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STEM CELLS

A new pathway for stem cell ageing and renewal

Stem cells have the potential for self-renewal and are therefore able to persist throughout life in a diverse range of tissues. However, their self-renewing capacity declines with age. What mechanisms are responsible for the differences between young and ageing stem cells? The discovery of a novel pathway involving high-mobility group A2 (HMGA2), INK4A and ARF has recently provided exciting new insights.

Both INK4A and ARF expression increase in ageing tissues, suggesting that a pathway involving these tumour suppressor genes may mediate the differences in self-renewal between old and young stem cells. Sean Morrison and colleagues have now shown that HMGA2, a transcriptional regulator, reduces INK4A and ARF expression in young mice, thus promoting neural stem cell self-renewal. *Hmga2* was identified in a full-genome analysis that was carried out by the authors to search for genes that were preferentially expressed in stem cells and whose expression progressively declined with age.

The authors postulated that the concomitant decrease in HMGA2 expression and the previously reported increases in INK4A and ARF expression with ageing might indicate that HMGA2 is a negative regulator of INK4A and ARF. They found that INK4A and ARF expression increased in fetal and young, but not old, *Hmga2*$^{-/-}$ mice. Furthermore, neurospheres cultured from these mice were significantly smaller and produced fewer secondary multipotent neurospheres than wild-type controls, indicating a reduction in their potential for self-renewal. They also observed *in vivo* phenotypes in the *Hmga2*$^{-/-}$ mice that were consistent with reduced proliferation of neural stem cells of the central and peripheral nervous systems.

The authors were unable to directly detect HMGA2 binding to the *Cdkn2a* locus but found that HMGA2 binds to the *Junb* locus. As JUNB promotes INK4A and ARF expression in stem cells, they speculate that HMGA2 negatively regulates INK4A and ARF by interfering with JUNB expression, although this model will need to be functionally tested. This study highlights an important role for HMGA2 in the regulation of stem cell potential for self-renewal, and is consistent with previous studies that have indicated that *HMGA2* functions as a proto-oncogene. This might partly be due to its function as a negative regulator of INK4A and ARF.

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ORIGINAL RESEARCH PAPER Nishino, J., Kim, I., Chada, K. & Morrison, S. J. Hmga2 promotes neural stem cell self-renewal in young but not old mice by reducing p16^{Ink4a} and p19^{Arf} expression. *Cell* **135**, 227–239 (2008)
FURTHER READING Vescovi, A.L., Galli, R. & Reynolds B. A. Brain tumour stem cells. *Nature Rev. Cancer* **6**, 425–436 (2006)