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23346 | Uncovering the mechanisms of protection during *Mycobacterium tuberculosis* infection

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Background & Aims: Tuberculosis (TB) is one of the most devastating infectious diseases affecting humankind, having caused 1.25 million deaths in 2023. The identification of effective protective mechanisms in TB could critically contribute to the urgent need of new therapies to stop TB. It is known that genetically related *Mycobacterium tuberculosis* (Mtb) isolates shape the immune response and disease outcomes. Using the natural genetic diversity of Mtb as a tool to understand protection in TB, my project focuses on the slow progressing infection caused by Mtb isolates of lineage 6 (L6), in which we hypothesize that critical protective mechanisms operate. **Methods:** Analyses of *in vitro* (macrophages) and *in vivo* (mouse) infections were performed in susceptible C3HeB/FeJ or resistant C57BL/6 mice, to compare the immune response and outcome of infection caused by Mtb belonging to L6 or L4. **Results:** *In vitro* (macrophage) infections showed that both Mtb L6 and Mtb L4 isolates grow overtime, but Mtb L6 grows slower than Mtb L4. *In vivo*, we found that C57BL/6 mice infected with Mtb L6 offer a unique model of full protection. Strikingly, flow cytometry analysis revealed a faster recruitment of activated CD4+ T cells to the lungs in the Mtb L6-infected C57BL/6, which might suggest that protection may be achieved by this early T cells recruitment. **Conclusions:** Our results indicate that a slower growth of Mtb L6 in macrophages together with earlier T cell responses in the lung may underlie fully infection control. The ongoing RNA-sequencing analyses will highlight putative protective immune mechanisms operating in this model, of great interest to devise new strategies to control TB.

Keywords: Tuberculosis, *Mycobacterium tuberculosis* infections, Immune response.