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Telomerase-dependent senescence and inflammation with ageing in the zebrafish brain

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In humans, limited telomerase expression leads to telomere shortening and consequent replicative senescence with ageing. Senescent cells are thought to contribute to inflammation via secretion of inflammatory factors (SASP). Both telomere shortening, decreased expression of telomerase, and senescence have been associated with neurodegenerative diseases. Whether increased senescence in the aged brain is caused by limited telomerase expression and/or telomere dysfunction and whether these drive neuro-inflammation, it remains unclear. We hypothesize that telomerase limitation with ageing leads to an accumulation of senescent cells and associated inflammation in the brain, contributing to disease. We used zebrafish as an ageing model, in which, like in humans, telomere-shortening is a key driver of cellular senescence and SASP. Using a combination of immunofluorescence, enzymatic assays and RNA Sequencing, our work shows that the zebrafish brain displays increased senescence and inflammation with ageing. These are anticipated in the absence of telomerase ($tert^{-/-}$), suggesting to be telomerase dependent. Importantly, our data suggest that increased inflammation correlates with increased blood-brain barrier permeability and with macrophages infiltration from the periphery. Remarkably, telomerase-dependent accumulation of senescence in the brain occurs not only in the expected proliferative areas but also in non-proliferative ones, where it is unlikely due to telomeredependent replicative exhaustion. Together, our work suggests that telomerase, including via potential non-canonical, telomere-independent functions, has a protective role against the accumulation of senescence and neuro-inflammation with ageing.