High throughput screening for identification of mycolactone targets : Relations between M. ulcerans and nervous system

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Résumé en anglais	Buruli ulcer is an infectious disease transmitted by arthropod vectors harboring *Mycobacterium ulcerans*, a *mycobacterium* which belong to the same family of bacteria causing tuberculosis and leprosy. The infection causes painless swelling and severe skin lesions. One key feature of *M. ulcerans* bacterium is its ability to secrete a necrotic toxin, the mycolactone within small lipophilic vesicles, which are critical for the bacterial induced cytotoxicity. The biological knowledge as well as the preventive and therapeutic means for this invalidating disease is still very limited. Our first approach was to investigate whether the mycolactone toxin could be involved in the neutralization of pain by acting directly on the peripheral nervous system without causing destruction of nervous fibers. By use of live time fluorescence microscopy and appropriate markers, we showed that the addition of toxin at sub-toxic dose provokes modification of ionic currents of neuron cells. Based on this ability of the toxin, a molecular high throughput methodology was developed for the screening of a genome wide siRNA library and small molecules inhibitors to enable the search of the cellular targets for the toxin. The cell-based assay relies on automated confocal microscopy on macrophages coupled with dedicated image analysis. These two screening allowed us to identify a putative toxin target, and a toxin inhibitor. A binding assay confirmed that the putative target is a receptor of the toxin. Together these results allowed us to build a potential signaling pathway activated by the mycolactone and implicated in ionic channel activities. The second approach was to confirm this model in the mouse model of *M. ulcerans* infection and its role in the hypoesthesia of the lesions. Toxin inhibitor, daily administered to mice, which were experimentally infected by *M. ulcerans*, conducted to the absence of the hypoesthesia of the lesions. Furthermore, a histological study of neuronal fibers did not show a destruction of neuronal cells. Moreover, *in vitro* studies have showed that *M. ulcerans* are able to colonize neuronal cells. Then, these results suggested that the hypoesthesia of the M. ulcerans lesions could be caused by a non-destructive process of nervous cells.
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