

Genome Dynamics, Cellular Senescence and Age-related Neurodegeneration

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Genome maintenance systems are crucially important for postponing aging in multiple tissues. Evidence for this importance derives largely from the often dramatic premature aging of many genetically engineered mouse models with compromised genome maintenance -- and the premature aging of humans with certain germ line mutations genome maintenance genes. Perhaps the best-studied consequence of deficient genome maintenance is cancer -- driven in large measure by mutations that arise as a result of faulty DNA repair. However, neurodegeneration is another common outcome of deficient genome maintenance, and is less completely understood. Within the brain, there are two broad categories of cells that can be compromised by excessive DNA damage and/or deficits in DNA repair: post-mitotic neurons, which cannot give rise to cancer, and the mitotically competent support cells, including astrocytes, which are at risk for neoplastic transformation. One of the major cellular responses that protect organisms developing cancer is a multi-faceted stress response termed cellular senescence. There is little doubt that the senescence response is a powerful mechanism that protects both mice and humans from cancer for roughly half the species-specific life span. However, because senescent cells gradually accumulate with age, and adopt a complex pro-inflammatory senescence-associated secretory phenotype (SASP), we and others have shown that senescent cells can drive multiple age related pathologies in older organisms. Among the cells types that become senescent in the brain are astrocytes. We find that senescent astrocytes can create a pro-inflammatory milieu in the brain -- which is known to drive or exacerbate neurodegeneration. In addition, our preliminary data suggest that senescent astrocytes are deficient in glutamate transporters, suggesting they can also promote neurodegeneration through glutamate toxicity. We now have mouse models -- and prototype pharmacological interventions -- that can selectively eliminate senescent cells from mice. We have used the mouse models show that eliminating senescent cells holds promise for ameliorating neurodegenerative diseases resulting from failed genome maintenance and other drivers of age-related brain dysfunction.