ASP-American Geriatrics Society Foundation for Health in Aging Award

AWARD RECIPIENT

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PROJECT

"Age-Related Change in Angiotensin Receptors and its Contribution to Chronic Inflammation"

MENTORSHIP TEAM

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Chronic, low-grade inflammation is implicated in the pathogenesis of many common and disabling diseases in older adults. Most of these diseases are slowly progressive and have a clear association with advancing age. The etiologies that trigger chronic inflammatory activation in older adults are likely heterogeneous and include multiple chronic disease states, redox imbalance, senescent cells, and increased body fat. There is also evidence that age-related changes in the renin-angiotensin system (RAS) may contribute to the development of chronic inflammation observed in older adults. Angiotensin, the main RAS effector hormone, interacts with both angiotensin II type 1 receptor (AT_1R) and angiotensin II type 2 receptor (AT_2R). Both AT_1R and AT_2R are expressed on endothelial and immune system cells. An altered ratio between AT_1R and AT_2R, induces inflammation in animal models. The effects of aging on the expression of AT_1R and AT_2R in humans and the contribution of changes in AT_1R and AT_2R to increased inflammation in older adults has not been previously studied. Our preliminary evidence suggests that frail older adults have up-regulation of AT_1R and down-regulation of AT_2R expression, and implicate for interleukin-6 (IL-6) in this imbalance

We hypothesize that aging is associated with changes in AT_1R and AT_2R expression in immune system cells and that these changes are driven by age-related alterations in DNA methylation of AT_1R and AT_2R genes. Further, we hypothesize that these changes contribute to the increased production of inflammatory cytokines in older individuals, which in turn will further heighten the divergence in AT_1R and AT_2R expression.

To test our hypotheses, we will:

1. Measure changes in gene expression, protein synthesis, and specific gene DNA methylation of AT_1R and AT_2R in immune system cells from young, robust, and frail human subjects (20 in each group) using quantitative polymerase chain reaction (Q-PCR), western blot, confocal microscopy, and DNA methylation analysis.
2. Evaluate the contribution of AT_1R and AT_2R to cytokine production in older individuals by incubating immune system cells from the same individuals with specific AT_1R or AT_2R blockers and measuring cytokines with enzyme-linked immunosorbent assay and Bio-Plex cytokine assays at baseline and in response to treatment.
3. Assess the feedback of inflammation on AT_1R and AT_2R expression by incubating immune system cells from the same subjects with IL-6. Q-PCR and western blot will be used to quantify the change in expression of AT_1R and AT_2R in response to IL-6 treatment.

If we are successful in meeting our specific aims, important progress will have been made in understanding age-related molecular changes that may contribute to chronic inflammation late in life. Given that there are already available pharmacological agents that impact the RAS pathways, positive findings in this proposal could lead to a great variety of clinical translational studies. These studies would enable the study of these agents on the modulation of expression of AT_1R and AT_2R, and the related consequences of influencing their biologically active status and contribution to inflammation in older individuals. In addition, epigenetic changes in AT_1R and AT_2R genes that influence receptor expression may lead to much broader studies of age-related epigenetic change that influence molecular aging processes.

The ASP-American Geriatrics Society Foundation for Health in Aging Award will help me with the critical support needed to continue cutting-edge research in late life inflammation and frailty and it will facilitate my successful transition to an independent investigator.