DNA DAMAGE AND NEURONAL SENESCENCE: DIFFERENTIAL VULNERABILITIES OF NEURONS IN DIFFERENT CORTICAL LAYERS

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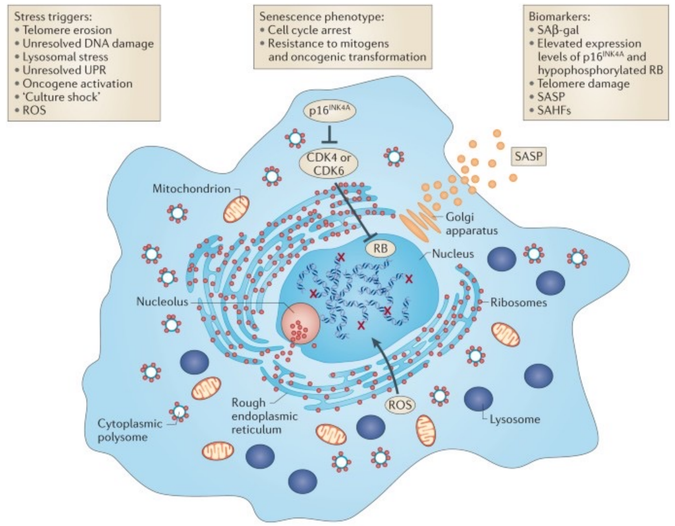
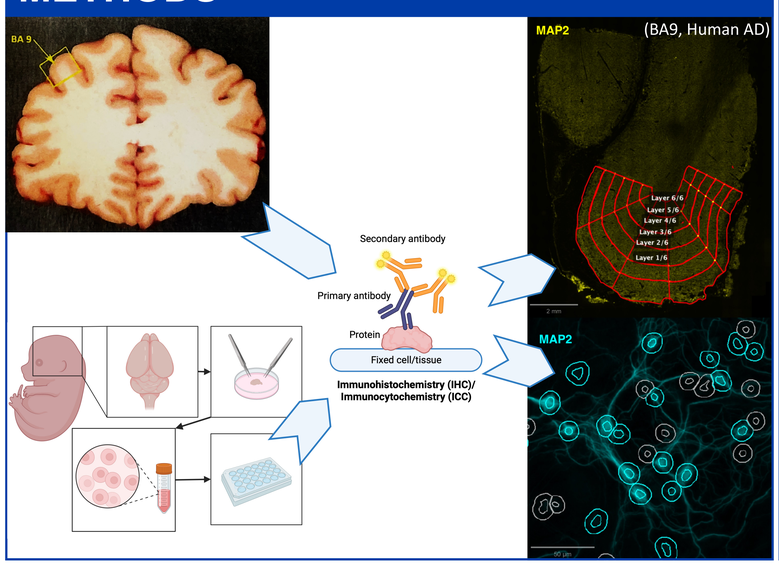
INTRODUCTION

Cellular senescence is a state of permanent arrest in cell growth and division that is triggered in response to environmental stressors such as oncogenic stimuli and DNA damage that distort cellular homeostasis. The accumulation of senescent cells is seen as a large contributing factor to natural aging and the natural process for senescence is seen as a protective mechanism against cancer as cells are actively preventing their cell cycle activity. The upregulation of senescent-associated markers has been linked to AD pathology and the presence of DNA damage in both human and mouse neurons. This led to the proposal that neurons enter a senescent-like state to avoid apoptosis and death while triggering the release of the SASP as NFT accumulation increases.



Sharpless, N., Sherr, C. (2015) *Nat Rev Cancer* **15**, 397–408

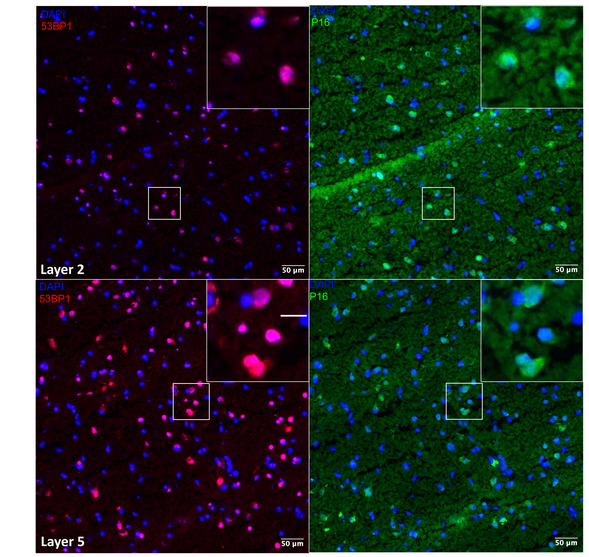
METHODS

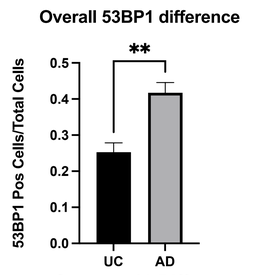


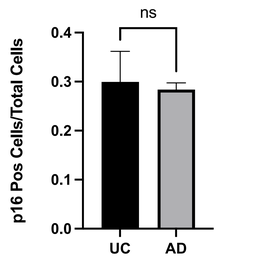
RESULTS

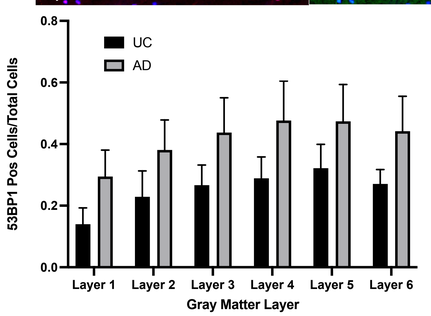
1. DNA Damage and senescence are variable through the cortices of an aging brain.

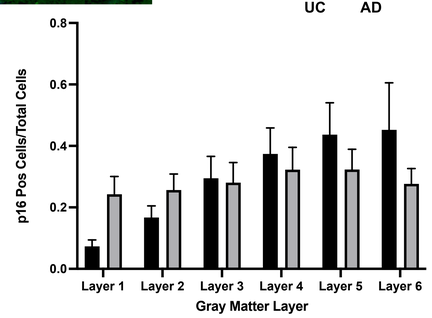
(BA9, Human Unaffected Control)





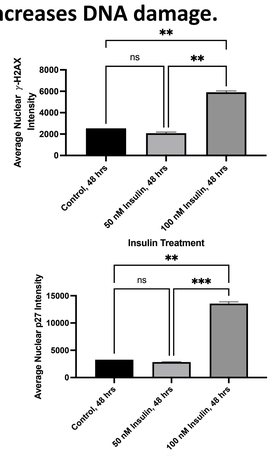


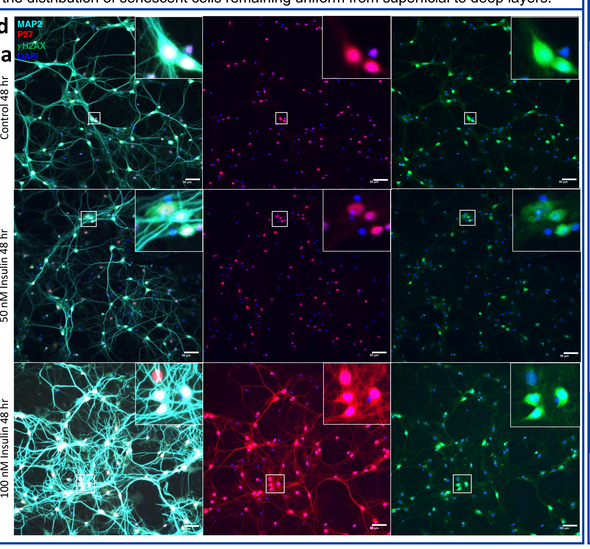




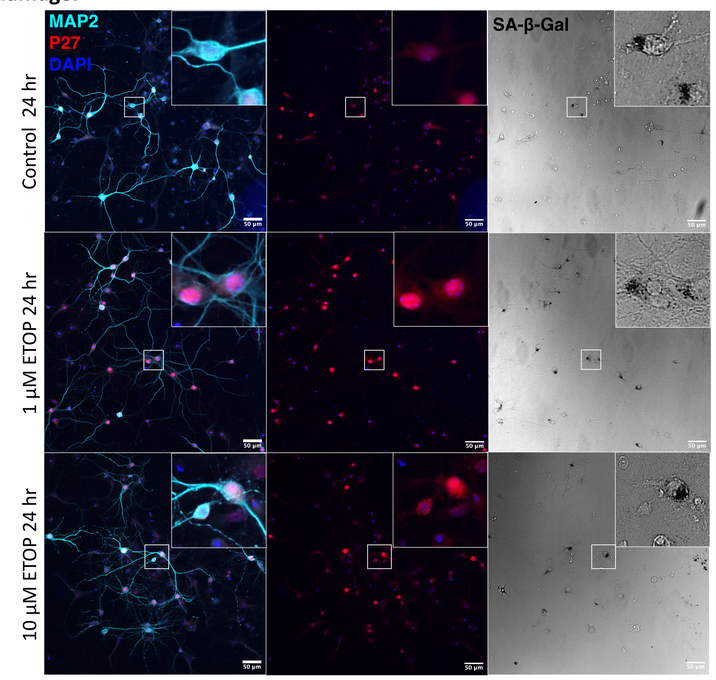
Overall neuronal DNA damage is significantly increased in Alzheimer's BA9 neurons, and this increase is uniform across all cortical layers. By contrast, overall senescence is unchanged with the distribution of senescent cells remaining uniform from superficial to deep layers.

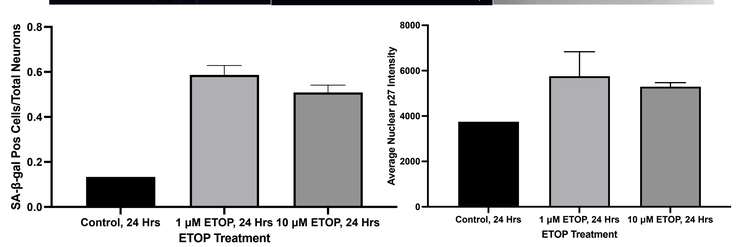
2. Inducing senescence in cultured neurons through hyperinsulinemia increases DNA damage.





2. Inducing DNA damage in cultured neurons with Etoposide increases DNA damage.





CONCLUSIONS / FUTURE DIRECTIONS

- The human AD cortex has an increase in overall DNA damage, as shown previously.
  - The effect is seen in all cortical layers
  - There is a trend towards DNA damage increasing in deeper layers
- The human AD cortex does not have an increase in overall senescence.
  - In UC, by contrast the density of senescent cells is reduced in the upper layers and increased in the deeper layers
  - In AD, senescent cells are distributed uniformly across all cortical layers
- The suggestion is that, in AD, senescence and DNA damage are uncoupled
- In vitro induction of senescence with hyperinsulinemia also induces DNA damage, leaving the correlation. In vitro induction of DNA damage with etoposide also induces senescence, leaving the correlation with the in vivo findings unclear.

- Future Directions:
  - Increase repeats of in vivo and in vitro experiments to achieve greater statistical power
  - Correlate DNA damage and senescence, with AD pathology (Aβ plaque density)
  - Expand the analysis to non-neuronal cells

ACKNOWLEDGEMENTS

Fulin Ma[1] and Prof. Karl Herrup[1] helped with experimental design and mentorship
Human tissue was from NeuroBioBank, National Institutes of Health (Bethesda, MD. USA)
Financial support: University of Pittsburgh, the NIH (NS120922 and AG069912), and Pennsylvania Department of Health (Project Number:4100087331)