Understanding and Reversing Age Related Decline in Neurogenesis

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Half-time report
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Background. The largest risk factor for developing neurodegeneration and cognitive decline is aging. Neurogenesis, the formation of new neurons from neural stem cells (NSCs), persists throughout life and have the potential to replace lost neurons. However, neurogenesis is limited to specific niches in the brain, and declines with age. During aging NSCs and their progenitors, e.g. neuroblasts, accumulate intrinsic changes that could contribute to the neurogenic decline. In addition, changes in the niche as well as systemic changes also affect neurogenesis. Microglia, resident immune cells in the brain, become more activated with age, and levels of inflammation increase both systemically and in the brain.

Results. We are studying how microglia and inflammation in the neurogenic niches changes during aging and how this affects neurogenesis. We have recently identified the chemokine receptor Cxcr5 as a novel regulator of neuroblast proliferation and migration in the aged brain, and we are continuing to study the role of another chemokine receptor, Cx3Cr1, on neurogenesis during aging. In addition, we are using bulk and single cell RNA sequencing of neuroblasts isolated from mice at different age to dissect how neurogenesis is regulated during aging.

Furthermore, we are exploring whether in vivo reprogramming could be used to rejuvenate the neurogenic niches. We have found that overexpression of Sox2 increases proliferation in the subventricular zone and formation of new neurons in the olfactory bulb in aged mice to levels similar to that of young adult mice.

Significance. Neurodegenerative diseases are widespread, cause significant suffering and disabilities and some are ultimately fatal. Aging is the single most important risk factor for developing neurodegeneration and with increasing life span incidence will continue to rise. Aging without disease is also associated with cognitive decline and decreased neurogenesis.

By understanding how neurogenesis is regulated and developing strategies to restore or initiate neurogenesis we open up for novel therapeutic intervention in age related cognitive decline and neurodegenerative disorders.