Macrophages and Pulmonary Pathogenesis in Young and Aged SIV-Infected Rhesus Macaques

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Challenges associated with aging and HIV

• Population of persons with HIV is growing older
  – Increasing longevity via ART
  – Increasing number of new infections in persons over age 50

• Chronic diseases of aging occur earlier in persons with HIV (i.e. accelerated aging)
  – Pulmonary disease
  – Cardiovascular disease
  – Certain cancers, cognitive and renal impairment
  – Bone demineralization
  – Age-related immune dysregulation
The level of monocyte turnover predicts disease progression in the macaque model of AIDS

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Figure 3. Increased monocyte turnover in SIV/SHIV-infected rhesus macaques.

- Total number of monocytes remains steady during SIV infection and progression to AIDS
- Turnover of blood monocytes increases during terminal progression to AIDS
Rationale and outline of study

• Inflammation plays a prominent role in HIV infection pathogenesis and chronic diseases of aging

• Macrophages
  – Innate immune responses
  – Regulate inflammation
  – Sites of virus replication
  – Predominant immune response cells in the lung

• Studies to examine blood monocyte and lung macrophage dynamics
  – Younger adult rhesus macaques
    • Uninfected “normal”
    • SIV infection
  – Older adult rhesus macaques
    • Uninfected “normal”
    • SIV infection
  – Implications for future studies
Turnover of AM (BAL) does not correlate with monocyte turnover during SIV infection in young macaques
Identification of macrophages in whole lung (uninfected young adult rhesus macaques)
Differentiation between Blood Monocytes and Lung IM & AM (uninfected young adult rhesus macaques)
Macrophages comprise to majority of immune response cells in the Lung (uninfected young adult rhesus macaques)
Turnover rate of Lung IM does correlate with increasing blood monocyte turnover in young adult SIV-infected macaques

\[ r = 0.9023 \]
\[ p < 0.0001 \]**

\[ r = 0.6434 \]
\[ p = 0.0278 \]*
SIV infection of lung AM & IM increases in young adult rhesus macaques expressing increased monocyte turnover
Younger adult rhesus macaques

- Monocyte turnover increases during SIV infection and terminal disease progression to AIDS
- 2 major macrophage populations in the lung
  - BAL is comprised of AM
    - Lower baseline turnover rate
    - Turnover rate *does not* increase in correlation to increasing monocyte turnover rate during SIV infection and progression to AIDS
  - IM in lung tissue
    - Higher baseline turnover rate
    - Turnover rate *does* correlate with increasing monocyte turnover rate during SIV infection and progression to AIDS
- SIV infects both IM and AM
- BAL does not reflect the entire lung macrophage dynamics that shift during SIV infection and disease progression to AIDS
Histological changes in lung tissue of older rhesus macaques
Declining AM:IM (AI Ratio) in the Lungs of Older Monkeys (FC)
Comparison of cellular composition in lung tissue of younger and older uninfected rhesus macaques
Decline AM:IM (Al Ratio) occurs in the lung of older rhesus macaques
Decreased IL-12 and TNF-α secretion in response to ex vivo LPS stimulation with aging in rhesus macaques
Phenotypically Analysis of AM & IM

Blood monocyte (CD14+)

CD31 FITC  CD64 FITC  TLR9 PE  CD11c APC  CD36 APC  CD209 PE

Isotype control  Antibody
Increased CD31 Expression on AM of Old Rhesus Macaque
Increase CD31 Expression on IM of Old Rhesus Macaque
Uninfected older adult rhesus macaques

• Architecture of lung: atrophy of alveoli septum
• AM:IM decline
  – Decreased number of AM (vs IM increase in number)
• Decline in BAL AM responsiveness to inflammation stimuli
• Increased CD31 expression on AM and IM with aging
Decline AM:IM (AI Ratio) occurs in the lung of older rhesus macaques.
SIV infection of Lung Tissue Heterogeneously in Old Rhesus Macaque During Acute Phase
Increased the turnover rate of IM in older rhesus macaque during acute phase SIV infection.
Summary - Cellular changes in the lung of older rhesus macaques

- Decreased AM:IM ratio in older uninfected animals resembled the decrease in AM:IM ratio following SIV infection in younger adults, but this may be caused by different mechanisms
  - Young adult chronic SIV infection: increased IM
  - Older uninfected: decreased AM
- Increased NK & CD8 T cells were observed in the lung of older macaques
- Decreased IL-12 and TNF-a secretion with aging by BAL AM in response to ex vivo LPS stimulation
- Increased expression of CD31 on IM and AM in the lung of older rhesus macaques
- Increased turnover of IM (but not AM) in the lung of older rhesus macaques during acute phase of SIV infection
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