Impact of mycolactone, a macrolide produced by *Mycobacterium ulcerans*, on the dynamics of human T cells

BIOLOGIE & SANTÉ 2011

Laure Guenin-Macé[1], Florent Carrette[2], François Asperti-Boursin[2], Georges Bismuth[2], Anne-Caroline Chagny[3], Virginie Casarotto[3], Jacques Eustache[3], Nicolas Blanchard[3] & Caroline Demangel[1].

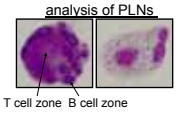
[1]Pathogénomique Mycobactérienne Intégrée, Institut Pasteur, Paris
[2]Institut Cochin, Université Paris Descartes, CNRS (UMR 8104), Paris, France
[3]Université de Haute-Alsace, Ecole Nationale Supérieure de Chimie de Mulhouse, Laboratoire de Chimie Organique et Bioorganique EA4566, Mulhouse

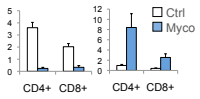
Background

Mycolactone is a toxin produced by *M. ulcerans,* the causative agent of Buruli ulcer, a neglected tropical disease characterized by severe necrotic cutaneous lesions. In addition to cytotoxic effects, mycolactone has immunomodulatory properties. Here we show that mycolactone alters T cell homing by suppressing the expression of L-selectin (CD62-L). Furthermore, we identify the miRNA let-7b as a novel mechanism of control of CD62-L expression.

Mycolactone induces T cell depletion in peripheral lymph nodes (PLNs)

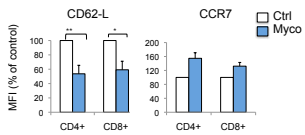
Mycolactone injection into mice induces a depletion of T cells in the PLNs. A concomitant increase in blood suggests that mycolactone alters T cell homing.





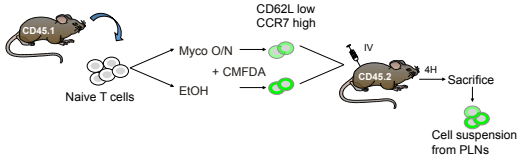
Mycolactone modulates the expression of homing receptors by T cells and impairs their homing capacity.

FACS analysis of homing receptor expression by T cells from treated and control mice.



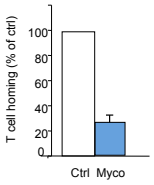
The expression of CD62-L and CCR7 is altered at the surface of PLN and blood T cells from mycolactone treated mice.

Adoptive transfer experiment



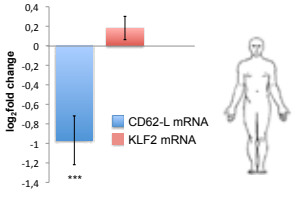
T cells exposed to mycolactone prior to transfer were recovered in the PLNs at lower frequencies than unexposed T cells.

FACS analysis gated on CMFDA$^+$ CD45.2$^-$ cells

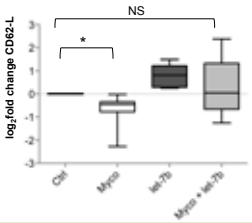


In HPBLs mycolactone downregulates CD62-L mRNA through the modulation of let-7b miRNA

CD62-L and KLF2 mRNA levels in HPBLs after a 4h treatment.

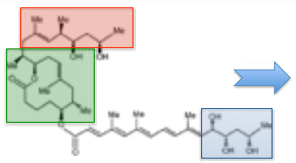


Induction of let-7b miRNA in HPBLs counteracts the mycolactone-induced downregulation of CD62-L.



In human PBLs, CD62-L mRNA are reduced after 4h of mycolactone treatment. Using a microRNA array approach we observed a downregulation of let-7b miRNA in mycolactone treated cells. Induction of let-7b in HPBLs induced an increase of CD62L mRNA and counteracted the effect of mycolactone.

Structure-function analysis of mycolactone.



Cytotoxicity
Immunosuppressive properties
Homing receptor expression…

Our work elucidates for the first time a molecular mechanism by which mycolactone modulates mammalian gene expression. Mycolactone has been shown to block the expression of cytokines and chemokines by human leukocytes without major impact on gene transcription. Over-expression of let-7b in T cells did not restore their capacity to produce IL-2 upon activation, suggesting that mycolactone might suppress the expression of target genes that are induced during cell activation by modulating other miRNAs. A detailed analysis of the miRNA transcriptome of cells activated in the presence of mycolactone should allow one to better understand the molecular pathways targeted by this toxin.

CONTACT :

Laure.guenin-mace@pasteur.fr
Caroline.demangel@pasteur.fr