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ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

SEMINAR

GHI Floor Seminar

Monday, May 2nd, 2016
@ 14.00 p.m.

Conference Room AI 1153

Caroline BARISCH

Université de Genève

Hosted by Prof. Bruno Lemaitre

Breaking fat!
How mycobacteria become obese in Dictyostelium mutants lacking lipid droplets!

Lipid droplets (LDs) store energy in form of neutral lipids and exist in virtually every cell type ranging from simple organisms such as bacteria and amoebae to plants and mammals. Induction of foamy, LD-filled macrophages, is a general host response to mycobacterial infection and develops shortly after granuloma formation. Intracellular mycobacteria have been seen either in close apposition to LDs or even "plunging" inside these energy storage organelles, possibly corroborating that the bacteria are able to exploit host lipids for their own metabolism. The mechanism by which the bacteria get access to these cytosolic lipid stores is still unknown.

Using the *Dictyostelium discoideum*/*Mycobacterium marinum* infection system as a model for foamy macrophages, we have found that *M. marinum* exploits lipids from host lipid droplets to build up its own lipid inclusion during infection. Strikingly, the *Dictyostelium* homologue of perilipin and the murine perilipin 2 surrounded bacteria that had escaped to the cytosol of *Dictyostelium* or microglial BV-2 cells, respectively. In addition, bacterial growth was inhibited in perilipin knockout cells.

To test which lipids are preferentially transported into the mycobacterium-containing compartment, we interfere with host enzymes involved in triacylglycerol (TAG) synthesis. Interestingly, the Long Chain Fatty Acid CoA Synthase (LC-FACS) 1, an enzyme that activates fatty acids and transfers them from endosomes to the cytosol, is recruited to the mycobacterium-containing compartment. In addition, diacylglycerol acyltransferase 2 (Dgat2) -GFP decorated LDs were seen clustering around presumably cytosolic bacteria at late infection stages.

Dictyostelium mutants lacking both Dgat enzymes are unable to generate triacylglycerols and lipid droplets. Instead, the exogenous fatty acids are esterified predominantly into phospholipids, inducing uncontrolled proliferations of the endoplasmic reticulum membrane. Strikingly, *M. marinum* is able to exploit this alternative source of host (phospho)lipids resulting in rapid reversal of endoplasmic reticulum-proliferation that disappears from infected cells early during infection. In addition, the bacteria build up many more lipid inclusions compared to the wild type. This excessive "fattening" is not accompanied by a significant change in intracellular growth and metabolic activity, and thus provides evidence that the storage of neutral lipids does not necessarily induce dormancy.