Transcriptomics unveils molecular signatures of LAMDA (Lewy-associated molecular dysfunction from aggregates) and senescence in TgA53T mouse model of α-synucleinopathy and senolytic treatment delays disease onset.

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Emerging evidence indicates that cellular senescence is a pathological factor in aging and neurodegenerative diseases, including Parkinson's Disease (PD). Because α-synuclein (αS)-linked pathology and neurodegeneration is mechanistically linked to the pathogenesis of PD, we examined the pathological relationship between α-synucleinopathy and cellular senescence.To study the in vivo relevance, we used a transgenic mouse model of α-synucleinopathy (TgA53T), where rapid and reliable onset of disease was induced by inoculation with human αS PFF. Analysis of TgA53T mice shows that α-synucleinopathy is associated with increased levels of senescence markers including signs of DNA damage response (DDR; γH2Ax, HMGB1), $p16^{INK4a}$, $p21^{Cip1}$ and SASP factors. The nanostring-nCounter transcriptomic analysis also shows an increase in senescence markers. Cellular localization of senescence markers via immunohistochemistry and RNAscope analysis show that multiple cell types exhibit increased p16 and/or p21, but neurons with αS aggregates are first to show increased senescence markers. Goralski TM, Henderson MX et al.; Nat Commun. 2024 Mar defined a conserved molecular signature in aggregate-bearing neurons in both mice and human PD, termed LAMDA (Lewy-associated molecular dysfunction from aggregates). The LAMDA signature encompasses key features of neurodegenerative diseases, suggesting that even within a diseased brain, cells with aggregates undergo cell-autonomous changes. Our Single nuclei sequencing also confirmed distinct LAMDA signatures in excitatory neurons. To determine the pathologic significance of senescence, the mice were treated with senolytic cocktail [Dasatinib (12 mg/kg) and Quercetin (50 mg/kg) (D+Q)]. Behavior analysis shows that D+Q treatment attenuated preclinical motor and cognitive dysfunction in TgA53T mice. More importantly, D+Q treatment significantly delayed the onset of α-synucleinopathy and reduced neuropathology, including αS pathology, neuroinflammation, and neurodegeneration. D+Q treatment also reduces senescence markers in TgA53T mice. Finally, TgA53T/$Ercc1^{-/\Delta}$ mice develop αS pathology sooner following αS PFF inoculation compared to TgA53T/$Ercc1^{+/\Delta}$ mice, showing that increased senescence accelerates αS pathology. Our data show that cellular senescence is induced by α-synucleinopathy first in neurons and secondarily in glial cells. Further, targeting senescent cells using senolytics may provide neuroprotection from α-synucleinopathy.

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