MONOCYTE SENESCENT PROTEINS ARE ASSOCIATED WITH COGNITION, BRAIN STRUCTURE, AND PLASMA AD BIOMARKERS

Tugce Duran, PhD[1]; Yang An, MS[1]; Murat Bilgel, PhD[1] ;Michael R. Duggan, PhD[1]; Cassandra O. Blew, BS[1];
Nathan Basisty, PhD[2]; Bradley Olinger, PhD[2]; Reema Banarjee, PhD; Susan M. Resnick, PhD[1]; Keenan A. Walker, PhD[1]

[1]*Laboratory of Behavioral Neuroscience, National Institute on Aging, National Institutes of Health;* [2] *Translational Geroproteomics Unit, National Institute on Aging, National Institutes of Health*

Let's connect!

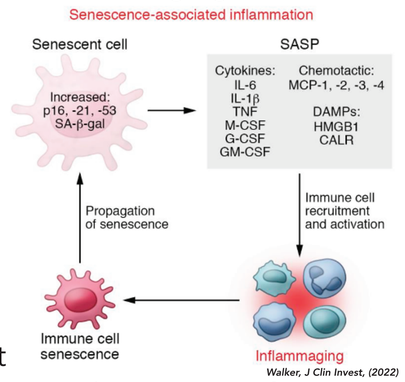
Hypotheses:

Cellular senescence is a key driver of aging and disease:

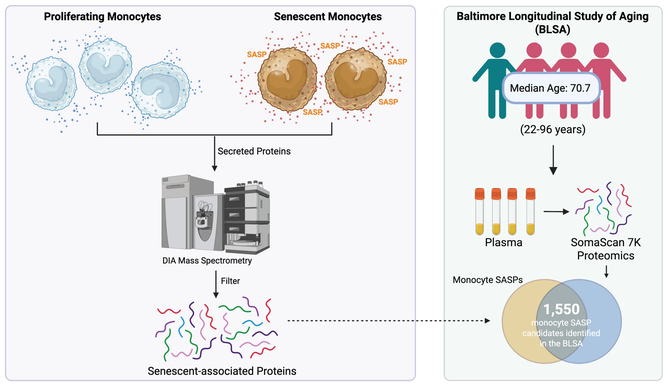
- Senescence-associated proteins in plasma increase with age.
- Higher senescence burden is associated with greater cognitive decline and brain atrophy.
- This relationship may link to Alzheimer's disease pathology.

Background:

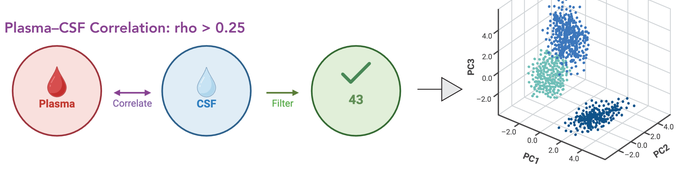
- **Senescent immune cells** (SICs), such as **monocytes**, can induce cellular senescence and **inflammatory protein expression** via **senescence-associated secretory phenotype (SASP)** signaling with advancing age[1-3].
- However, it remains unknown how **monocyte SASP proteins** are associated with **Alzheimer's disease (AD)**.
- This study identifies **16 plasma SASPs** that differentially associate with **cognition**, **brain structure**, and **plasma AD biomarkers**.



Methods:



We identified 43 monocyte SASP proteins with central nervous system (CNS) relevance, defined by a positive plasma–CSF correlation.



Principal component (PC) analysis of these 43 proteins generated three latent signatures (PC1-PC3), defined by top-loading proteins (n=16, 4-7 per PC). Adjusted linear models evaluated associations between baseline PC scores and cognitive, imaging, and plasma AD biomarkers.

Table. Participant demographics at baseline

Variables:	Overall (n=1316)	Missingness %
Age, mean (SD)	67.69 (14.05)	0
Sex, M (%)	628 (47.7)	0
Education years, mean (SD)	16.84 (2.47)	0.2
Race, Non-White (%)	370 (28.2)	0.2
APOE4 Status, Carriers (%)	337 (28.2)	9
Cognitive Status, Impaired (% MCI or Dementia)	28 (2.1)	0
Subsequently Impaired (SI), n (%)	274 (20.8)	0

Findings:

PCA-derived SASP signatures and senescence responses across cell types.
We identified senescence-associated changes by log2 fold-change in expression of 43 SASP proteins following induction of cellular senescence in iPSC-derived neurons by Doxo (concentration: D50), and in peripheral blood mononuclear cells (PBMCs) and astrocytes with etoposide (ETIS) or ionizing radiation (IRIS).

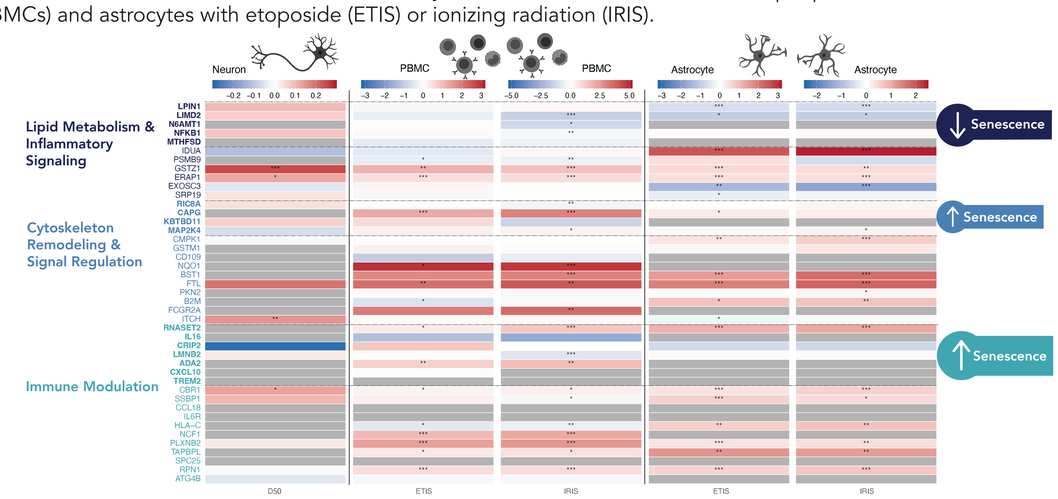


Figure 1. Longitudinal trajectories of SASP-derived PC1-PC3 by subsequent cognitive status.

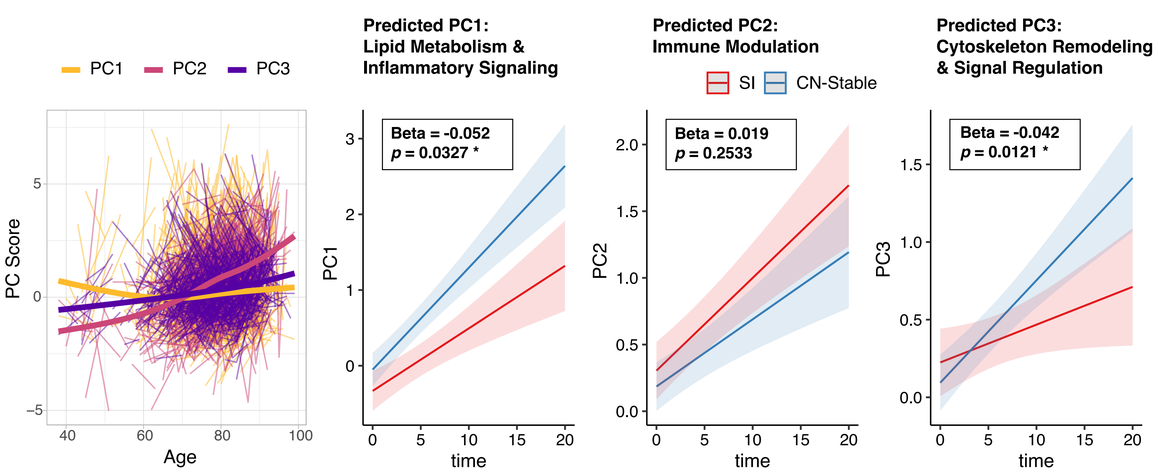


Figure 2. Associations between SASP-derived PC1-PC3 x time and cognitive outcomes.

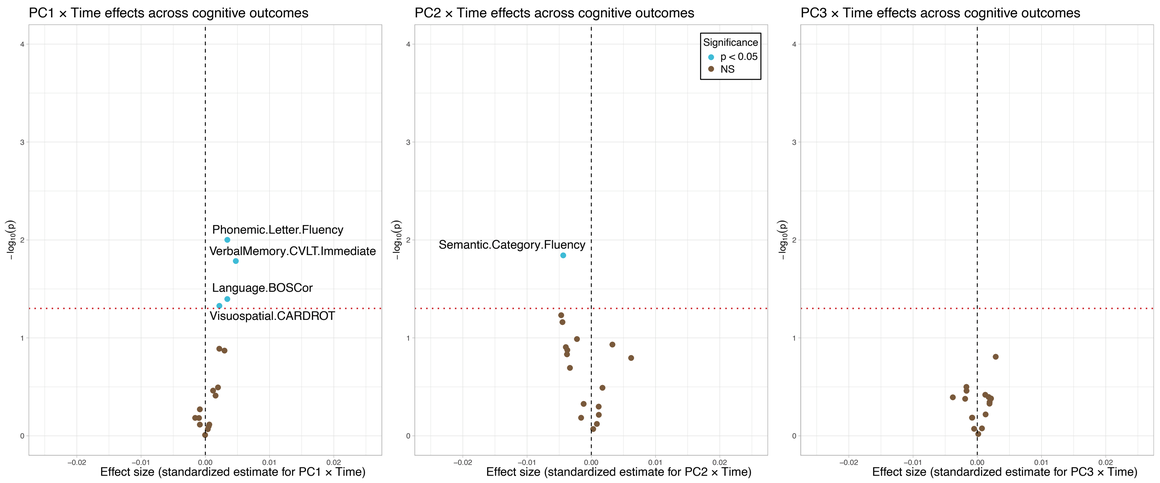
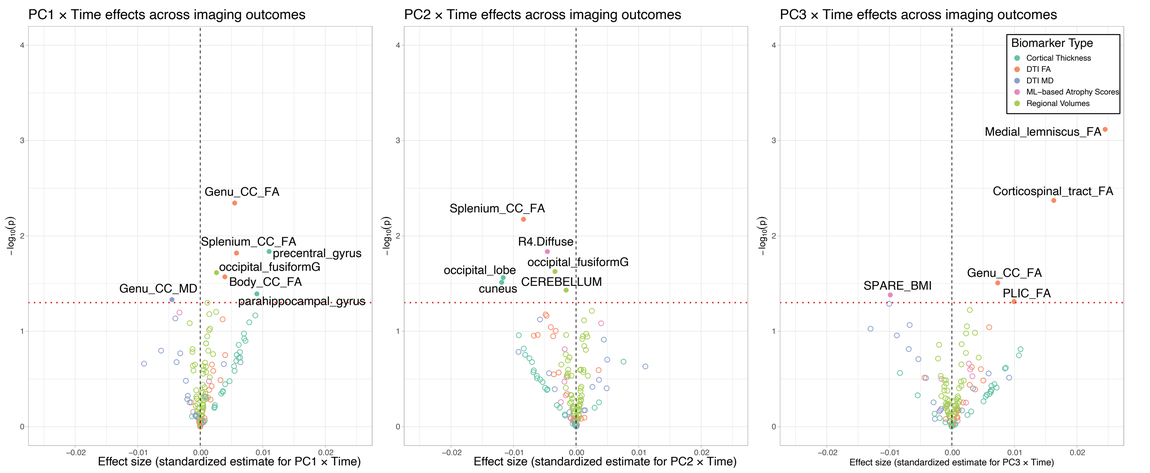
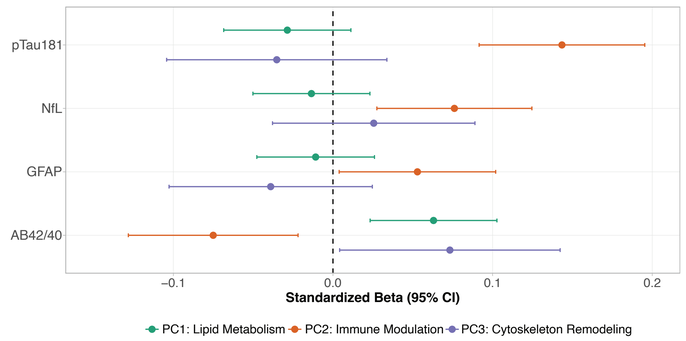


Figure 3. Associations between SASP-derived PC1-PC3 x time and MRI-based imaging outcomes.



Results:

Figure 4. Plasma AD Biomarkers.



- In **Figure 1**, we observed that longitudinal trajectories of SASP-derived PC1 (characterized by lipid metabolism and inflammatory signaling) and PC3 (cytoskeleton remodeling and signal regulation) differed between subsequently impaired (SI) and cognitively normal (CN) stable individuals.
- Baseline PC1: Lipid Metabolism was associated with less decline in verbal memory and fluency, language, and visuospatial abilities, whereas PC2: Immune Modulation was associated with faster decline in verbal fluency (**Figure 2**).
- Further longitudinal analyses showed that higher PC2 was associated with faster decline in brain structural integrity while PC1 and PC3 showed less decline (**Figure 3**).
- Additionally, all SASP-derived PCs were associated with the Aβ42/40 ratio; however, only PC2 was additionally associated with higher pTau181, NfL, and GFAP (**Figure 4**).

Conclusion:

Distinct groups of CNS-relevant monocyte-derived SASPs
(i) exhibit differential longitudinal trajectories among individuals who subsequently develop cognitive impairment, and
(ii) are associated with longitudinal cognitive changes, and
(iii) AD plasma biomarkers, particularly PC2: Immune Modulation signature, likely reflecting inflammatory signaling and altered intracellular regulatory processes.
Future work should explore underlying mechanisms and how sex and amyloid status modify these patterns.

References:

1. Walker et al., 2022 (DOI: 10.1172/JCI158448)
2. Olinger, Banarjee et al., 2025 (DOI: 10.1038/s43587-025-00877-3)
3. Schmitz et al., 2023 (DOI: 10.3389/fimmu.2023.1132653)

Acknowlegment:

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