Interleukin-1 manipulation by *Mycobacterium tuberculosis*: impact to the infection establishment and progression

**Introduction**

Interleukin-1 (IL-1β) is a pro-inflammatory cytokine of great importance to the early protection against tuberculosis (TB), since experimental studies in mice show that deficiency in the IL-1 signaling results in rapid establishment of infection and death. Our group has recently described that *Mycobacterium tuberculosis* clinical isolates associated with mild (4I2) or severe (6C4) TB in humans induce high or low levels of IL-1β, respectively, in human macrophages. To further investigate how these differences impact the establishment and course of infection, we infected wild type mice and mice lacking IL-1R in the myeloid compartment with *M. tuberculosis* (4I2 or 6C4).

**Aim**

- Investigate if different modulation of IL-1β and TB severity could be modeled in vivo by *M. tuberculosis* strains.
- Decipher if the lower severity of 4I2 strain is linked to the induction of IL-1β, studying the impact of cell specific IL-1 receptor signalling on the pathogenesis of TB.

**Methodology**

_4I2_ and _6C4_ mice were aerosol infected with *M. tuberculosis* 4I2 or 6C4 and the organs were harvested, processed and analyzed at 15 and 30 post infection (p.i.).

**Results**

_C57BL/6_ mice infected with _M. tuberculosis_ 6C4 present higher bacterial loads in the lung and liver and more severe pathology than mice infected with 4I2.

**Conclusion**

According to the results, it was possible to recapitulate, in the mouse model, distinct severities of disease provoked by different _M. tuberculosis_ strains. _M. tuberculosis_ 6C4 showed a higher bacterial load at the local of infection, more dissemination to the liver and a larger area of lung lesion than 4I2, compatible with the severe form of TB described in humans. IL-1R-deficient mice in myeloid cells when infected with the higher IL-1β inducer strain (4I2) were less able to control the infection in comparison to WT, showing higher bacterial burden, severe pathology, more cell infiltration and increased inflammatory responses. Therefore, the low severity of 4I2 infection compared to other strains, seems to be linked to the high induction of IL-1β.

Future perspectives include performing a similar experience to compare LyzM and WT mice when infected with 6C4 and study the contribution of other cellular compartments, such as epithelial and endothelial cells in the IL-1 signaling. With this study and future ones, we expect to better understand the complex immune response of TB.

**References**