Analysis of SecA2-dependent substrates in Mycobacterium marinum identifies protein kinase G (PknG) as a virulence effector

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The pathogenicity of mycobacteria is closely associated with their ability to export virulence factors. For this purpose, mycobacteria possess different protein secretion systems, including the accessory Sec translocation pathway, SecA2. Although this pathway is associated with intracellular survival and virulence, the SecA2-dependent effector proteins remain largely undefined. In this work, we studied a Mycobacterium marinumsecA2 mutant with an impaired capacity to initiate granuloma formation in zebrafish embryos. By comparing the proteomic profile of cell envelope fractions from the secA2 mutant with wild type M.marinum, we identified putative SecA2-dependent substrates. Immunoblotting procedures confirmed SecA2-dependent membrane localization for several of these proteins, including the virulence factor protein kinase G (PknG). Interestingly, phenotypical defects of the secA2 mutant are similar to those described for pknG, including phagosomal maturation. Overexpression of PknG in the secA2 mutant restored its localization to the cell envelope. Importantly, PknG-overexpression also partially restored the virulence of the secA2 mutant, as indicated by enhanced infectivity in zebrafish embryos and restored inhibition of phagosomal maturation. These results suggest that SecA2-dependent membrane localization of PknG is an important determinant for M.marinum virulence.

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