Immunometabolic circuits in host defense

Mihai G. Netea
The cellular immune response to *M. tuberculosis*. Following aerosol infection with *M. tuberculosis*, resident lung alveolar macrophages (1a), neutrophils (1b), and lung DCs (1c) can become infected, leading to the production and secretion of antimicrobial peptides, cytokines, and chemokines. The balance of lipid mediators, such as prostaglandin E2 (proapoptotic) or lipoxin (LXA4) pronecrotic, within infected macrophages plays a major role in determining downstream pathways leading to the induction of either apoptosis or necrosis. Infected apoptotic cells can be taken up by resident lung DCs or efferocytosed by uninfected lung macrophages (1c).

*M. tuberculosis*–infected DCs migrate to the local lung-draining lymph nodes by 8–12 days post infection. DCs migrate to the lymph nodes under the influence of IL-12(p40)2 and IL-12p70 and that of the chemokines CCL19 and CCL21 (2), to drive naive T cell differentiation toward a Th1 phenotype (3). Protective antigen-specific Th1 cells migrate back to the lungs in a chemokine-dependent manner 14–17 days after the point of initial infection/exposure (4) and produce IFN-γ, leading to macrophage activation, cytokine production, the induction of microbicidal factors including iNOS (5), and bacterial control.
Bacillary loads (CFU) were enumerated in the lungs on days 1, 21, 42, and 100 after infection. In these experiments, we were unable to detect any CFU in the lungs of mice that received INH alone (Fig. 2C and fig. S8, A and B). Indeed, in some mice treated with MET (500 mg/kg) administered MET alone or MET in combination with either isoniazid (INH) or both isoniazid and MET, there was a significantly reduced bacterial load compared to controls. MET enhances the efficacy of conventional anti-TB drugs and restricts mycobacterial growth by inducing autophagy. The host cell innate immune response is significantly increased upon MET therapy, as evidenced by the upregulation of pro-inflammatory cytokines and activation of the NF-kB pathway. These phenomena were not observed in our experiments either at early or late stages of infection. The results indicate that MET as an adjunct therapy can enhance the efficacy of conventional anti-TB drugs and improve the control of tuberculosis infection. Further studies are needed to explore the mechanisms of action of MET and its potential for use in the treatment of multidrug-resistant tuberculosis.
Metformin and host-directed therapy in tuberculosis

A

% of TB + DM patients having pulmonary cavities

\( n = 109 \)  
\( n = 164 \)

B

% of survival

Days after initiation of anti-TB therapy

\( * \)

TUBERCULOSIS

Metformin as adjunct antituberculosis therapy

Amit Singhal,1* Liu Jie,1† Pavanish Kumar,1† Gan Suay Hong,2 Melvin Khee-Shing Leow,3,4 Bhairav Paleja,1 Liana Tsenova,5,6 Natalia Kurepina,5 Jinmiao Chen,1 Francesca Zolezzi,1 Barry Kreiswirth,5 Michael Poidinger,1,7 Cynthia Chee,2 Gilla Kaplan,5,8 Yee Tang Wang,2 Gennaro De Libero1,9*

http://stm.sciencemag.org
Metformin and host-directed therapy in tuberculosis

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INTRODUCTION

Pulmonary TB

Extrapulmonary TB

Lung

Heart

Spine

Lymph node

Brain

Kidney

Bone marrow

Reduction of inflammation

Reduction of Mtb burden

Insulin receptor

Metformin

Activation

AMPK

T cell activation and cytolytic activity

CD8+ T cell

Macrophage

Mtb

Prostaglandin E2

Verapamil

Ca2+ channel

HDAC inhibitors

mTOR

Metformin

Zileuton

COX-2 inhibitors

S-LO

Nucleus

HDAC

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References

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‡ Gilla Kaplan,
§ Barry Kreiswirth,
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,* Gennaro De Libero

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Trained immunity versus tolerance

**Infection or vaccination**

Epigenetic reprogramming in innate immune cells

- Histone modification
- DNA methylation
- Modulation of miRNA
- Long-noncoding RNA expression

Trained immunity transcriptional & functional programs

**Adaptive states**

- Mucosal tolerance
- Limitation of tissue damage in infection

**Training programs**

- Innate immunity maturation
- Nonspecific protection by vaccines

**Maladaptive states**

- Immune paralysis in sepsis
- Hyperinflammation in tissues
- Atherosclerosis

**Tolerance programs**

Potential health effects from non-specific stimulation of the immune function in early age: The example of BCG vaccination
Does this happen in vivo in humans?

Kleinnijenhuis et al, PNAS, 2012
BCG enhances monocyte-derived cytokines

M. tuberculosis

S. aureus

C. albicans

Kleinnijenhuis et al, PNAS, 2012
BCG effects on epigenetics and transcription

M. tb  
S. a  
C. a (hyph)

Before BCG
3 months post BCG

Kleinnijenhuis et al, PNAS, 2012
What are the pathways distinguishing Training vs Tolerance?

Saeed, Quintin et al, Science, 2014
What are the pathways distinguishing Training vs Tolerance?

Saeed, Quintin et al, Science, 2014
Glucose metabolism and host defense

• The metabolic pathways through which immune cells metabolize glucose are crucial for immune activation
• Cellular metabolism has a signaling function linking immune signals and long-term epigenetic reprogramming of cell function
• Understanding cellular metabolism of immune cells during infection (TB) is crucial to fully describe the cell function
• Modulation of cell metabolism may represent a novel therapeutic target in improving host defense in tuberculosis
Thank you!

Our lab
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Leo Joosten
Reinout van Crevel

University of Groningen
Vinod Kumar
Cisca Wijmenga

Dept. Molecular Biology - Radboud
Sadia Saeed
Joost Martens
Colin Logie
Henk Stunnenberg

Max Plack - Berlin
Macarena Beigier-Bompadre
Stefan Kauffman

Harvard University
Clary Clish
Ramnik Xavier

University of Minho, Braga
Agostinho Carvalho
Ricardo Silvestre
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Lluis Quintana-Murci
Mihai Netea
Norman Pavelka

Microbiome
Ramnik Xavier
Cisca Wijmenga
Eran Elinav

Epigenomics
Ido Amit
Gioacchino Natoli
Joachim Schulze
Brian Brown

Immunometabolism
Luke O’Neill
Edward Pearce
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Tom van der Poll

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Reinout van Crevel
Eicke Latz
Bali Pulendran

Systems biology of disease
Adrian Hill
Leo Joosten
Eoin Mckinney

Organizers: Mihai Netea (Radboud UMC), Leo Joosten (Radboud UMC), Zoltan Fehervari (Nature Immunology)

www.humanfunctionalgenomics.org