

Mouse models of TB with metabolic comorbidities

- Limited T2D models
- ≠ human TB pathology
- ≠ human immunity



- Low cost
- High throughput
- Abundant reagents
- Genetic tools
- Knowledge base

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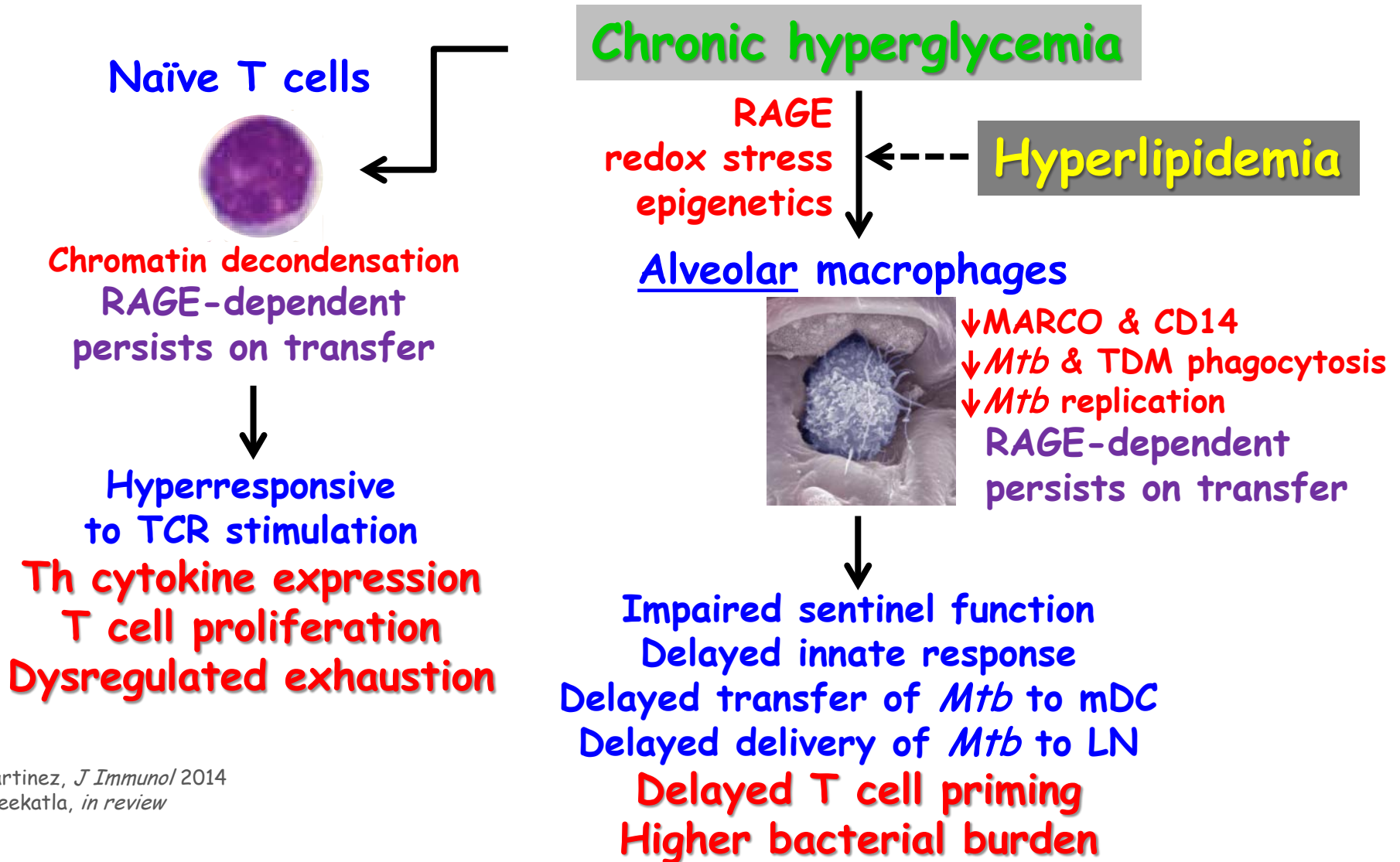
Sadly, no conflicts of interest

In the next 15 minutes...

- Summarize mouse data on TB/DM comorbidity
- Link immunopathy with diabetic complication pathways
- Relevance of mouse data to human TB/DM comorbidity
- Implications for TB/DM treatment & prevention
- Gaps, needs and future directions

Summary

Martens, *Infect Immun* 2006
Martens, *J Leukoc Biol* 2008



Martinez, *J Immunol* 2014
Cheekatla, *in review*

Martens, *AJRCMB* 2006
Vallerskog, *J Immunol* 2012
Martinez, *in review*

Of mice and (wo)men

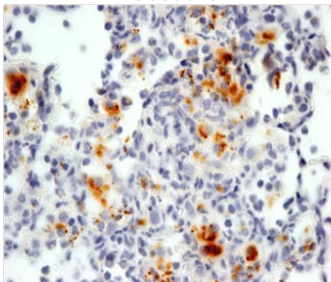
Mouse

- Alveolar MΦ-restricted defect in sentinel function
- Delayed adaptive immunity
- Higher bacterial load
- More immune pathology
- Higher cytokine levels
- Correlates with DM severity
- RAGE-dependent

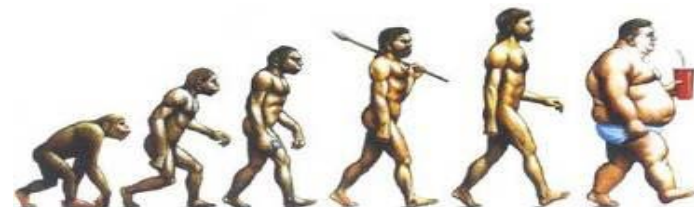
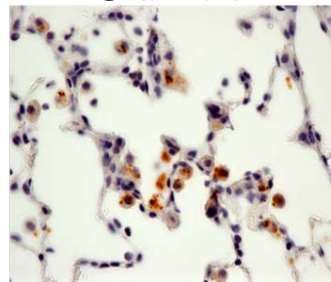
Human

- Increased risk for PTB
- More lower lobe disease
- Delayed sputum conversion
- More cavitory disease
- Worse TB outcomes
- More recurrent TB
- Higher cytokine levels
- Correlates with DM severity

Control



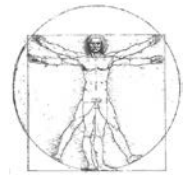
Diabetic





Predictions

Translation



Diabetic complication pathways drive immunopathology

→ Correlation with DM severity; metabolic memory

Rx pathway inhibitors; tight glycemic control in TB?

Delayed innate response to AM Φ infected by inhaled *Mtb*

→ Increased risk for *Mtb* infection, LTBI progression and lower lobe TB

Rx DM prevention

Greater immune pathology

→ Higher M&M; more pulmonary impairment after TB

Rx immunomodulatory HDTs

Direct and additive/synergistic effects of lipotoxicity

→ T2D > T1D/TB; is pre-DM a TB risk factor?

Rx immunomodulatory HDTs; hypolipidemic drugs

Metaflammation in TB

→ Glycemic impairment after TB; exacerbation of DM complications

Rx metformin, LSM (treat pre-DM)

Knowledge gaps

- Early events in host-pathogen interaction
- Effects of DM on memory T cell generation & stability
- Effects of DM on T cell senescence
- Mechanisms of TB-associated metaflammation
- Correlation of mouse & human TB/DM -omics

Need\$

- Tractable mouse models of T2D
- Team science & collaborative networks

Future directions

- Mouse genetic diversity
- Bacterial environment in diabetic hosts
- Preclinical testing of ATT and HDTs
- Preclinical testing of DM complication pathway blockers
- Preclinical testing of preventive and therapeutic vaccines