MOI Project 12

Functional analysis of lymphotoxin-β receptor-dependent effector mechanisms during the immune response against intracellular pathogens

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Project Aim:

The central research themes of our project focus on the immunological functions of cytokine receptors of innate immunity and interferon-γ-induced murine 65kDa Guanylate-binding proteins (mGBPs) in the infection with intracellular pathogens.

Lymphotoxin β receptor (LTβR) belongs to the TNF/TNFR superfamily, playing vital roles in regulating inflammatory responses, immune defense against infections, secondary lymphoid organ organogenesis, and maintaining the structural integrity of lymphoid organs.

The role of LTβR in *Toxoplasma gondii* infection remains insufficiently studied, despite numerous immunological studies conducted on LTβR$^{-/-}$ mice with various pathogens. Previous work has demonstrated that mice deficient in the LTβR exhibit increased susceptibility to *T. gondii* infections. These mice show reduced expression of mGBPs, which are essential for survival during *T. gondii* infection. Further investigations have revealed decreased frequencies of cytotoxic CD8^{+} T cells and defects in IgM production, IgG production switching, and disrupted differentiation of IgG plasma cells in LTβR$^{-/-}$ mice post *T. gondii* infection. The proposed work aims to characterize these findings precisely and identify the molecular and cellular factors regulated by LTβR in defense against *T. gondii* infection.

Key objectives include:

1. Characterizing B-cell differentiation, frequencies, and numbers in bone marrow and spleen post-infection.

2. Investigating the role of LTβR in myeloid and dendritic cells by generating mouse lines with deleted LTβR specifically in these cell types.

3. Elucidating the regulation of interferon-inducible GTPases of the 65 kDa family (GBPs) by LTβR through in vitro studies.

4. Conducting transcriptome studies to identify LTβR-regulated candidate genes essential for controlling *T. gondii* infection.

5. Evaluating the cellular distribution of *T. gondii* parasites during infection using fluorescent parasites in wild-type and LTβR$^{-/-}$ mice.

The project aims to provide insights into LTβR-mediated immune regulation and its impact on host defense against *T. gondii* infection, potentially leading to the identification of novel therapeutic targets for combating intracellular pathogens.