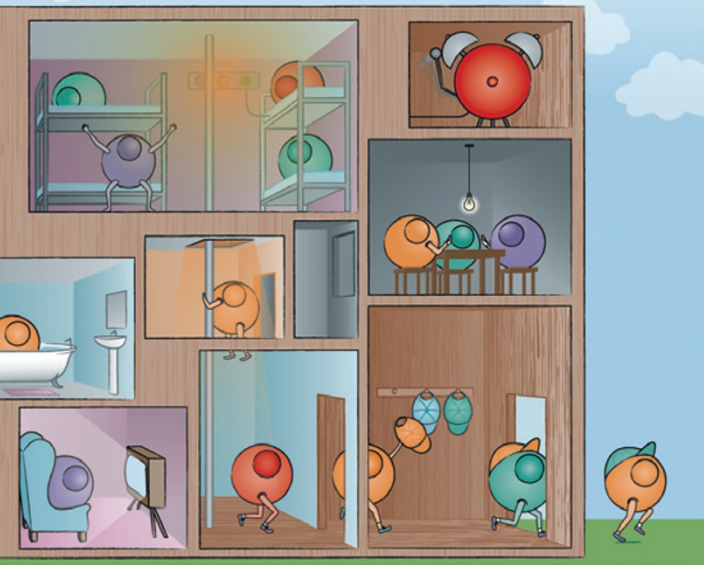
STEM CELLS

# Keeping alert



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Adult stem cells are thought to exist in two possible states: a non-cycling, quiescent state (G0) and a cycling, activated state. Now, Rando and colleagues show that the quiescent state can be subdivided, as they identify a distinct 'alert' state ($G_{Alert}$) in which cells are 'primed' to rapidly respond under conditions of stress or injury.

The authors observed that when a mouse limb was injured, stem cells in a muscle of the opposite limb (contralateral satellite cells (CSCs)) had cycling properties that differed from those of stem cells in the injured tissue (activated satellite cells (ASCs)) and from those of stem cells from uninjured animals (quiescent satellite cells (QSCs)) in G0. CSCs had a higher propensity to divide than QSCs but a lower tendency to do so than ASCs.

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In addition, isolated CSCs displayed accelerated cell cycle entry: they required a shorter time to complete the first division compared to QSCs, although subsequent divisions of all three stem cell populations occurred at a comparable rate.

Phenotypically, CSCs were more similar to QSCs than to ASCs: CSCs were only slightly bigger than QSCs, whereas ASCs underwent dramatic enlargement. However, analysis of the transcriptional profiles of each stem cell group suggested that CSCs represent an intermediate state between QSCs and ASCs, which the authors termed $G_{Alert}$. CSCs are also characterized by increased mitochondrial activity compared to QSCs. Importantly, the engraftment efficiency and self-renewal capacity of CSCs confirm that they are not committed progenitor cells, but rather a distinct population of stem cells. Of note, CSCs can still be considered as quiescent, as at the population level the vast majority of CSCs are not actively cycling.

The cycling and metabolic features of the $G_{Alert}$ state of CSCs have been previously linked, in other systems, to the mTOR complex 1 (mTORC1) signalling pathway. Consistent with this observation, stem-cell-specific knockout of *Tsc1* (tuberous sclerosis 1), an inhibitor of mTORC1 signalling, caused QSCs to acquire the properties of CSCs in the absence of injury. Moreover, stem-cell-specific ablation of *Rptor*, an essential component of the mTORC1 signalling complex, completely abolished the presence of CSCs in response to injury. Thus, mTORC1 signalling is necessary and sufficient for the alert response — that is, the transition from a G0 to a $G_{Alert}$ state.

So, what initiates the transition from a G0 to a $G_{Alert}$ state? The authors found that signalling through the hepatocyte growth factor (HGF) receptor cMet, which is activated following injury and known to induce mTORC1 signalling, was required for the alert response. Interestingly, following tissue repair (~1 month after injury), when the HGF activation cascade subsides, CSCs reverted to QSCs, which indicates that the $G_{Alert}$ state is reversible.

Finally, the authors found that CSCs had improved muscle regenerative function. Interestingly, their alert state was induced by multiple types of injuries (including to the bone and skin). Moreover, other types of adult quiescent stem cells, namely fibro-adipogenic progenitors and long-term haematopoietic stem cells, could similarly adopt properties of the alert state, and this change also occurred in response to distant injuries to other tissues. These findings suggest that stem cell conversion to the $G_{Alert}$ state is a general and reversible response to injury.

These studies indicate the existence of functionally distinct populations of quiescent stem cells. The $G_{Alert}$ state, in which cells are poised to efficiently repair tissue, seems to be an adaptive response similar to that of immune cells, in which the response to injury is influenced by previous experiences.

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**ORIGINAL RESEARCH PAPER** Rodgers, J. T. *et al.* mTORC1 controls the adaptive transition of quiescent stem cells from $G_0$ to $G_{Alert}$. *Nature* http://dx.doi.org/10.1038/nature13255 (2014)
**FURTHER READING** Cheung, T. H. & Rando, T. A. Molecular regulation of stem cell quiescence. *Nature Reviews Mol. Cell Biol.* **14**, 329–340 (2013) | Wang, Y. X. & Rudnicki, M. A. Satellite cells, the engines of muscle repair. *Nature Rev. Mol. Cell Biol.* **13**, 127–133 (2011).