Stem Cell Aging? Blame It on the Niche

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The molecular basis for the neural stem cell quiescence-to-activation transition has become an important focus in the study of adult neurogenesis. Recently in Cell, Kalamakis et al. (2019) show that aged neural stem cells face greater barriers to exiting quiescence, imposed by the niche through inflammation and altered Wnt signaling.

Neural stem cells (NSCs) generate newborn neurons in a process referred to as neurogenesis, supporting cognitive functions in the brain throughout life in at least two areas: the ventricular-subventricular zone (V-SVZ) of the lateral ventricles and the subgranular zone of the hippocampus. However, neurogenesis dramatically decreases with age, coinciding with an array of age-related pathologies in the brain. Recently, many studies have identified alterations in how stem cells throughout the body enter and exit quiescence as a key feature of their dysfunction with aging and have begun to explore the molecular mechanisms driving quiescence. In NSCs, quiescence is now understood to be driven largely by extrinsic signals from the niche and involves a shift in metabolism and proteostasis (Knobloch et al., 2017; Leeman et al., 2018; Shin et al., 2015; Silva-Vargas et al., 2016). In a recent Cell study, Kalamakis et al. (2019) use mathematical modeling and numerous in vitro and in vivo experiments to suggest that an increase in quiescence driven by the aged niche is the major factor driving the decrease in neurogenesis with aging in the V-SVZ.

This same group has modeled the age-dependent decline in neurogenesis in the hippocampus, concluding that with age, hippocampal NSCs remain quiescent for longer periods of time (Ziebell et al., 2018). In the Kalamakis et al. (2019) study, the authors used a similar but more simplistic mathematical model and also found that time in quiescence increased with aging in V-SVZ NSCs. To validate their prediction, they treated young and old mice with temozolomide (TMZ), a chemotherapeutic drug that kills activated NSCs (aNSCs) and leads to activation of quiescent NSCs (qNSCs). Following a period of recovery after TMZ treatment, they found that whereas young animals were able to fully recover their aNSC number, old animals were able to recover only half of their original aNSC number, demonstrating that old NSCs were not exiting quiescence at the same rate as young NSCs.

To identify what was driving the increase in quiescence in old NSCs, the authors performed live-cell imaging on freshly sorted NSCs in vitro from a young or old mouse brain and found that both ages had similar potential to differentiate and proliferate. Further, when the authors performed principal component analysis on RNA sequencing in young and old qNSCs and aNSCs, they discovered that NSCs were transcriptionally similar between ages. These data suggested that NSCs intrinsically age very little and that the aged niche is largely responsible for the increase in quiescence in the aged V-SVZ.

Recently, several studies have identified the niche as an important component regulating qNSC activation. Silva-Vargas et al. (2016) showed that secreted factors from the lateral ventricle choroid plexus drive changes in proliferation of V-SVZ NSCs. Further supporting this, single-cell RNA sequencing of hippocampal NSCs revealed that the switch from quiescence to activation involves a large wave of receptor internalization, suggesting that qNSCs exist in a primed state awaiting signals from the niche to begin activation (Shin et al., 2015).

To identify what specific signals came from the niche, Kalamakis et al. (2019) performed RNA sequencing on five cell types present in the V-SVZ of 2- or 7-month-old mice and found substantially increased inflammatory signaling at 7 months, suggesting that inflammatory cues present in the niche may be negatively affecting neurogenesis. Further supporting this finding, they measured an increased number of NSCs expressing IL-33, a cytokine that induces interferon production in the NSC niche. To test the role of interferons on NSC function, they treated NSCs in vitro with inflammatory interferons and found that NSCs had a reduced proliferation rate. Next, the authors moved in vivo, using interferon alpha/gamma receptor knock-out (IFNAGRKO) mice. They labeled cells in S-phase with BrdU, followed by a 3 week chase, and found that the number of newly activated NSCs that retained BrdU (suggesting they had been quiescent during the chase) did not change with age in IFNAGRKO mice. These results suggested that neutralizing inflammation stops the age-related decline in qNSC activation in the aged V-SVZ.

Kalamakis et al. (2019) further identified additional niche-specific factors that may be neutralized to improve aging by using implantation of a mini-osmotic pump into the lateral ventricles releasing specific antibodies. Treatment with an antibody neutralizing the inflammatory cytokine CXCL10, previously shown to be upregulated in the blood plasma of aging mice (Villeda et al., 2011), increased neurogenesis in an aged brain, demonstrating that acute inhibition of inflammation in the aged brain could restore qNSC activation, a proof of principle for future translational studies.

Further, many studies have established altered Wnt signaling in the pathogenesis of aging. Elimination of the Wnt antagonist sfrp3 results in increased qNSC activation in the hippocampus (Sun et al., 2015), and genetic inhibition of sfrp3 rescues neural progenitor proliferation in the aged hippocampus (Cho et al., 2019). Adding to this series of studies, Kalamakis et al. (2019) found that sfrp5, another Wnt antagonist
in the sfrp family, was upregulated in aged qNSCs. Again using their mini-osmotic pump, they delivered an antibody neutralizing sfrp5 to the lateral ventricles of aged mice and found an increase in the proportion of aNSCs to qNSCs in the V-SVZ.

Taken together, Kalamakis et al. (2019) suggest that quiescence is the major factor driving NSC aging and that the key to restoring the proper balance between quiescence and activation is to understand and subsequently control the factors that potentiate the barrier to exiting quiescence, which at least in part is driven by inflammatory signals and altered Wnt signaling imposed by the aged niche (Figure 1). More specifically, this study validates specific targets that demonstrate translational potential for increasing neurogenesis acutely during aging. Importantly, while increased activation of qNSCs in the aging brain can expand the number of newborn neurons, what mode of division these aged qNSCs choose when entering the cell cycle will determine whether the remaining NSC population will be maintained or depleted. Further studies identifying regulators of the balance of self-renewing versus differentiating divisions will be needed to address these questions.

Additionally, while cellular signaling from the niche can raise or lower the barrier for qNSC activation, other barriers also can limit NSCs from exiting quiescence. For example, it is well established that metabolism is distinctly different between qNSCs and aNSCs, and activation of specific metabolic pathways can be instructive for cellular behavior (Knobloch et al., 2017). Separately, Leeman et al. (2018) recently showed that qNSCs carry increased aggregated protein levels compared with aNSCs and that a key component of qNSC activation involves clearance of these aggregated proteins. Indeed, we have shown that aged NSCs in vivo carry increased ubiquitinated protein levels, further suggesting a role for aggregated protein clearance in qNSC activation (Moore et al., 2015). In summary, these studies suggest that both extrinsic and intrinsic mechanisms drive the balance between quiescence and activation and open the door to future research investigating how extrinsic niche-derived signals may influence intrinsic barriers to exiting quiescence. Understanding how these molecular constraints interact will more fully unravel the molecular and cellular cues mediating NSC quiescence throughout life.

Figure 1. The Old Niche Increases the Barrier to Quiescence Exit for Neural Stem Cells

YOUNG NICHE

OLD NICHE

INFLAMMATION (Interferons, Oligo)

WNT ANTAGONISTS (sfrp1, sfrp3)

ACTIVATION

quiescence

ACTIVATION

Neural stem cells have greater barriers to quiescence exit due to niche-specific factors in the aged brain, including increased Wnt antagonists and inflammation.

REFERENCES


tive capacity in the aging brain. Cell 176. Published online March 7, 2019.


