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ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

GHI Floor Seminars

Special seminar by invited speaker

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Dissecting the immunopathogenesis of Mycobacterium abscessus infection in zebrafish embryos

Mycobacterium abscessus is a rapidly growing, nontuberculous, multidrug resistant mycobacterium, which can cause severe lung infections. This mycobacterium, like other mycobacteria, has a lipid-rich hydrophobic cell wall containing unique lipids, of which glycopeptidolipids (GPL) have emerged in recent years as major immunomodulators. *M. abscessus* presents smooth (S) and rough (R) morphotypes and the difference is determined by the presence or absence, respectively, of GPL. Epidemiological studies suggested that the R variant is involved in more severe clinical forms, with a hyper-proinflammatory response. However, the underlying physiopathological mechanisms remain largely unknown. A zebrafish embryo model was developed to investigate the pathogenesis of *M. abscessus* infection. In contrast to the S variant, the R variant induces a more robust and lethal infection in embryos, characterized by the formation of extracellular cords and abscesses, often found in the Central Nervous System. The high propensity of *M. abscessus* R to form cords *in vivo* prevents the bacilli from being phagocytosed by macrophages and neutrophils and promotes the induction of a strong inflammatory response that leads to rapid tissue damage and to larval death. We conducted a comparative stepwise dissection of the inflammatory response in S and R pathogenesis. Our results highlight the importance of both macrophages and neutrophils in controlling cord formation and production/maintenance of protective granulomas. Moreover, this experimental model emphasizes the requirement of a functional CFTR protein in innate immunity and resistance to *M. abscessus* infection, which is particularly relevant to infections in cystic fibrosis patients who are vulnerable to *M. abscessus* infections.

References:

A. Bernut, M. Nguyen-Chi, I. Halloum, J.L. Herrmann, G. Lutfalla, and L. Kremer. 2016. *Mycobacterium abscessus*-induced granuloma formation is strictly dependent on TNF signaling and neutrophil trafficking. *PLOS Pathog*. **12:** e1005986.

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A. Bernut, J.L. Herrmann, K. Kissa, J.F Dubremetz, J.L. Gaillard, G. Lutfalla, and L. Kremer. 2014. *Mycobacterium abscessus* cording prevents phagocytosis and promotes abscess formation. *Proc. Natl. Acad. Sci USA*. **111:** E943-952.

Host: Raphael Sommer (Cole lab)

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12:15, room AI 1153

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