Mechanism of Functional Decline: Role for Frailty in HIV and Aging

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HIV and Aging

- The introduction and success of antiretroviral therapy (ART) has led to an aging HIV+ population, altering the characteristics of the HIV/AIDS epidemic.
- Within this aging population, there is an increased risk for and burden of comorbidities typically associated with age.
- Examples include cardiovascular disease, chronic kidney disease, osteoporosis, and neurocognitive disorders.
- Increases in age-related comorbidities may predispose HIV-infected persons to a particularly vulnerable state known as frailty.

Frailty

- In geriatrics literature, frailty is defined as an increased vulnerability to stressors in the face of limited physiological reserve.
- Frailty has been associated with a range of aberrant, dynamic, multisystem physiological stress responses affecting neuroendocrine, metabolic, musculoskeletal, cognitive, and immune systems.
- Disruption of key stress response systems driven by underlying aging-related cellular and molecular pathogenesis adversely impact muscle mass and quality, strength, endurance, and efficiency of energy expenditure.
- Fried et al defined the original frailty phenotype involving impairment in at least 3 of 5 domains.
  - Physical slowness measured by walking speed.
  - Weakness measured by grip strength.
  - Fatigue.
  - Low physical activity.
  - Unintentional weight loss.
- The frailty phenotype (FP) independently predicts a number of adverse outcomes.
  - Acute illness, falls, cognitive decline, disability, institutionalization, and mortality.

HIV and Frailty

- Similarities between frailty, aging, and HIV infection were recognized early in the HIV era.
  - Weight loss, immune activation, and high levels of cytokines were features of untreated HIV also common in aging populations.
- After the introduction of ART, focus shifted to the effect of chronic treated HIV infection on health and longevity as life expectancy increased.
  - HIV-associated non-AIDS (HANA) conditions have become major health concerns.
  - Frailty is increasingly being recognized as an important factor to identify HIV-infected persons at high risk for adverse health outcomes.
The role of Inflammation in frailty status in HIV-infected populations

Inflammation

- The aging immune system is characterized by a low level chronic systemic inflammatory state, termed inflamming
- Elevated circulating levels of markers of inflammation (CRP, IL-6, TNF-α)
- Associated with increased morbidity and mortality in older adults
- Chronic heightened inflammation contributes to the pathogenesis of frailty in the geriatric population, directly or through other intermediate pathophysiological processes
- Frailty is associated with increased serum levels of CRP, IL-6 and CXCL-10, TNF-α, and neopterin

Differences in Inflammatory Markers (A), Markers of Immune Activation and Senescence (B), and Markers of Hormonal Regulation (C) by frailty status among HIV-infected Men

Comparison of T-lymphocyte immune activation (CD38 and HLA-DR expression on CD4+ and CD8+ T cells) between low- and high-functioning groups
Conclusions

- Mounting evidence supports the role of chronic inflammation as a contributing factor to frailty in older adults, and this is likely to be true in people with chronic, treated HIV infection, who have higher levels of systemic inflammation

The role of Cytomegalovirus in physical function impairment of older, HIV-infected adults
The role of immunometabolism in mechanisms of immune dysfunction and development of age-associated comorbidities and functional decline in HIV infection.

Immune Activation reprograms T cell glucose metabolism from oxidative phosphorylation to glycolysis (Warburg Effect)

High Glut1 expression of CD4+ T cells is associated with poor immune recovery in ART-treated HIV+ persons

Model: metabolic exhaustion drives CD4+ T cell loss in HIV+ Individuals
Recruitment of older HIV+ men for frailty study (Melbourne HIV Silver Aging Study)

MFI of GLUT-1 on monocyte subsets from non-frail and frail individuals

Plasma levels of sCD163 and sCD14 according to Frailty status

Plasma levels of sCD163 and sCD14 according to continuous Frailty Index
Increased blood monocyte glycolytic activity is associated with frailty and poor quality of life in older HIV+ men

Conclusions

- Increased CD4+ T cell glycolytic activity is associated with functional decline (metabolic exhaustion)
- Host-directed therapies to normalize glucose metabolic activity in T cells and monocytes may improve functional activity and reduce inflammation

Microbiome Alterations in HIV: A Possible Driver of Functional Decline

- The microbiome helps shape the innate and adaptive immune system with a delicate balance of pro- and anti-inflammatory responses
- Tryptophan catabolites, in particular kynurenine and quinolinic acid, are associated with immune activation
- Microbial dysbiosis may modulate health through SCFAs like butyrate, as they are an important energy source for colonocytes and can control barrier function

Role of Microbiome in Aging and HIV Populations

- Increased IDO/TDO
- Healthy Microbiota
- Frailty
- Microbial Dysbiosis
- Increased risk of Comorbidities: Frailty, CVD, Diabetes, Cancer, UTI, and Increased mortality

Immune Activation and Inflammation
- CRP, IL-6, CXCL10
- Metabolic Changes
- ↑ Glycolysis
- ↓ Butyrate

Comorbidities
- CVD, Cancers, Kidney and Liver Disease,
- Neurocognitive Impairment
- CMV Infection
- ↓ CD4 counts
- ↑ CRP, IL-6, TNF-α

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Join us to discover the role Microbiome plays in the pathogenesis, prevention and treatment of HIV/AIDS
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