HES1, two programs: promoting the quiescence and proliferation of adult neural stem cells

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Adult neural stem cells are mostly quiescent and only rarely enter the cell cycle to self-renew and generate neuronal or glial progenies. The Notch signaling pathway is essential for both the quiescent and proliferative states of neural stem cells. However, these are mutually exclusive cellular states; thus, how Notch promotes both of these programs within adult neural stem cells has remained unclear. In this issue of Genes & Development, Sueda and colleagues (pp. 511–523) use an extensive repertoire of mouse genetic tools and techniques to demonstrate that it is the levels and dynamic expression of the Notch transcriptional effector Hairy and Enhancer of Split 1 (HES1) that enables this dual role.

During brain development, neural stem cells (NSCs) proliferate continuously while generating neuronal progenitors and glia and eventually differentiate. In adults, a small number of NSCs populate specialized niches within the hippocampal dentate gyrus and the lateral ventricles. While a fraction of these adult NSCs proliferates to generate neuronal progenitors or glial cells, they are primarily quiescent. This quiescence preserves the NSC pool into old age, ensuring that neurons can be generated when needed (Urbán and Guillemot 2014).

The Notch pathway is essential for both the proliferative and quiescent states of NSCs (Imayoshi et al. 2010). Proliferation and quiescence are alternative cellular states and involve mutually exclusive cellular programs; thus, how Notch promotes both of these programs within adult NSCs is a puzzling and unaddressed question. In this issue of Genes & Development, Sueda et al. (2019) determine that it is the levels and dynamic expression of the Notch effector protein Hairy and Enhancer of Split 1 (HES1) that enables this dual role.

In previous work, the investigators had determined the mechanism through which Notch signaling promotes the proliferation of embryonic NSCs and had shown how inhibition of this pathway drives neuronal differentiation (Imayoshi et al. 2013). Specifically, they had determined that Notch signaling induces proliferation via activating the expression of the transcriptional repressor HES1, whose protein levels oscillate due to autorepression (Hirata et al. 2002). The oscillation of the HES1 protein then induces the out of phase oscillation of its target gene, Achaete-scute homolog 1 (Ascl1), which in turn activates the transcription of positive regulators of cell cycle progression. Conversely, inhibition of the Notch pathway down-regulates HES1 below a critical level, resulting in sustained, rather than oscillatory, ASCL1 expression and the induction of neuronal genes (Imayoshi et al. 2013).

Thus, in embryonic NSCs, the activation or inhibition of the Notch signaling pathway determines whether a NSC proliferates or differentiates, respectively (Fig. 1).

In adult NSCs, the mutually exclusive programs of both quiescence and proliferation are promoted by Notch signaling (Imayoshi et al. 2010). Thus, in this present study, the investigators addressed the perplexing question of how Notch signaling promotes both states. Using an extensive repertoire of mouse genetic tools, they examined the relationship between HES1 and ASCL1 in quiescent and proliferating adult NSCs. Using HES1 and ASCL1 fusion reporter mouse lines, they compared the in vivo expression of these proteins in NSCs of the adult hippocampus and lateral ventricles. They observed HES1 oscillations in both the proliferating and quiescent states. However, HES1 oscillated at markedly higher levels in the quiescent state (in which ASCL1 was undetectable) than in the proliferating state (in which ASCL1 was expressed and oscillated in the opposite phase). These observations suggested a model in which high oscillatory HES1 in quiescent NSCs leads to the strong suppression of ASCL1 and to quiescence, whereas low oscillatory HES1 stimulates proliferation by enabling the oscillatory expression of ASCL1.
In conclusion, this study and the investigators’ previous works have established a framework to understand how the dynamic expression patterns of HES1, ASCL1, and other basic helix–loop–helix proteins can influence the quiescence, proliferation, and differentiation of NSCs. Importantly, these mechanisms appear conserved, for example, another study in this issue of *Genes & Development* by Lahmann et al. (2019) demonstrated that the oscillations of HES1 controls the balance between proliferation and differentiation of activated muscle stem cells. In the future, it will be important to determine how the dynamic expression patterns of HES1 and related proteins are influenced by niche signals and, in turn, by physiological regulators of stem cell activity such as injury and aging.

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