



## Regulation of mycolactone, the *Mycobacterium ulcerans* toxin, depends on nutrient source

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**BACKGROUND:**

*Mycobacterium ulcerans*, a slow-growing environmental bacterium, is the etiologic agent of Buruli ulcer, a necrotic skin disease. Skin lesions are caused by mycolactone, the main virulence factor of *M. ulcerans*, with dermonecrotic (destruction of the skin and soft tissues) and immunosuppressive activities. This toxin is secreted in vesicles that enhance its biological activities. Nowadays, it is well established that the main reservoir of the bacilli is localized in the aquatic environment where the bacillus may be able to colonize different niches. Here we report that plant polysaccharides stimulate *M. ulcerans* growth and are implicated in toxin synthesis regulation.

**METHODOLOGY/PRINCIPAL FINDINGS:**

In this study, by selecting various algal components, we have identified plant-specific carbohydrates, particularly glucose polymers, capable of stimulating *M. ulcerans* growth in vitro. Furthermore, we underscored for the first time culture conditions under which the polyketide toxin mycolactone, the sole virulence factor of *M. ulcerans* identified to date, is down-regulated. Using a quantitative proteomic approach and analyzing transcript levels by RT-qPCR, we demonstrated that its regulation is not at the transcriptional or translational levels but must involve another type of regulation. *M. ulcerans* produces membrane vesicles, as other mycobacterial species, in which are the mycolactone is concentrated. By transmission electron microscopy, we observed that the production of vesicles is independent from the toxin production. Concomitant with this observed decrease in mycolactone production, the production of mycobacterial siderophores known as mycobactins was enhanced.

**CONCLUSIONS/SIGNIFICANCE:**

This work is the first step in the identification of the mechanisms involved in mycolactone regulation and paves the way for the discovery of putative new drug targets in the future.

Résumé en anglais

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