Internship Proposal

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Project Title:
Dissecting the Aryl Hydrocarbon Receptor (AHR) roles during Immune Response to Infection by Mycobacterium tuberculosis

Level:

Master Student

Project Summary:

Tuberculosis (TB) is caused by infection with Mycobacterium tuberculosis. It has been estimated that, in 2023, 10.8 million people developed TB, and 1.25 million deaths were caused by this disease worldwide. To fight TB, the development of improved therapies is a strategic priority. However, critical gaps in our understanding of the immune response to this infection hinder progress.

The Aryl Hydrocarbon Receptor (AHR) is a cytosolic pattern recognition receptor that senses microbial ligands and modulates the host immune response. Our group showed that the AHR binds and senses M. tuberculosis-derived molecules (e.g. phthiocol), regulating various host defense mechanisms to infection. Strikingly, mice lacking AHR infected with M. tuberculosis succumb earlier than WT mice, placing AHR as a key receptor in resistance to TB. Moreover, our work demonstrated that AHR modulation impacts TB antibiotic treatment efficacy, unveiling AHR as a promising target in host-directed therapy against TB.

Here, we aim to assess AHR's activation kinetics during M. tuberculosis infection and disease progression, dissect the AHR-elicited responses and their impact on host defense against infection, and explore targeting AHR as a therapy against TB.

Work to be developed by the student:

The student will:

•work in the BSL3 laboratory;

•process organs from infected mice for cell analysis by fluorescence microscopy and flow cytometry, and for bacteria quantification;

•perform cell staining for flow cytometry;

•analyze flow cytometry data using FlowJo software;

•perform immune staining for microscopy;

•prepare samples for RNA-seq and analyze data.

References:

•Barreira-Silva, P., Lian, Y., Kaufmann, S. H. E., & Moura-Alves, P. (2024). The role of the AHR in host-pathogen interactions. Nat Rev Immunol. https://doi.org/10.1038/s41577-024-01088-4

•Moura-Alves, P., Fae, K., Houthuys, E., Dorhoi, A., Kreuchwig, A., Furkert, J., Barison, N., Diehl, A., Munder, A., Constant, P., Skrahina, T., Guhlich-Bornhof, U., Klemm, M., Koehler, A. B., Bandermann, S., Goosmann, C., Mollenkopf, H. J., Hurwitz, R., Brinkmann, V., . . . Kaufmann, S. H. E. (2014). AhR sensing of bacterial pigments regulates antibacterial defence. Nature, 512(7515), 387-392. https://doi.org/10.1038/nature13684

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