Enhanced Molecular Aging in Late-Life Depression: the Senescent-Associated Secretory Phenotype

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Objective: *This study aims to investigate whether a systemic molecular pattern associated with aging (senescent-associated secretory phenotype [SASP]) is elevated in adults with late-life depression (LLD), compared with never-depressed elderly comparison participants.* **Design:** *Cross-sectional study.* **Participants:** *We included 111 older adults (80 with LLD and 31 comparison participants) in this study.* **Measurement:** *A panel of 22 SASP-related proteins was extracted from a previous multiplex protein panel performed in these participants.We conducted a principal component analysis to create the SASP index based on individual weights of each of protein.* **Results:** *Participants with LLD showed a significantly increased SASP index compared with comparison participants, after controlling for age, depressive symptoms, medical comorbidity (CIRS-G) scores, sex, and cognitive performance ($F_{(1,98)} = 7.3$, $p = 0.008$). Correlation analyses revealed that the SASP index was positively correlated with age ($r = 0.2$, $p = 0.03$) and CIRS score ($r = 0.27$, $p = 0.005$), and negatively correlated with information processing speed ($r = -0.34$, $p = 0.001$), executive function ($r = -0.27$, $p = 0.004$) and global cognitive performance ($r = -0.28$, $p = 0.007$).* **Conclusions:** *To the best of our knowledge, this is the first study to show that a set of proteins (i.e., SASP index) primarily associated with cellular aging is abnormally regulated and elevated in LLD.These results suggest that individuals with LLD display enhanced aging-related molecular patterns that are associated with higher medical comorbidity and worse cognitive function. Finally, we provide a set of proteins that can serve as potential therapeutic targets and biomarkers to monitor the effects of therapeutic or preventative interventions in LLD.* (Am J Geriatr Psychiatry 2017; 25:64–72)

Key Words: late-life depression, aging, senescent associated secretory phenotype, cognitive performance

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Late-life depression (LLD) is a common mental disorder in older adults.[1] The occurrence of LLD is associated with increased risk of age-related disorders—for example, cardiovascular, cerebrovascular, and neurodegenerative disorders.[2] The exact neurobiological mechanisms of LLD are being characterized and likely involve the abnormal regulation and interaction of multiple biological processes and structural and functional brain abnormalities.[3]

A key to understanding the neurobiology of LLD is identifying how it interacts with aging-related brain and systemic biological changes. Understanding this interplay can provide insight into mechanisms by which LLD is associated with negative health outcomes common among older adults, such as higher risk of dementia, increased mortality, cardiovascular comorbidities, and disability.[4,5] Recent studies have examined biomarkers related to cellular senescence in patients with major depression. In a large population-based study, leukocyte telomere length was significantly reduced in the participants with a current or history of depression.[6] Young and older depressed adults show heightened oxidative stress and pro-inflammatory states, increased endoplasmic reticulum stress, and loss of proteostatic control.[7,8] In a large-scale gene expression study of brain tissue, most major depressive disorder (MDD)-related genes were positively correlated with age-dependent changes observed in control participants,[9] and notably showed greater age-related expression changes in MDD participants, demonstrating accelerated molecular processes in adult midlife MDD.

In an in vitro study, Coppé et al.[10] showed that different senescent fibroblast cell lineages actively secrete a common set of proteins that lead to cell cycle arrest and induce senescence in nearby cells. This set of "senescent-associated secretory phenotype" (SASP) proteins include inflammatory and immune-modulatory cytokines and chemokines, growth factors, and cell surface molecules. Abnormal expression of SASP-related proteins has been found in aging-associated disorders such as malignancies, osteoarthritis, and chronic obstructive pulmonary disease.[11–14] Senescent glial cells (i.e., astrocytes and microglia) can also secrete SASP-related proteins and can induce senescent changes in the brain.[15]

Some clinical features that are common in individuals with LLD, such as comorbid medical illnesses, cerebrovascular changes, cognitive dysfunction (in particular, executive function and processing speed), and brain atrophy are also observed during the nonpathological aging process.[16–18] These changes have a greater effect size in LLD compared with nondepressed age-matched individuals, however.[19,20] No integrative mechanisms have been proposed so far to explain these relationships. Therefore, we measured expression levels of proteins constituting the SASP index and compared values between LLD individuals and age-matched never-depressed comparison participants. We hypothesized that LLD individuals would present with an enhanced SASP profile compared with never-depressed older adults. We further evaluated whether the SASP profile is associated with demographic and clinical characteristics, cognitive performance, and brain structural neuroimaging markers in LLD participants. We hypothesized that the SASP index would significantly correlate with older age, higher medical comorbidity burden, greater cognitive dysfunction, and greater cerebrovascular disease (measured by white matter hyperintensities) and gray matter atrophy.

METHODS

Participant Recruitment and Cognitive Assessment

Data from 80 older adults with remitted LLD and 31 older adults with no previous history of major depression or other major psychiatric disorder (comparison group) were included in this analysis. All of the participants were enrolled in a research clinic based at the University of Pittsburgh's NIMH-sponsored Advanced Center for Intervention and Services Research for Late-Life Mood Disorders. All LLD participants had previously met DSM-IV criteria for current unipolar MDD without psychotic features and were successfully treated to response (i.e., Hamilton Depression Rating of 10 or less for 2 consecutive weeks) in pharmacotherapy and/or interpersonal psychotherapy intervention trials.

Exclusion criteria for all participants encompassed substance abuse within the past year, unstable medical illness (precluding participation in clinical trials for depression), history of psychosis, bipolar disorder, neurologic disorder (including dementia), or significant head trauma (defined as loss of consciousness >30