

ASP-AMERICAN GERIATRICS SOCIETY FOUNDATION FOR HEALTH IN AGING AWARD



AWARD RECIPIENT

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PROJECT

"IMMUNOLOGIC DYSREGULATIONS AND INFLAMMATION IN THE PATHOGENESIS OF FRAILITY OF OLD AGE: THE ROLE OF CHRONIC CYTOMEGALOVIRUS INFECTION"

MENTORSHIP TEAM

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Frailty is a common geriatric syndrome that is characterized as a wasting state of decreased physiologic reserve, loss of physiologic complexity, and an accumulation of deficits. Frailty is an independent risk factor for poor outcomes in older adults. A physiologic phenomenon consistently observed in frail older individuals beyond age-related changes is a generalized inflammatory state. Inflammation is hypothesized to play an important role in the pathogenesis of frailty through its effects on multiple physiologic systems. Our overall objective is to elucidate the mechanisms of immunologic dysregulation and identify potential initiators of the inflammation that underlie and antecede the development of frailty.

Cytomegalovirus (CMV) infection drives alterations in the distribution of T-cell subsets and has been shown to be associated with frailty. We hypothesize that CMV infection plays an important role in the pathogenesis of frailty in a subset of humans who eventually become frail. In these individuals, CMV maintains a heightened state of immune activation and causes an accumulation of CMV-specific T-cells that are likely dysfunctional and lead to a restricted T-cell receptor repertoire diversity. Restricted T-cell receptor repertoire diversity could produce dysregulations in T-cell homeostasis, which can lead to inflammation and autoimmunity. We hypothesize immune system dysregulations contribute to and antecede the development of frailty and its manifestations.

The specific aims of my research are to:

1. Determine the relationships among measurable CMV-induced immunologic parameters, alterations in T-cell phenotypes and T-cell receptor repertoire diversity, and

frailty in a cross-sectional case-control study using data and samples from the Women's Health in Aging Study (WHAS).

2. Determine whether the frequency of CMV reactivation is associated with frailty by measuring CMV viral load in repository serum samples from multiple serial time points.
3. Determine whether the immunologic alterations identified above antecede the onset of frailty by performing a nested case-control study using longitudinal data in WHAS. We will develop a model based on these parameters to predict the development of frailty.

The long-term objectives of this research are to identify potential targets along the pathophysiologic pathway of frailty that are amenable to preventive and therapeutic interventions. The findings from research will also enable clinicians to identify the older adults most vulnerable to develop frailty so that a preventive program can be started before the onset of frailty. Such interventions can decrease the substantial morbidity, mortality, and socioeconomic burdens caused by frailty.

The ASP-American Geriatrics Society Foundation for Health in Aging Award will allow me to conduct this research and support my career development through the interdisciplinary nature of my mentorship team. This support comes at an important period in my career development. Through this research, I will acquire the crucial skill set and expertise in geriatrics and immunology and embark on the path to becoming an independent investigator focused on improving the health of older adults.