Virulence factors for *Mycobacterium tuberculosis*

Jean Pieters, Ph.D.
Biozentrum, University of Basel
Switzerland

Dissemination and Infection of *M. tuberculosis*

Single cell level?

Not so for *M. tuberculosis*
- How does *M. tuberculosis* resist the destructive environment of the macrophage—role of bacterial and host proteins;

- How does the host override the virulence mechanisms employed by *M. tuberculosis* to survive within macrophages;

- How can we use this knowledge for the development of drugs to combat tuberculosis?
Host Factors involved in M. tuberculosis survival

- WD Repeat containing protein (TACO, for Tryptophan Aspartate containing COat protein);
- Member of the evolutionary conserved coronin protein family;
- Recent bioinformatic analysis identified 723 coronin proteins from 358 species.
Mammalian Coronin Protein Family

- **Cor 1 (1A)**: NH2-CCUD-COOH, WD40 Repeats, Ubiquitous, Immune cells, neurons
- **Cor 2 (1B)**: NH2-CCUD-COOH, WD40 Repeats, Immune cells, fibroblasts
- **Cor 3 (1C)**: NH2-CCUD-COOH, WD40 Repeats, Ubiquitous
- **Cor 4 (2A)**: NH2-CCUD-COOH, WD40 Repeats, Brain
- **Cor 5 (2B)**: NH2-CCUD-COOH, WD40 Repeats, Brain
- **Cor 6 (ClipnE)**: NH2-CCUD-COOH, WD40 Repeats, Ubiquitous
- **Cor 7**: NH2-CCUD-COOH, WD40 Repeats, Immune cells, brain, fibroblasts

**Images:**
- **Control vs. Live mycobacteria**
  - **Coronin 1-568**
  - Control: Red
  - Live mycobacteria: Red with yellow-green

- **Control vs. Killed mycobacteria**
  - **Coronin 1-568**
  - Control: Red
  - Killed mycobacteria: Red with green
1. Mechanism of action;

2. Normal role for coronin 1.
Intracellular Killing of Mycobacteria in the Absence of Coronin 1

Coronin 1-Dependent Survival of *M. tuberculosis* within Macrophage Phagosomes

Understanding the Role for Coronin 1 in vivo
Severe T cell Depletion in the Absence of Coronin 1

Lymphocyte Populations in Peripheral Blood

Normal T cell Development and Selection but Deficient Peripheral T Cell Survival in the Absence of Coronin 1

Role for Coronin 1 in T Cell Receptor Mediated Signaling?
No Calcium Mobilization in the Absence of Coronin 1

- T cell ligands
- Tyrosine phosphorylation of membrane adaptors
- Activation of phospholipase Cgamma1
- IP3 generation/Ca^{2+} mobilization
- Calcineurin activation
- Interleukin 2 production
- T cell survival

**Graph:**
- X-axis: Time (sec)
- Y-axis: Relative calcium flux
- '+/+' line vs. '/-' line

**Legend:**
- '+'
- '-'

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**Figure S3**

**Table:**

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**X-axis:**

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**X-axis:**

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Jan Massner, Philipp Mueller
Mycobacterial Entry Triggers Ca\textsuperscript{2+} Fluxes in Macrophages
-in a Coronin 1-dependent Manner-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image1.png}
\caption{Graph showing the relative fluorescence over time for WT and Car 1-/- in response to mycobacterial entry.}
\label{figure1}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{image2.png}
\caption{Diagram illustrating the process of mycobacterial entry and Ca\textsuperscript{2+} fluxes in macrophages, highlighting the role of Coronin 1.}
\label{figure2}
\end{figure}
Cyclosporin A and FK506 Treatment Leads to Transfer of Mycobacteria to Lysosomes

LysoTracker

CsA (WT)

FK506 (WT)

M. tuberculosis

T cell ligands

Receptor

Receptor

Coronin1

IP3/Ca++ mobilization

Calcineurin activation

CsA

FK506

Death of M. tuberculosis and T cells

Infected macrophage

Foamy macrophages

Lung

Blood vessels

Macrophage

Lymphocyte