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FROM QUIESCENCE TO PROLIFERATION AND BACK: THE ACTIVE LIFE OF NEURAL STEM CELLS

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The adult neurogenic niche in the hippocampus dentate gyrus (DG) is maintained through the proliferation of neural stem cells with radial glia-like morphology (RGL), which are mostly in a reversible state of quiescence. Signals from the local niche promote quiescent RGLs to enter cell cycle (or "activate") and through several rounds of cell division, to generate new DG granular neurons that participate in learning and memory processes. However, quiescence is not a fixed state, as it involves distinct intermediate sub-states with sets of differentially expressed transcripts (reviewed, in Mira and Morales, 2019). Thus, whereas most of RGLs in the DG will remain in a dormant state of deep quiescence throughout life, the transitions back and forward from an active state to a temporal shallow quiescence or resting state, will ensure the lifelong maintenance of the stem cell population.

The fundamental questions that our laboratory is trying to understand are: i) how RGLs transit from the different sub-states of quiescence to activation and ii) how quiescence is acquire in the first place during the development of the DG. In relation to the first aspect, we have recently determined that SoxD transcription factors (Sox5 and Sox6) are enriched in activated RGLs. Using inducible conditional inactivation of *Sox5* and/or *Sox6* in adult mice, we have demostrated that SoxD factors transcriptionally activate *Ascl1* in RGLs, and are consequently required for RGL activation and new neuron generation in the DG. In relation to the second question, we have determined that the developmental loss of Sox5 expression ($Sox5^{Nestin}$ mice) causes by P30 an enhancement of RGLs proliferation, a reduction in RGL deep quiescence and an increase in neurogenesis, which leads to a reduction of the RGL pool at later stages. These results reveal define windows during postnatal DG development when the balance between dormant and resting quiescence ensures the life-long maintenance of the adult neurogenic niche.