The Study of Bovine Tuberculosis Through a One Health Approach

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Objective: *Mycobacterium bovis* (Mb) responsible for bovine TB, and *Mycobacterium tuberculosis* (Mtb) for human TB, are greater than 99.9% identical at the genetic level. It has been shown that the human pathogen, Mtb, shows reduced ability to cause disease in cattle (PMID: 20049086); furthermore, epidemiological studies have shown that Mb is less able to cause disease in humans (PMID: 5297551). However, the genetic reason(s) why one is an animal pathogen and the other human pathogen is not known. If we were able to determine the basis for the ability of these pathogens to cause disease, we would be able to develop better control tools, such as vaccines and diagnostics, to control these diseases in both humans and animals.

Mb causes a chronic infection preferentially targeting the lung. The early steps after infection that influence the physiopathology of the disease are still poorly understood. We aim to get a deeper understanding of the physiopathology of bTB in the target species i.e. bovine and in the target organ, the lung. We compared the host tissue responses after Mb and Mtb infection. Such comparative study of human and animal pathogens is a key example of the One Health concept that explores the interrelation of human and animal health.

Key findings: We set up a protocol for *ex vivo* infection of bovine lungs (Precision-cut lung slices; PCLS) that helps deciphering early steps following infection in the natural environment.

We performed *in situ* imaging of PCLS infected with a fluorescent Mb strain, and localized our bacilli in the alveolar compartment, in contact with pneumocytes, near or inside alveolar macrophages.

We are currently analyzing the global tissue signature following infection by two Mb strains (AF2122 and Mb3601) and two Mtb strains (H37Rv and BTB1558). We performed a transcriptomic analysis using two different technologies, NanoString nCounter Analysis System and Fluidigm Biomark; and measured cytokines/chemokines in culture supernatant using a bovine 15-plex assay. We measured induction of inflammatory genes and chemokines for granulocyte recruitment. Tissue responses were found to be higher at day 2 post infection than day 1. So far, we found limited differences of host responses against the different strains but interestingly we recorded striking differences when comparing two breeds (Blonde d'Aquitaine *versus* Charolaise).

Impact: We aim to improve our comprehension of host-pathogen interactions *ex vivo* while reducing reliance on animal experiments, and contribute to future disease control strategies through a One Health approach.

Keywords: innate immunity, cattle, *Mycobacterium bovis, ex vivo,* One Heatlh