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CELL DIVISION

Back and forth

> …reversibility is not a passive property of non-dividing cells…

In contrast to terminally differentiated or senescent cells, quiescent cells retain the ability to resume proliferation following prolonged cell-cycle arrest. Roberts and colleagues now shed light on the mechanism that underlies this reversibility.

Regulated overexpression of the cyclin-dependent kinase (Cdk) inhibitor p21 in fibroblasts results in their cell-cycle arrest. When p21 expression was reversed to normal levels after 4 days, cells failed to re-enter the cell cycle and had a senescent phenotype. So, reversibility is not a passive property of non-dividing cells, but how is it achieved?

The authors observed that the transcriptional repressor hairy and enhancer of split 1 (HES1) is more abundant in quiescent cells compared with proliferating cells. Fibroblasts were therefore transduced with various HES1 constructs and subsequently arrested by overexpressing p21. Cells that expressed wild-type HES1 resumed proliferation following downregulation of p21 expression, whereas those expressing mutant HES1 were unable to re-enter the cell cycle and had a senescent phenotype. Naturally quiescent fibroblasts that were transduced with a dominant-negative HES1 mutant also became irreversibly arrested due to senescence. Together, these findings demonstrate that HES1 is necessary and sufficient for reversible quiescence.

STOCKBYTE

Furthermore, terminal differentiation of fibroblasts by the transcription factor MYOD was inhibited by HES1. Importantly, terminal differentiation is accompanied by irreversible cell-cycle arrest. So, HES1 preserves reversibility both in the context of quiescence and terminal differentiation.

Given that senescence might function as a pathway for tumour suppression and HES1 can suppress oncogene-induced senescence, the authors hypothesized that HES1 might contribute to tumorigenesis. They analysed a skeletal muscle tumour cell line that expresses MYOD constitutively but that, for unknown reasons, resists terminal differentiation. Tumour cells have increased HES1 levels, and expression in the tumour cells of a dominant-negative HES1 mutant resulted in reduced proliferation and increased differentiation. Notch signalling partially controls HES1 expression, and its inhibition, which results in reduced HES1 expression, also increased differentiation. Therefore, Notch signalling might contribute to tumorigenesis through increased HES1 expression and suppression of MYOD-dependent differentiation. So, tumour cells have some characteristics of quiescence: resistance to irreversible arrest caused by either senescence or terminal differentiation, and both are mediated by HES1.

But how does HES1 maintain reversibility? The authors propose that "HES1, which is part of a large chromatin-modifying complex, may counteract the heterochromatin assembly pathways present in irreversibly arrested cells." This hypothesis is supported by the requirement of the DNA-binding and corepressor-recruiting activities of HES1 for maintaining reversibility, as well as the observation that HES1 suppresses the formation of senescence-associated heterochromatin foci.

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ORIGINAL RESEARCH PAPER Sang, L. *et al.* Control of the reversibility of cellular quiescence by the transcriptional repressor HES1. *Science* **321**, 1095–1100 (2008)
FURTHER READING Coller, H. A. What's taking so long: S-phase entry from quiescence versus proliferation. *Nature Rev. Mol. Cell Biol.* **8**, 667–670 (2007) | Campisi, J. & d'Adda di Fagagna, F. Cellular senescence: when bad things happen to good cells. *Nature Rev. Mol. Cell Biol.* **8**, 729–740 (2007)