Nature Reviews Neuroscience | Published online 21 Aug 2017; doi:10.1038/nrn.2017.109

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AGEING

Setting the speed

Several studies indicate that the hypothalamus has a role in regulating ageing, although exactly how this brain region exerts its influence on this process is not clear. Zhang, Kim and colleagues now show in mice that hypothalamic neural stem cells (NSCs) may be important in determining how quickly ageing proceeds.

In the adult rodent brain, NSCs can be detected in the hypothalamus, notably in the mediobasal hypothalamic region (MBH). In this study, the authors first examined whether ageing was associated with any changes in this NSC population. They found that cells that express transcription factor SOX2 and polycomb complex protein BMI1, which the authors used as markers of the hypothalamic NSCs, were abundant in the third ventricle wall in the MBH in young (2-month-old) mice but decreased in number with ageing and were nearly absent in aged (at least 22-month-old) mice.

Does the loss of NSCs at this location have a causal relationship with ageing? To answer this question, the authors ablated the majority of SOX2-expressing cells in the third ventricle wall of the hypothalamus in middle-aged (15-month-old) mice through the use of a virus-based technique. Strikingly, 3 months later, these mice showed poorer performance than age-matched control animals across various tasks, from those examining muscle strength and aspects of locomotion, to those assessing sociality and cognition. The performances of the mice with the ablated hypothalamic NSCs resembled those in normal mice at older ages, suggesting that the former were in an advanced state of ageing.

The authors used another virus-based technique in middle-aged mice to limit death of SOX2-expressing cells to the MBH portion of the third ventricle wall and the MBH parenchyma. In line with the other findings, these mice showed similarly accelerated physical and cognitive decline compared with controls. Indeed, when this technique was used in younger mice, the authors also noted a decrease in lifespan. Thus, NSCs specifically in the MBH seem to regulate the speed at which ageing proceeds.

Alongside these cell-ablation experiments, the authors examined whether they could combat the progression of ageing by implanting hypothalamic NSCs into the MBH of middle-aged mice. In the initial experiment, these cells did not survive well, which the authors attributed to an inflammatory environment in the hypothalamus. Thus, they repeated the experiments with isolated hypothalamic NSCs that stably expressed a dominant-negative form of IκBα and that were therefore resilient to inflammation mediated by nuclear factor-κB. The animals injected with these NSCs showed better performance than control mice across various tasks at 4 months after the injection as well as an increase in longevity, providing further evidence that such cells regulate the speed of ageing.

How do MBH NSCs regulate ageing? The authors showed that cultured hypothalamic NSCs release an abundance of exosomes that are rich in microRNAs. Moreover, they found that these exosomes were an important source of cerebrospinal fluid microRNAs, and that the level of these exosomal microRNAs decreased with ageing. The authors treated middle-aged mice in which SOX2-expressing cells had been partially ablated with microRNA-carrying exosomes that were secreted from such cells and showed that, interestingly, exosome treatment prevented many of the premature ageing effects of ablation of SOX2-expressing cells. Similarly, treatment of middle-aged mice that were not subjected to any cell ablation with these microRNA-carrying exosomes for 4 months slowed many of the effects of ageing, suggesting that hypothalamic NSCs may exert their effects in part through the release of such extracellular vesicles.

Together, these data indicate that, in mice, hypothalamic NSCs, partly via the release of microRNA-carrying exosomes, regulate the speed of ageing.

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> “NSCs specifically in the MBH seem to regulate the speed at which ageing proceeds”

ORIGINAL ARTICLE Zhang, Y. *et al.* Hypothalamic stem cells control ageing speed partly through exosomal miRNAs. *Nature* **548**, 52–57 (2017)