Immunity to *Mycobacterium tuberculosis*

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- One third of the world’s population is infected with *M. tuberculosis*
- 2 million TB deaths annually
- TB is a leading cause of death among people co-infected with HIV
Inhalation of aerosolized *M. tuberculosis*

Infection of Alveolar Macrophages

Immunity (90-95%)

Latency

Reactivation Tuberculosis (5-10%)

Host immune response to *Mycobacterium tuberculosis* (*M.tb*)

- Innate immunity
- Defective Adaptive Immunity
- Adaptive Immunity

Disease < 10%

Latent Infection

Immunosuppression

- Reactivation < 10%
- Containment > 90%

How does immunity generate a response to pulmonary *M. tb* infection?

**Immunity to Mycobacterium tuberculosis**

1. Innate Immunity and Dissemination
2. T cell priming
3. T cell recruitment
4. Effector function

![Diagram of immune response to *M. tb* infection](image)

- **Early immunity**
- **Late immunity**
- **Control**
- **Plateau**
- **Recrudescence**

*Other Pathogens*

- *M. tb*
- 3-5 Days
- 12-14 Days

*LN T cell priming and recruitment*
Immunity to M. tuberculosis

Innate immunity plays two major roles during the course of pulmonary Mtb infection:

1. Controlling early pathogen growth
2. Instructing adaptive immunity
Alveolar macrophages are the first line of immune defense. The classical paradigm of macrophage responses includes activation by toll-like receptors (TLR) and phagocytosis, leading to the production of cytokines such as IFN-γ and IL-12. Divangahi & Behr, J Immunol 181:7157, 2008.
NOD2 deficient mice are susceptible to *Mtb* infection

New paradigm of macrophage response to *M.tb*

Apoptosis: an innate defense mechanism targeted by Mtb

Induction of necrosis evades host defense mechanisms; allows Mtb to infect other cells
Virulent *Mtb* inhibits apoptosis

![Microscope images of uninfected and infected cells](image1)

Plasma membrane repair mechanisms

![Diagram of calcium ions and NCS-1](image2)

Divangahi et al, *Nature Immunology* 2009
LAMP-1 is recruited to the surface of pro-apoptotic macrophages

Divangahi et al, Nature Immunology 2009
Does the death modality of *Mtb*-infected macrophages enhance innate immunity *in vivo*?

**A novel Adoptive transfer Model of *Mtb* infection**

- In vitro infection
- Adoptive transfer of infected Mφ
- Apoptosis of infected Mφ
- Necrosis of infected Mφ
- Inhibition of bacterial replication
- Enhanced bacterial growth
- RAG deficient mice
- I.t.
The fate of *Mtb* infected Mφ *in vitro* reflects the innate control of infection *in vivo*.

Does the death modality of *Mtb*-infected macrophages enhance T cell immunity?
MHC class I and II antigen processing machinery

Heath et al, Nature Reviews Immunology, 2001

Cross-Presentation

Nature Reviews Immunology

Cross-Presentation
Adoptive transfer Model of *Mtb* infection

Adoptive transfer of *Mtb*-infected pro-apoptotic Mφ initiates an early T cell immunity

Divangahi et al, *Nature Immunology* 2010
In vivo effect of pro-apoptotic Mφ

The fate of macrophage plays an essential role in host immunity against M.tb

Divangahi et al, Nature Immunology 2010

The fate of macrophage plays an essential role in host immunity against M.tb
Thank you