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TITLE: Multimodal Spatial Imaging Reveals Endogenous Adenine as a Metabolic Inducer of Senescence in Aging Kidneys

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ABSTRACT BODY:

Background: Cellular senescence is a key contributor to age-related kidney dysfunction, yet its underlying mechanisms remain poorly understood. Senescent cells are characterized by p53 activation, accumulation of cyclin-dependent kinase inhibitors (*p21* and *p16*), elevated β-galactosidase (β-gal) activity, and senescence-associated secretory phenotype (SASP). Given their distinct metabolic profile, we aimed to characterize the metabolomic signatures of senescent cells in aged kidneys to identify novel metabolic drivers of chronic kidney disease (CKD) in aging.

Methods: We used *p16*-tdTomato reporter mice, in which p16-expressing cells fluoresce red, enabling precise localization of senescent cells *in situ*. Matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) was performed on kidney tissues from these mice, marmosets, and KPMP participants. By integrating spatial metabolomics with optical imaging, we generated high-resolution multimodal maps of tissue architecture and metabolite distribution to profile the metabolic landscape of senescent regions in the kidneys.

Results: Untargeted spatial metabolomics identified adenine as one of the top four altered small-molecule metabolites in senescent regions of kidneys from 15-month-old *p16*-tdTomato mice. Multimodal imaging revealed adenine accumulation in β-gal-positive senescent regions. Elevated adenine levels were also observed in kidney cortex samples from older (>60 years) vs. younger (<40 years) human donors, 15-month-old vs. 3-month-old reporter mice, and 16-year-old vs. 3-year-old marmosets. Adenine administration to young mice induced mTORC1-mediated expression of *p21*, *p16*, and SASP markers. In *p16*-reporter mice, kidneys subjected to unilateral ischemia-reperfusion injury (IRI) exhibited increased senescence with colocalized adenine accumulation compared to contralateral kidneys one year post-injury. Notably, pharmacologic inhibition of endogenous adenine synthesis conferred renal protection and suppressed SASP in bilateral IRI and cisplatin-induced AKI mouse models.

Conclusion: These findings identify endogenous adenine as a metabolic driver of cellular senescence in aging and injured kidneys. Inhibiting its production may provide a novel therapeutic strategy to mitigate CKD progression associated with normal or accelerated aging.

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