



The Role of Tumor Necrosis Factor in Granuloma Formation and Reactivation TB

Jennifer Linderman (Chemical Eng., Biomedical Eng. at UM)

Denise Kirschner (Microbiology and Immunology at UM)

JoAnne Flynn (Microbiology and Molecular Genetics at U. Pitt)

Steve Kunkel (Pathology at UM)

R33 (Kirschner, Linderman, Flynn, Kunkel)

R01-EB012579-04 (Kirschner, Linderman, Flynn)

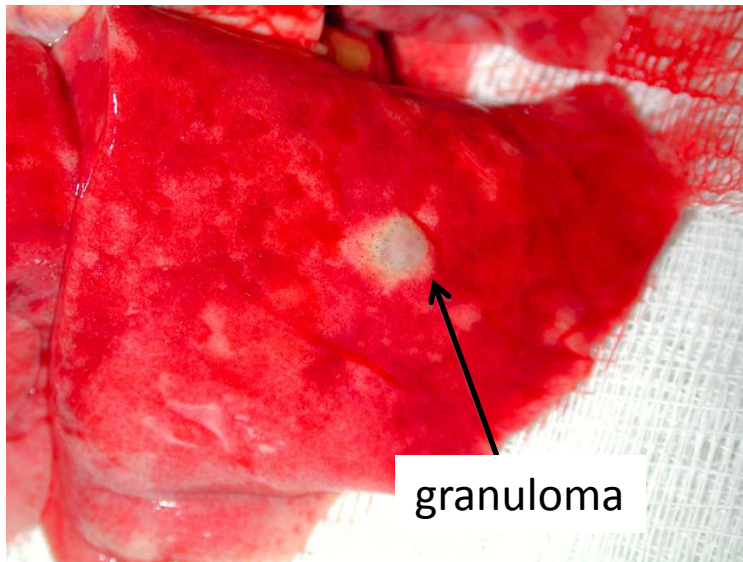
Tumor necrosis factor- α (TNF)

- *TNF is a key cytokine for control of TB (human, mouse, monkey)*
- *TNF is relevant to both formation and function of a granuloma.*

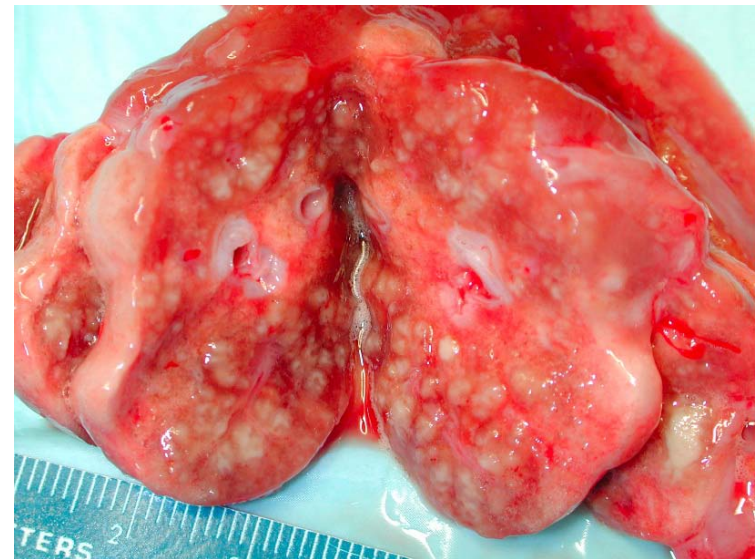
Important TNF activities in TB immune response:

- a) Induces macrophage activation (in conjunction with IFN- γ)
- b) Enhances immune cell recruitment to infection site
- c) Augments chemokine expression by macrophages
- d) Induction of apoptosis (programmed cell death)

Lung lobes from monkeys infected with *M. tuberculosis*

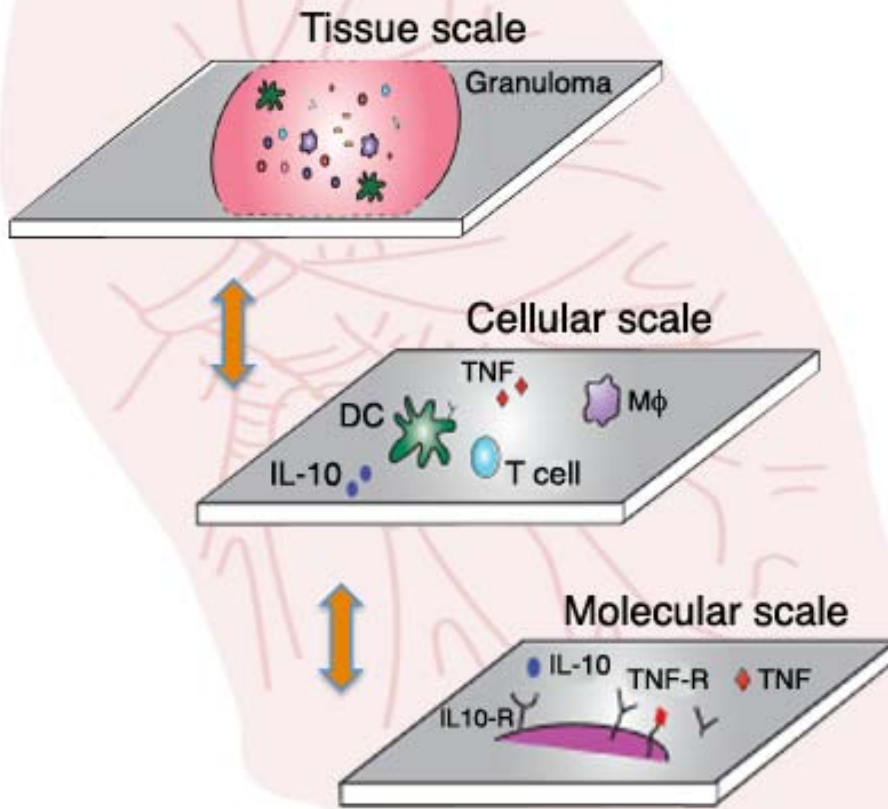


Control monkey 8 weeks post-infection



Anti-TNF Ab treated monkey
8 weeks post-infection

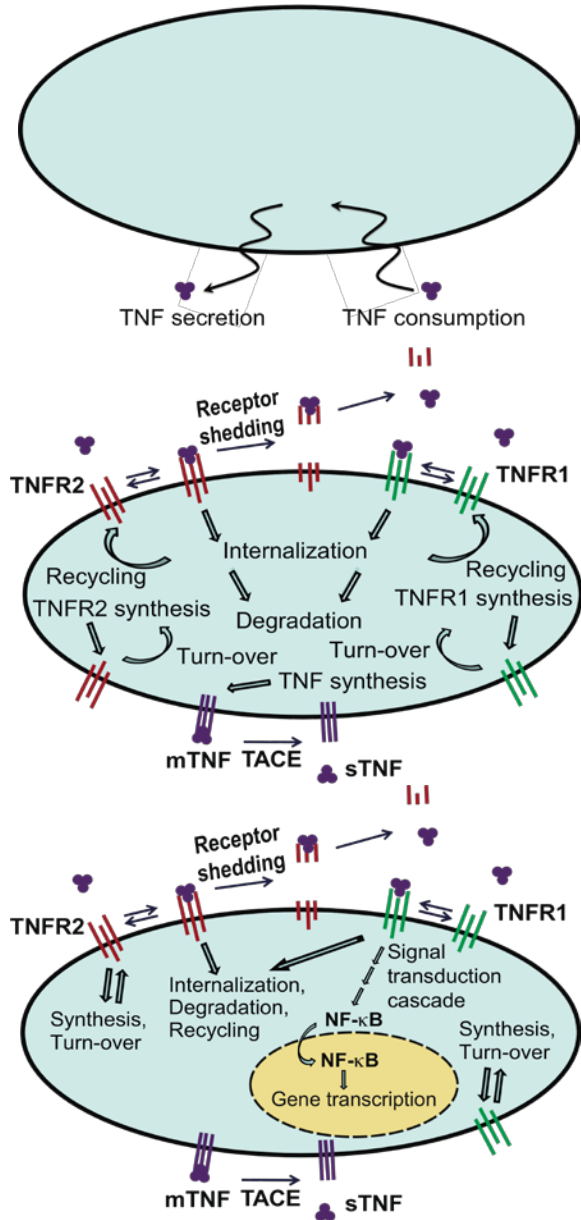
LUNG



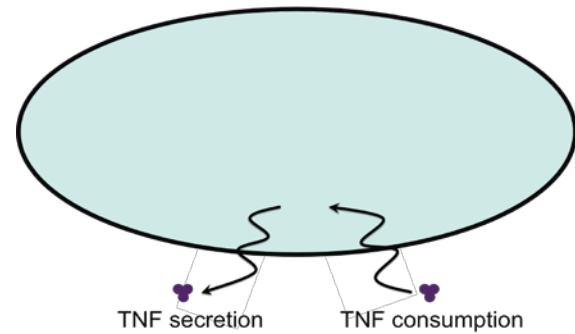
How does TNF affect granuloma development and function at different spatial and temporal scales?

Are there TNF-level processes that, if targeted, could present new strategies for disease therapy?

Tunable Resolution Models

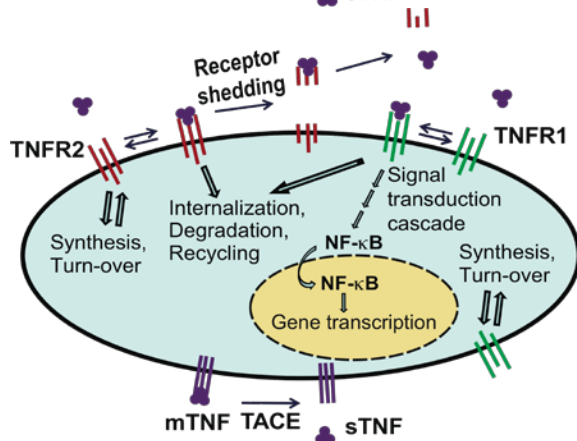
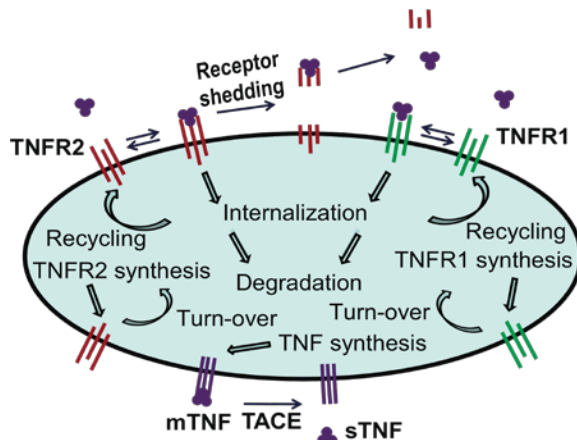


Tunable Resolution Models

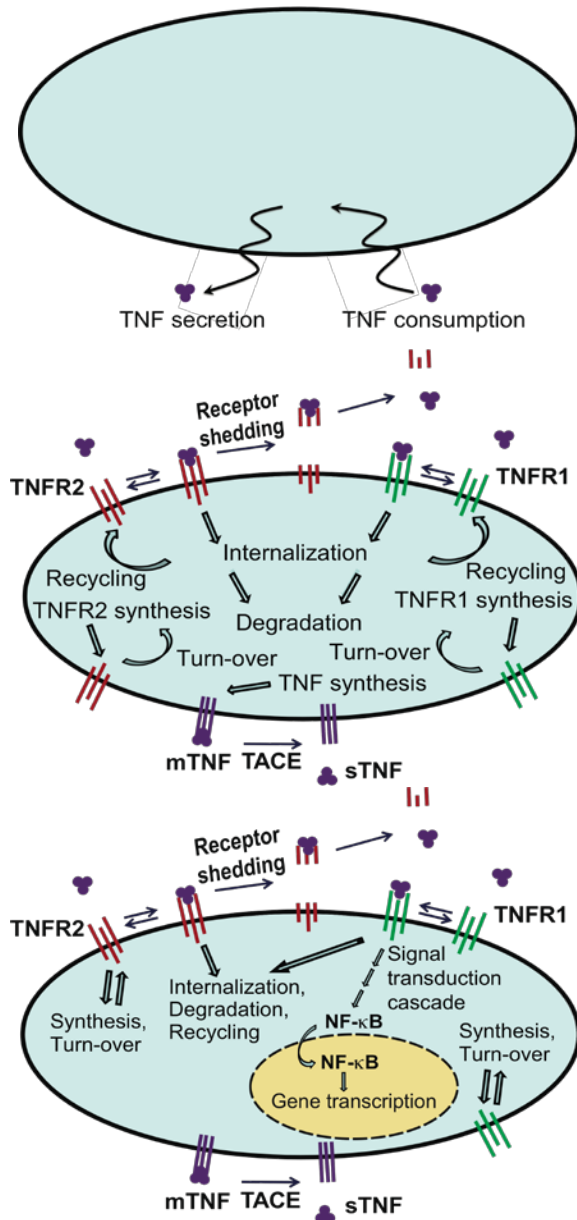


- ✓ What are the roles of TNF in control of *M. tuberculosis* infection?
- ✓ What is the outcome if we knockout all or specific TNF roles?

Ray, Flynn, Kirschner (2009). *J. Immunol.* 182: 3706-3717.



Tunable Resolution Models



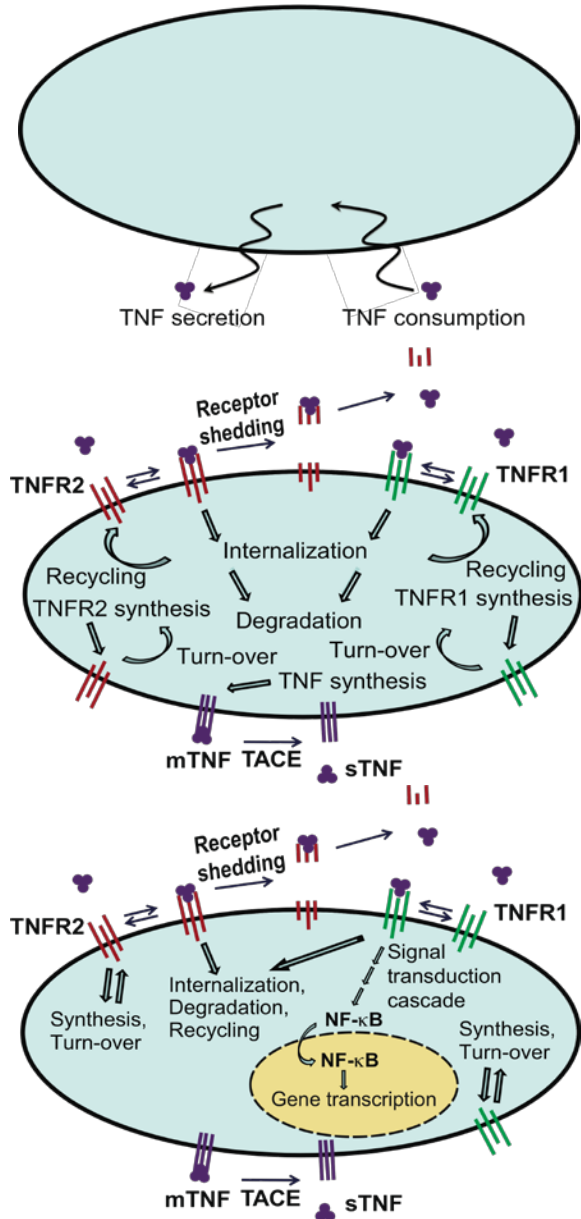
- ✓ What are the molecular mechanisms that control TNF concentration within a granuloma?
- ✓ Can manipulating TNFR-level processes change the outcome of infection?
- ✓ Which anti-TNF drugs (given for RA) pose the least risk for reactivation TB?

Fallahi-Sichani, Schaller, Kirschner, Kunkel, Linderman (2010). PLOS Comp. Biol. e1000778.

Fallahi-Sichani, El-Kebir, Marino, Kirschner, Linderman (2011). J. Immunol. 186: 3472-3483.

Fallahi-Sichani, Flynn, Linderman, Kirschner (2011). Submitted.

Tunable Resolution Models



- ✓ What are the roles of intracellular signaling molecules and processes?
- ✓ How do the dynamics (extent and timing) of TNF-induced responses affect the infection outcome?

Fallahi-Sichani et al., in preparation.