Immune Senescence in HIV Disease

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Determinants of Accelerated Aging in HIV Infection

Effects of treatment
- Residual viral replication
- Persistent viral expression (in LN)
- Altered Th17/T_{reg} ratio
- Collagen deposition
- Microbial translocation
- High pathogen load (cytomegalovirus, hepatitis C virus)
- Thymic dysfunction

Suboptimum CD4 gains → Residual inflammation → Immuno-senescence

Non-AIDS events and premature mortality

Volberding and Deeks, *The Lancet* 2010; 376:49-62
Human Immune System

Innate Immunity
- pDC
- mDC
- iNKT
- NK
- Mast cells
- Complement

Adaptive Immunity
- CD4 T cells
- CD8 T cells
- B cells
Innate Immune Aging
Senescent first line of defense: replicative senescence in pDC impaired frequency, function and telomere length
Adaptive Immune Aging
Aging and the Immune System

T Cell Compartment

• Thymic Involution
• Decreased Naïve T Cells
• Increase in Memory T Cells
• Increase T Cell Activation
• T Cell Clonal Expansion with Loss in T Cell Repertoire (ie CMV)
• Inversion CD4/CD8 Ratio
• Reduced TCR Signalling and IL2 Production
• Telomere Shortening
Imprints of accelerated aging on the thymus:
Impact of HIV on thymic volumes is more pronounced in younger HIV-infected individuals and is not altered differentially at older age

“Younger”
18-30 y

“Older”
≥45 y

Impaired T cell Homeostasis: Depletion of Naïve CD4 Cells and Accumulation of Terminal Effectors In HIV-Infected and Aging Subjects

Dysfunctional thymus in HIV-infected patients: Naive T cell counts do not reconstitute to the same degree as memory or total CD4+T cells.

ACTG 5015 unpublished.
What is immune aging?
Mechanism Leading To End Stage Senescence

Clonal expansion

antigen

T cell

T cell

T cell

End stage senescence T cells

Adaption Effros RB
Replicative Senescence in HIV-1-Infected Patients Is Comparable to Older HIV-Negative Subjects

Immune Activation Levels in HIV-1 Infected Patients Are Similar to Older HIV-Negative Subjects

Conclusion

HIV-induced activation leads to early senescence
Inflammageing

• Enhanced Pro-inflammatory Mediator (IL6, IL1, TNF-α)

• Reduced Anti Inflammatory Mediator (IL10)
Senescent T cells Affect Organ Function

**Cardiovascular Disease**
Correlates with increased levels of TNF RII, IL-6, TNF-α, acute phase marker CRP and coagulation marker 2D-dimer

**Neurocognitive (Alzheimer’s disease)**
Telomere length correlates with disease status

**Bone**
Correlate with osteoporotic fractures
IL-6, TNF-α correlates with bone loss
T Cell Activation, Senescence, and Atherosclerosis

CD8 Activation

CD8 Senescence

Kaplan et al, JID 2011
Inflammation
Activation
Coagulation
Microbial translocation

Viral Replication

Co-morbidities

CVD
Neurocog
Cancers
Liver Disease
Metabolic Disease

Premature Aging
Aging with HIV - Model

Gaps in Our Knowledge of HIV and Immune Senescence

Big Questions……

- Inflammation leads to Immune activation or vice versa
- Does Immune senescence lead to end organ senescence
- Does early senescence lead to early onset of Co-morbidities

What is the mechanism leading to immune senescence – implication for interventional strategy