, translocate in substantial percentages to the cytosol. In contrast, non-pathogenic or opportunistic mycobacteria remain predominantly phagolysosomal (Figure 1). Previously it was shown that translocation was abrogated when the ESX-1 secretion system was mutated (van der Wel et al., Cell 2007). Indeed the ESX-1 secretion system is essential for translocation, but a functional secretion is not for all species sufficient as some ESX-1 expressing mycobacteria remain phagosomal. These species are also less pathogenic. Our data demonstrate a clear correlation between the capacity to translocate and pathogenicity.

Discussion We thus demonstrate that ESX-1 is essential but not the determining factor for the subcellular localization of mycobacteria and conclude that the ability to translocate is a pathogenicity factor for mycobacteria.

Figure 1



Schematic representation of the cellular localization of pathogenic versus non-pathogenic mycobacteria. Pathogenic mycobacteria (*M. tuberculosis*, *M. leprae, M. bovis,* and *M. marinum)* translocate readily and in contrast, opportunistic or non-pathogenic species (*M. szulgai*, *M. avium, M. fortuitum, M. gilvum, M. kansasii* type I and V, *M. smegmatis* and *M. bovis* BCG) remain predominantly phagolysosomal.

Keywords: pathogenicity, mycobacterium tuberculosis, cellular localisation, ESX-1