

Aging is Associated with Changes in the Inflammatory Microenvironment and a Progenitor-Like Luminal Signature in the Mouse Prostate

Jonathan Fox, Preston Crowell, Hector Navarro, Johnny Diaz, Takao Hashimoto, Blake Feldmar, Emily Wu, Matteo Pellegrini, **Andrew Goldstein**

Department of Molecular, Cell & Developmental Biology, Department of Urology, Jonsson Comprehensive Cancer Center, Broad Stem Cell Research Center, David Geffen School of Medicine, University of California, Los Angeles

Background: Aging is the most significant risk factor for prostate cancer but the effects of aging on the cells-of-origin are not well understood. In most tissues, stem/progenitor cells are lost with age. However, little is known about progenitor cells in the aging prostate.

Methods: Immune profiling was performed on mouse and human prostate. Epithelial cells were isolated from young adult and old mouse prostates for transcriptional profiling and measurement of progenitor activity.

Results: Mass cytometry (CyTOF) revealed species-specific differences in prostate-infiltrating immune cell-types, with the mouse prostate demonstrating a predominance of myeloid cells and the benign human prostate containing mostly lymphocytes. The inflammatory milieu of the old mouse prostate more closely resembled the benign human prostate microenvironment, with an enrichment of T and B cells. RNA sequencing revealed a progenitor signature in old mouse prostate luminal cells, including elevated expression of the progenitor marker Trop2. Gene set enrichment analysis identified a significant overlap in gene expression between old mouse prostate luminal cells and a previously identified inflammation-associated CD38-low luminal progenitor subset from the benign human prostate. Upon comparing organoid-forming activity of basal and luminal cells from young adult or old mouse prostates, we identified no significant effect of aging on primary or secondary organoid formation. Luminal cells from old mouse prostates generated larger organoids than young adult luminal cells.

Conclusions: In contrast to many adult tissues, progenitor cells are not lost in aged prostate epithelium. Aging in the mouse prostate is associated with a luminal progenitor signature and an inflammatory profile more closely resembling the benign human prostate. We hypothesize that age-related inflammation of the prostate contributes to maintenance of epithelial progenitor activity, increasing prostate cancer risk.

Conflict of Interest: The authors declare no conflict of interest.

Funding Acknowledgements: We thank UCLA's Jonsson Comprehensive Cancer Center and Broad Stem Cell Research Center as well as the Department of Defense and American Cancer Society for support to perform these experiments.