Role of macrophages in HIV-1/M. tuberculosis co-infection

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Clinical synergy between HIV and Mtb

TB boosts HIV infection

A role for macrophages?

Mechanisms?

- Systemic level (Blood)

- In anatomical sites of co-infection
  - Cerebrospinal fluid
  - Lungs (BAL and tissue)
  - Pleural Effusion (PE)

- Co-infection: 400,000 deaths
- Tuberculosis 1.8 million deaths
- HIV/AIDS 1.1 million deaths

- Tuberculosis: 1.8 million deaths
- HIV/AIDS: 1.1 million deaths

- Mtb
- HIV-1

- Role of macrophages in HIV-1 / Mtb co-infection?

World Health Organization, 2016
Role of macrophages in HIV-1 exacerbation induced by TB-derived microenvironment?
In vitro model to mimic TB-associated microenvironment

Effect of TB-associated microenvironment on HIV-1 infection of macrophages?

Claire Lastrucci

Geanncarlo Lugo-Villarino
Maeva Dupont (PhD)
Shanti Souriant (PhD)

CmCTR
Conditioned medium of uninfected macrophages

CmMTB
Conditioned medium of Mtb-infected macrophages

Primary human monocytes

TB-induced M(IL-10) macrophages:
Their abundance in vivo correlates with TB disease severity

Lastrucci et al., Cell Research, 2015
TB-associated microenvironment increases HIV-1 production in macrophages

Day 0

- + CmCTR
- + CmMTB

Human monocytes

Day 3

- CD16
- CD163
- pSTAT3
- pSTAT3
- MerTK
- HIV-1

Day 13

- HIV-1 production (p24 ELISA)
- HIV-1 infection (IF)

CmCTR

CmMTB

Gag DAPI F-Actin

Multinucleated giant cells
Hallmark of HIV infection of macrophages

Verollet et al, J Immunol. 2010
Verollet et al, Blood. 2015
Oreinstein et al, Immunol., 2001
What is modified in TB-induced M(IL-10) macrophages?

**Collaboration**: B. Lagane (CPTP, Toulouse, France)

**Collaboration**: I. Vergne (IPBS, Toulouse, France)

**INFECTIVITY**

**CLEARANCE**

**CELL-TO-CELL TRANSFERT**

* Tunneling nanotubes (TNT)

Adapté de Simon et al. Nature Immunology. 2015

Dupont et al, Frontiers Immunol. 2018

Okafo et al., J Immunol, 2020

Eugenin et al., Cell. Immunol., 2009
TNT are enhanced in TB-induced M(IL-10) macrophages
TB boosts HIV-1 production in macrophages through IL-10/STAT3-dependent TNT formation

**TNT induced by a TB-derived microenvironment boost HIV-1 production ...**

... in a IL-10/STAT3 dependent manner
TB exacerbates HIV-1 infection through IL-10/STAT3-dependent TNT formation in macrophages

Specific gene expression in these cells?

Molecular mechanisms?

Souriant S et al. Cell Reports, 2019
Transcriptomic analysis of CmMTB-treated macrophages

- **CD169/Siglec-1:**
  - Lectin receptor expressed on myeloid cells
  - HIV-1 capture and transfer

Hammonds et al., Plos Path, 2016; Sewald et al., Science, 2015; Pino et al., Retrovirology, 2015; Izquierdos-Useros et al., Plos Biol, 2012
**Siglec-1/CD169 (induced by Type-I IFN) is upregulated** in TB-associated microenvironment and.....

...in co-infected patients

Collaboration L. Balboa
(Argentina)
In vivo relevance of Siglec-1⁺ M(IL-10) macrophages in co-infection

Rhesus macaques
SIV / TB active

Siglec-1

% Siglec-1⁺ alveolar macrophages

Siglec-1⁺ cells/mm² of lung tissue

Healthy
SIV
ATB
ATB-SIV

Healthy
SIV
LTB
LTB-SIV
ATB
ATB-SIV

thological score
*Siglec-1 silencing in CmMTB-treated macrophages reduces HIV-1 production/infection*

**Dupont M et al., eLife, 2020**
Role of macrophages in HIV/Mtb co-infection

- Identification of TB-induced Siglec-1+ M(IL-10) macrophages
- Cellular (TNT) and Molecular (Siglec-1) mechanisms involved in HIV-1 exacerbation by TB
- Potential biomarkers in co-infected patients
  (sCD163, sMerTK, Siglec-1 on monocytes)

Perspectives
- Role of Siglec-1+ macrophages in the lung
- Other lectins (DC-SIGN, MR, DCIR)
- Macrophage/T cell communication?

Souriant S et al. Cell Reports, 2019
Dupont M et al., eLife, 2020
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