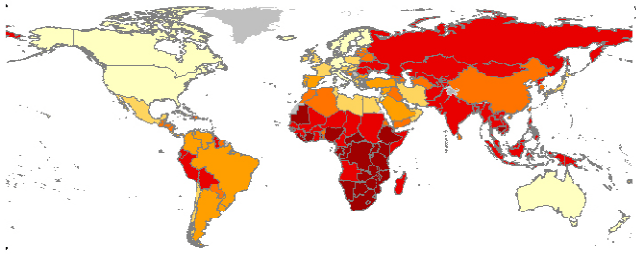
Immunity to *Mycobacterium tuberculosis*

Maziar Divangahi, PhD

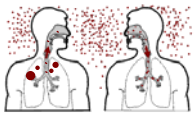
Meakins-Christie Laboratories, McGill University

maziar.divangahi@mcgill.ca

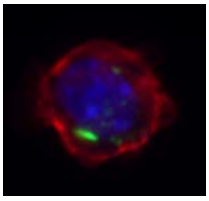


- One third of the world's population is infected with *M. tuberculosis*
- 2 million TB deaths annually
- TB is a leading cause of death among people co-infected with HIV

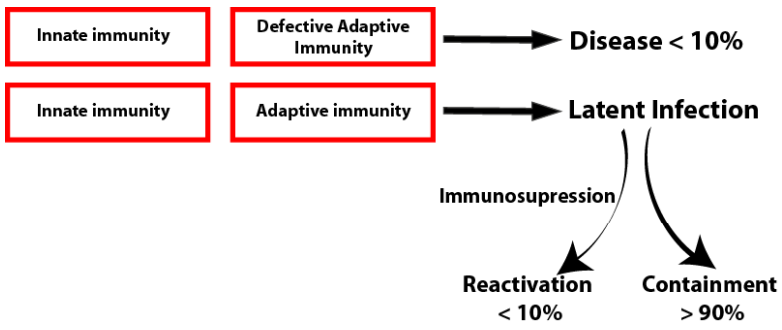
Inhalation of aerosolized *M. tuberculosis*



Infection of Alveolar Macrophages → Immunity (90-95%) → latency → Reactivation Tuberculosis (5-10%)



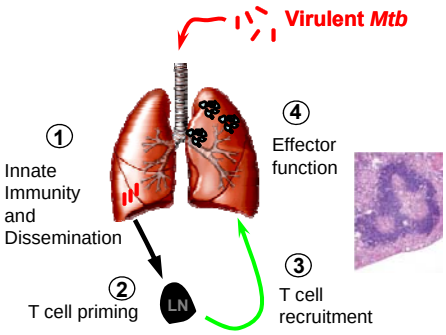
Host immune response to *Mycobacterium tuberculosis (M.tb)*

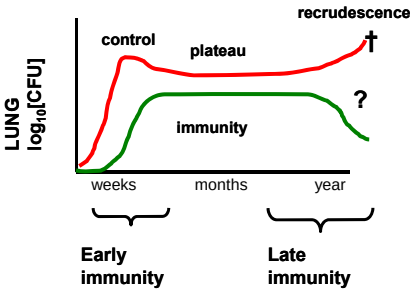


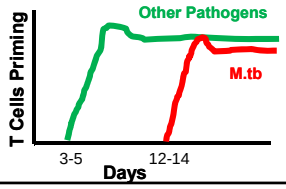
Salgame P., et al., *J.Clin.Immunol*, 2007

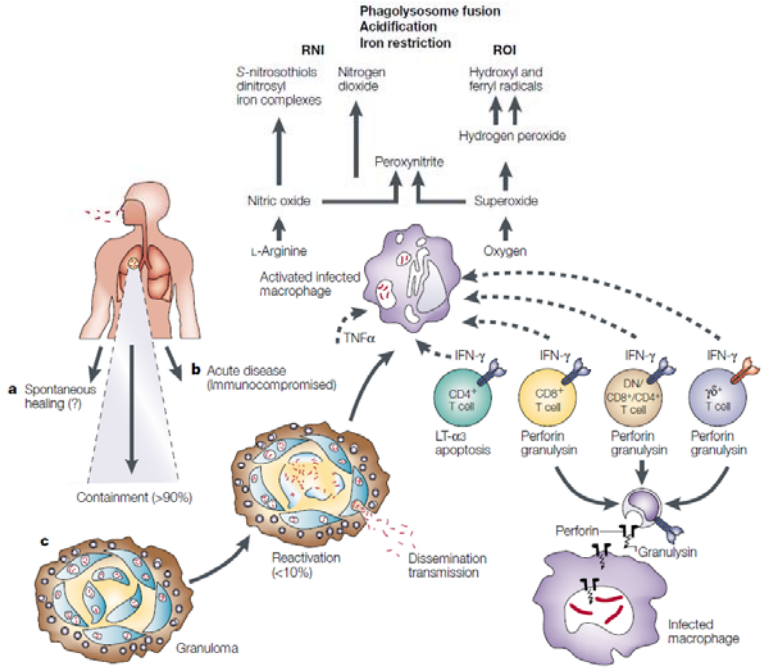
How does immunity generate a response to pulmonary *M.tb* infection?

Immunity to *Mycobacterium tuberculosis*



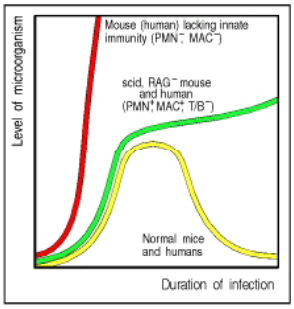


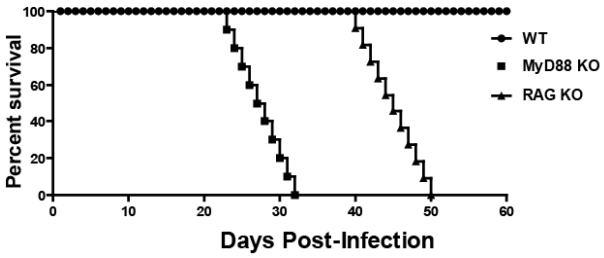




Kaufmanne, *Nature Reviews Immunology, 2001*

Immunity to *M. tuberculosis*

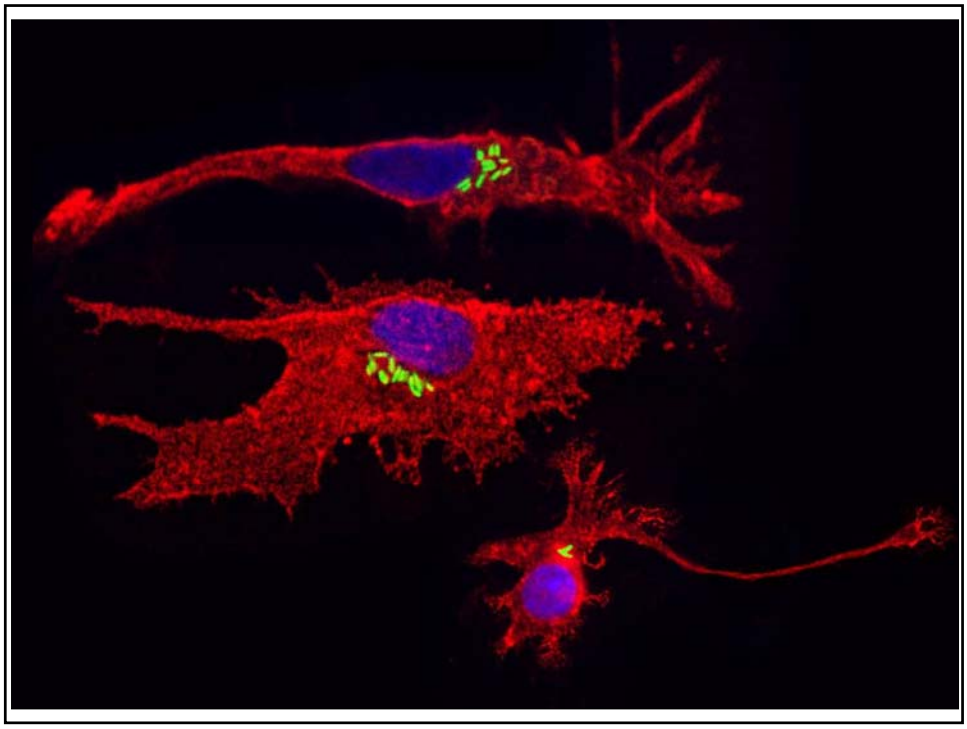




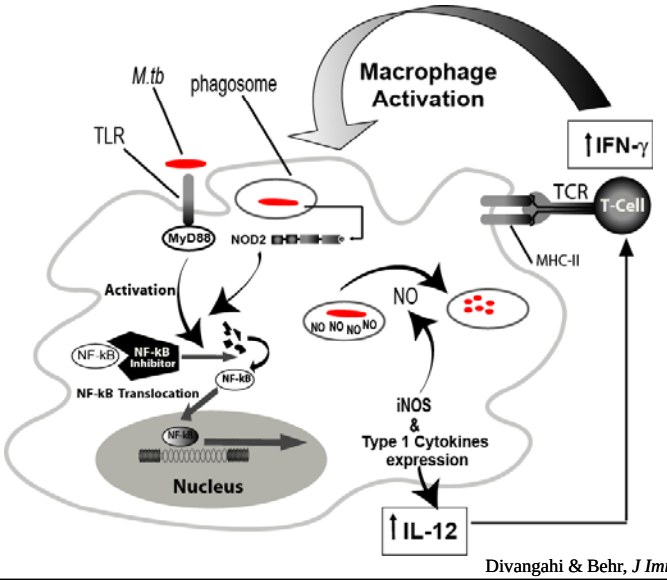
Fremond C., et al., *JCI*, 2004.
Feng C.G, et al., *JI*, 2005.

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

1. **Controlling early pathogen growth**
2. **Instructing adaptive immunity**

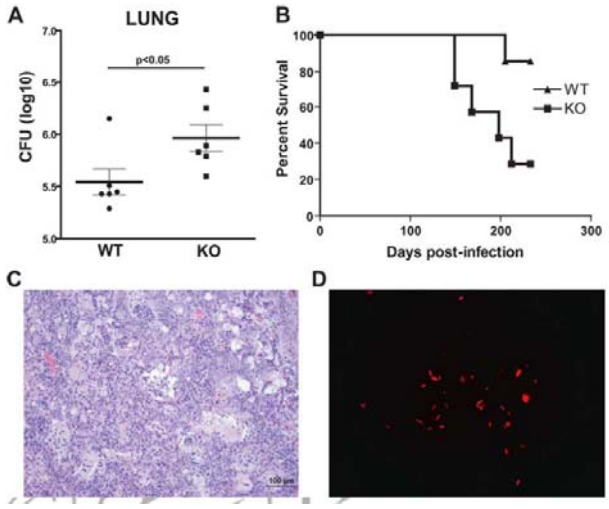


Classical paradigm of macrophage responses



Divangahi & Behr, *J Immunol* **181:**7157, 2008

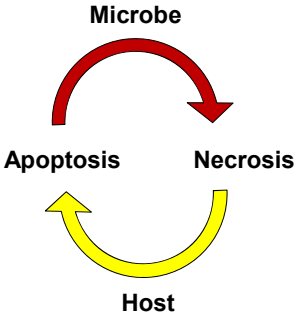
NOD2 deficient mice are susceptible to *Mtb infection*



Divangahi & Behr, *J Immunol* **181:**7157, 2008

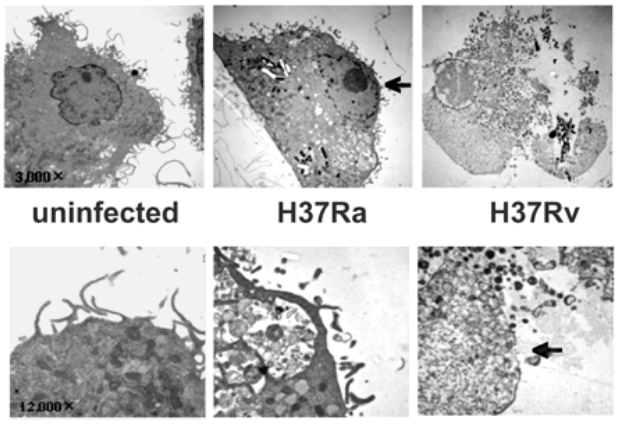
New paradigm of macrophage response to *M.tb*

Apoptosis: an innate defense mechanism targeted by Mtb



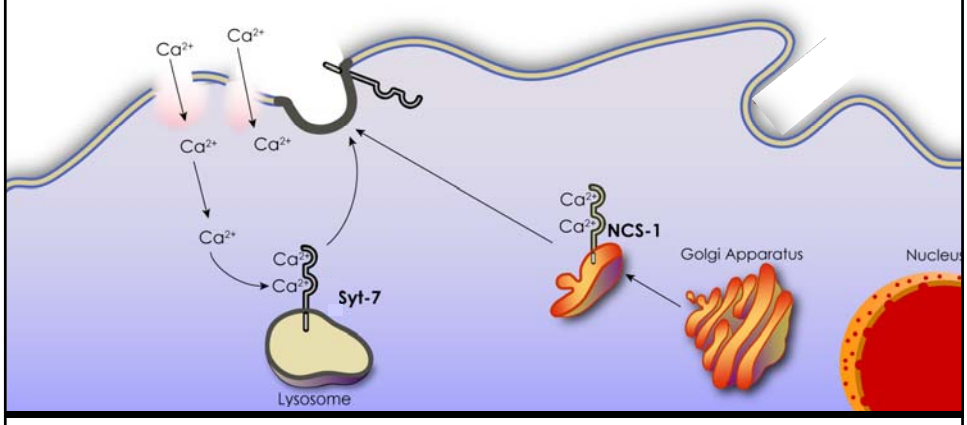
Induction of necrosis evades host defense mechanisms; allows Mtb to infect other cells

Virulent *Mtb* inhibits apoptosis

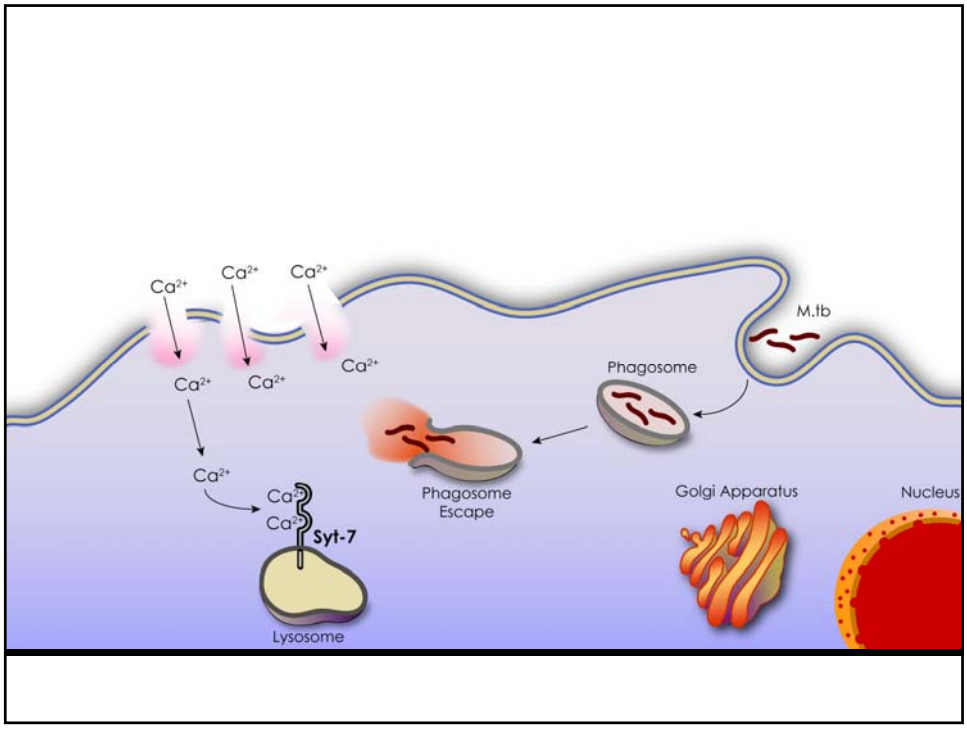


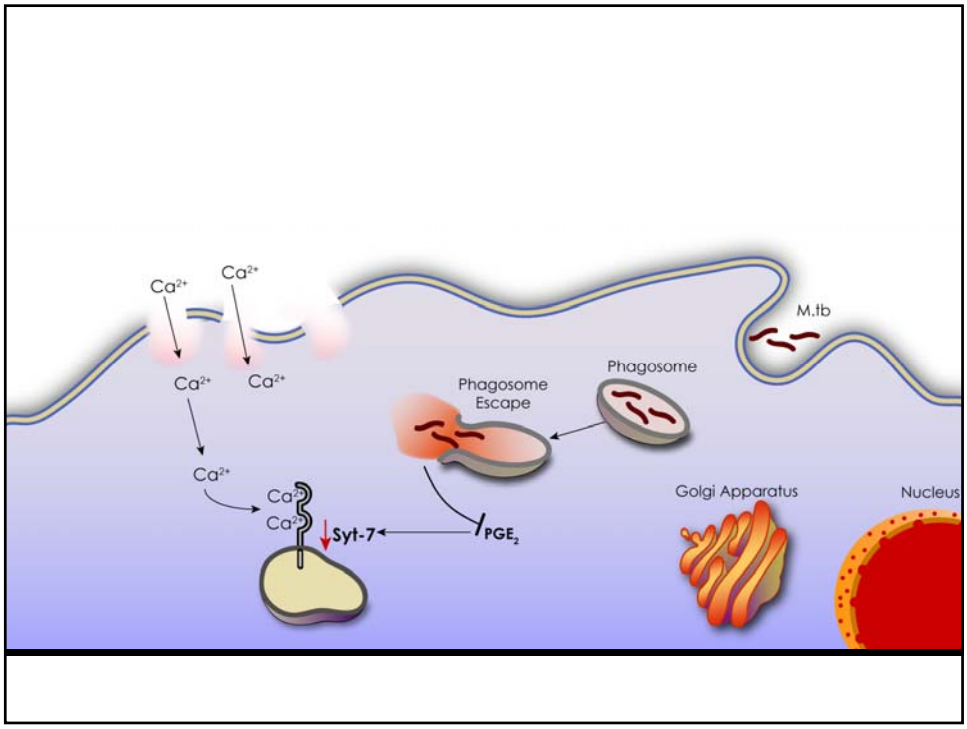
J Immunol **176:**3707, 2006

Plasma membrane repair mechanisms



Divangahi et al, *Nature Immunology* 2009


Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Ca2+
Syt-7
Lysosome
M.tb
Phagosome
Phagosome
Escape
Golgi Apparatus
Nucleus


Ca2+
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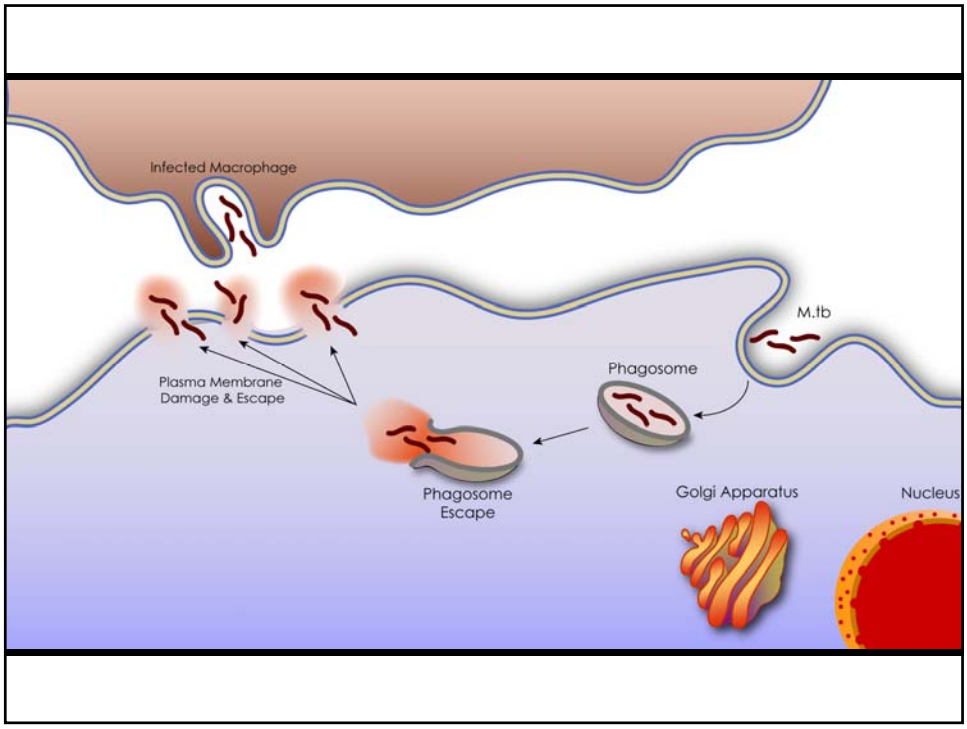
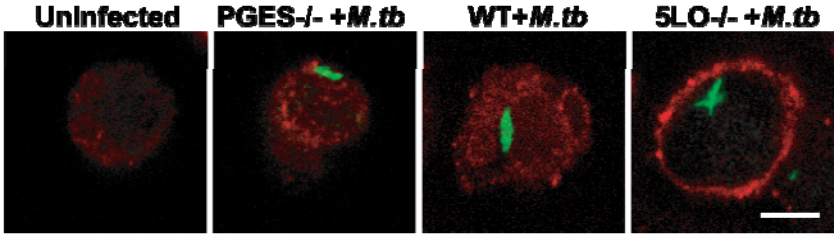
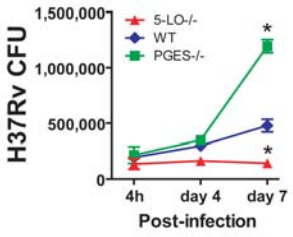


LAMP-1 is recruited to the surface of pro-apoptotic macrophages

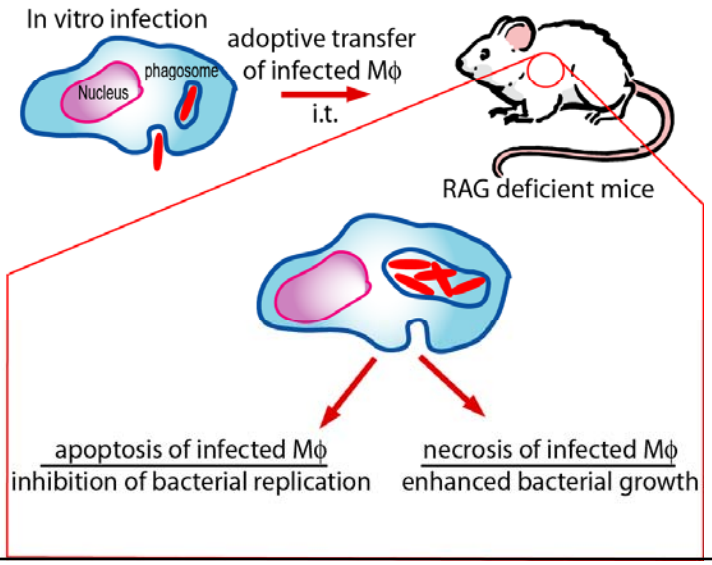




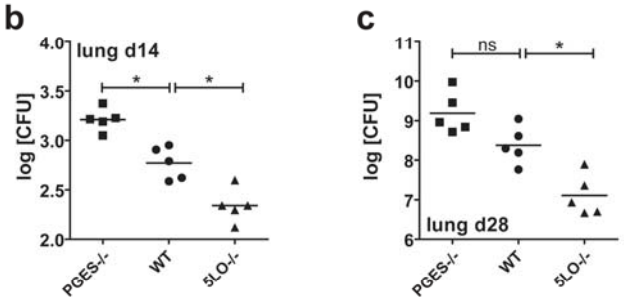
Divangahi et al, *Nature Immunology* 2009

Does the death modality of *Mtb*-infected macrophages enhance innate immunity *in vivo?*

A novel Adoptive transfer Model of *Mtb* infection



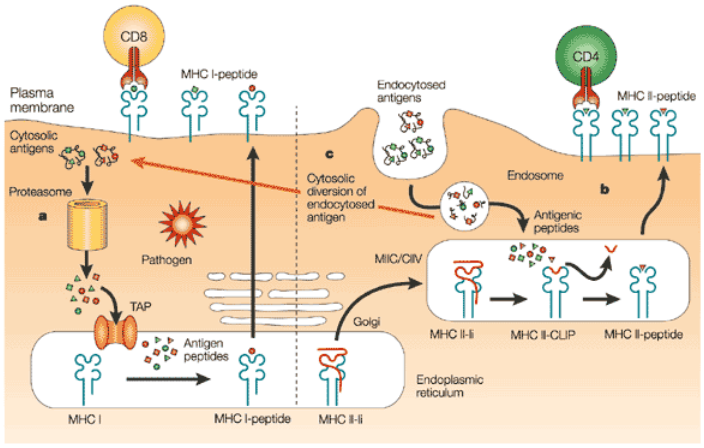
The fate of *Mtb* infected Mφ *in vitro* reflects the innate control of infection *in vivo*



Divangahi et al, *Nature Immunology* 2009

Does the death modality of *Mtb*-infected macrophages enhance T cell immunity?

MHC class I and II antigen processing machinary



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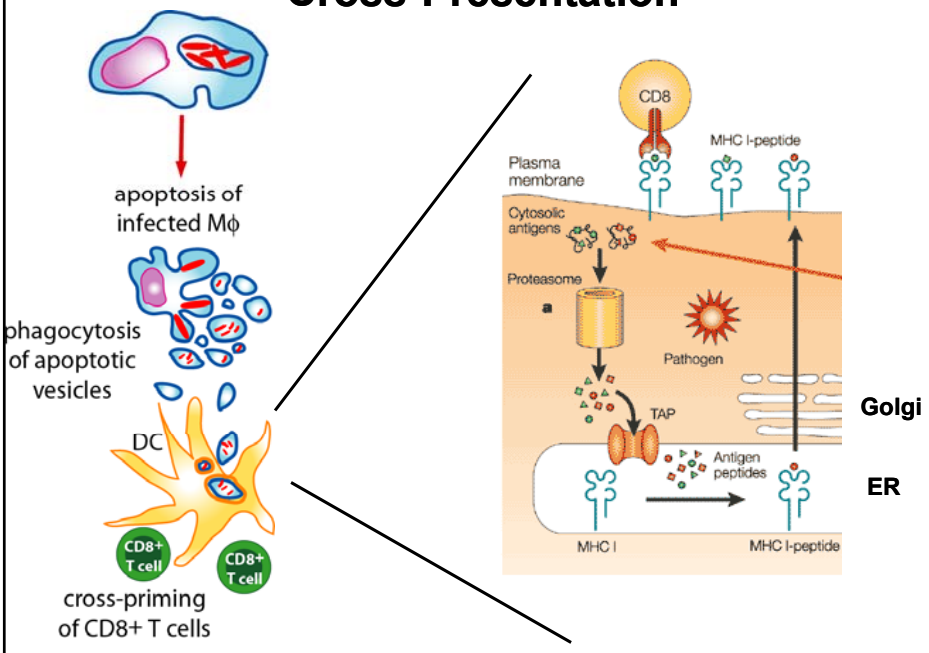
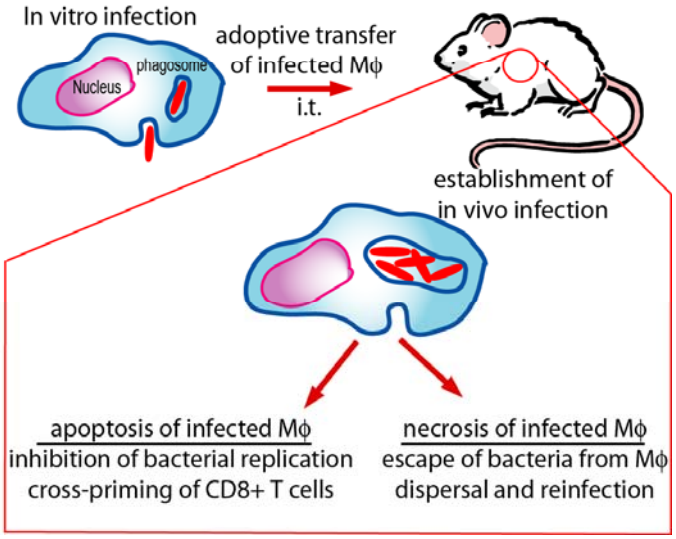
Invariant chain (Ii)
Class II-associated invariant peptide (CLIP)
Transporter associated with antigen processing (TAP)

Heath et al, Nature Reviews Immunology , 2001

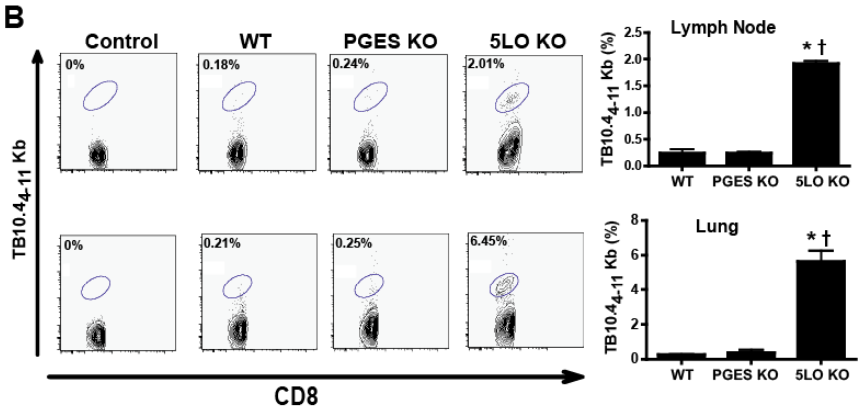
Cross-Presentation



Adoptive transfer Model of *Mtb* infection

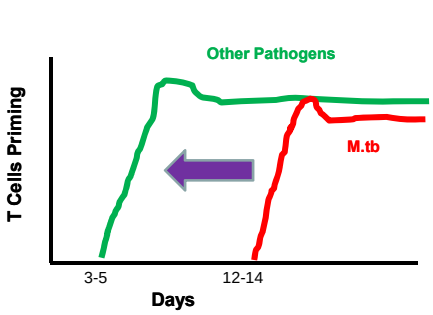


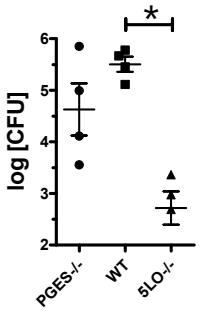
Adoptive transfer of Mtb-infected pro-apoptotic Mφ initiates an early T cell immunity



Divangahi et al, *Nature Immunology* 2010

In vivo effect of pro-apoptotic Mφ





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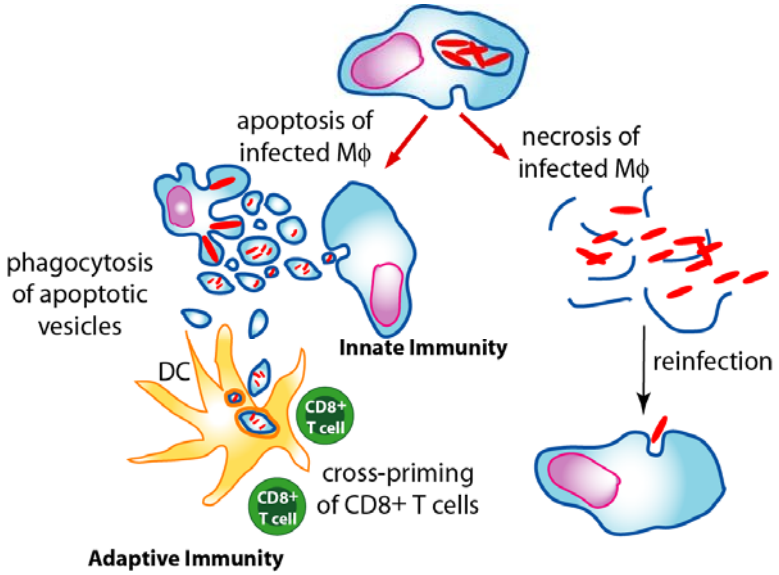
Divangahi et al, *Nature Immunology* 2010

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




Thank you