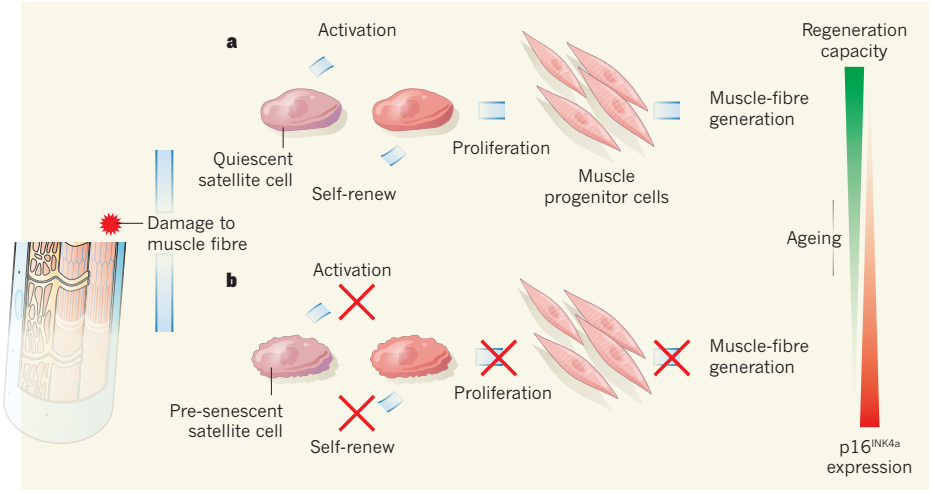

Figure 1 | Old age disrupts muscle regeneration. **a**, Satellite cells, a type of muscle stem cell, remain quiescent under normal conditions. After muscle damage, satellite cells become activated and re-enter the cell cycle to produce muscle progenitor cells that regenerate new muscle fibres. They also self-renew to replenish the stem-cell population. **b**, Sousa-Victor *et al.*[3] report that during ageing, geriatric satellite cells lose their reversible quiescent state owing to derepression of the gene encoding $p16^{INK4a}$, a regulator of cellular senescence. Instead, they adopt a senescent-like state (becoming pre-senescent cells), which impairs the regeneration process, including activation, proliferation and self-renewal.

in the regenerative capacity of satellite cells in geriatric, sarcopenic mice compared with old, non-sarcopenic mice. This phenomenon cannot be explained by a reduced satellite-cell pool, because the number of these cells was comparable in both groups of mice.

Next, the authors conducted a series of experiments in which satellite cells from geriatric and old animals were transplanted into young mice, and this definitively proved that the regenerative decline of geriatric muscle is due to changes intrinsic to satellite cells, independent of the host environment. Intriguingly, geriatric satellite cells exhibited a cell-cycle block and defective activation in response to injury both *in situ* and after transplantation, indicating a failure to maintain a reversible state of quiescence.

What factors could be responsible for this loss of quiescence? Through comparative analyses of the gene-expression programs of quiescent satellite cells of different ages, Sousa-Victor and co-workers narrowed down the list of candidates to the tumour-suppressor protein $p16^{INK4a}$, which is regarded as a master regulator of cellular senescence. In a series of experiments, the authors found evidence to support a link between *p16*^{INK4a} derepression and defective satellite-cell activation.

In a mouse model that underwent successive rounds of injury, the authors observed a depletion of self-renewing geriatric satellite cells over time, whereas normal satellite cells continued to self-renew. The pressure to proliferate in response to injury drove geriatric satellite cells into full-blown senescence, as evidenced by the expression of several classic markers of senescence. This correlated with reduced levels of phosphorylated retinoblastoma (Rb) protein, and with reduced expression of genes regulated by Rb and the transcription factor E2F, suggesting that the well-defined $p16^{INK4a}$/Rb/E2F signalling axis drives the conversion to senescence.

Sousa-Victor *et al.* genetically silenced $p16^{INK4a}$ expression and found that this restored self-renewal and proliferation in geriatric satellite cells. These results show that $p16^{INK4a}$ derepression in geriatric and progeric satellite cells leads to the loss of the reversible quiescent state and to the adoption of a senescent-like state, which impairs regeneration (Fig. 1b). The relevance of this work to human health is strengthened by Sousa-Victor and co-workers' finding that the $p16^{INK4a}$/Rb/E2F axis drives dysfunction in geriatric human satellite cells similarly to the way it does in mice.

Although $p16^{INK4a}$ expression during ageing has been shown to impair regeneration in blood, neural and pancreatic tissues[6], it has never been reported in aged satellite cells, despite previous gene-profiling studies[4]. The use of a clearly defined sarcopenic geriatric population may be the key to this discovery, which itself represents an important addition to a growing body of evidence[10,11] showing that $p16^{INK4a}$-induced senescence limits the regenerative capacity of stem cells during ageing and contributes to age-related pathologies. Because $p16^{INK4a}$ expression is also a barrier to stem-cell reprogramming[12,13], this research increases the potential benefits of transiently inactivating $p16^{INK4a}$ for regenerative medicine.

Sousa-Victor and colleagues' study provides a new view of satellite-cell ageing, but the results inevitably raise further questions. For example, what triggers the $p16^{INK4a}$/Rb/E2F senescence pathway during ageing? A recent study[9] found no evidence of significant accumulation of DNA damage in old satellite cells compared with young ones. Could it be that $p16^{INK4a}$ is derepressed owing to signals from neighbouring senescent cells, such as low-level systemic inflammation or elevated levels of reactive oxygen species?

Because satellite cells are not a uniform population, it is possible that a sub-population is more susceptible or immune to the quiescent-to-senescent switch. Along this line, it will be interesting to determine whether geriatric satellite cells that are activated on injury maintain full 'stemness'. Could any as-yet-unidentified, age-associated environmental factors be neutralized to postpone the $p16^{INK4a}$ induction in satellite cells of sarcopenic muscle? And, if so, could physical exercise delay $p16^{INK4a}$ induction?

Finally, this study presents yet another addition to the list of potential strategies to improve the regenerative capacity of aged tissue[11,14,15]. It may be worth considering whether the benefits of transiently reducing tumour-suppressor levels in stem cells outweigh the associated risks, in the context of preventing an age-related decline in regenerative potential. Whether these strategies can be safely implemented in the clinic to maximize human health span deserves thorough investigation in the near future. ■

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1. Ruiz, J. R. *et al. Br. Med. J.* **337,** a439 (2008).
2. de Brito, L. B. B. *et al. Eur. J. Prev. Cardiol.* http://dx.doi.org/10.1177/2047487312471759 (2012).
3. Sousa-Victor, P. *et al. Nature* **506,** 316–321 (2014).
4. Cheung, T. H. & Rando, T. A. *Nature Rev. Mol. Cell Biol.* **14,** 329–340 (2013).
5. Liu, L. *et al. Cell Rep.* **4,** 189–204 (2013).
6. Orford, K. W. & Scaden, D. T. *Nature Rev. Genet.* **9,** 115–128 (2008).
7. Jang, Y. C., Sinha, M., Cerletti, M., Dall'Osso, C. & Wagers, A. J. *Cold Spring Harb. Symp. Quant. Biol.* **76,** 101–111 (2011).
8. Chakkalakal, J. V., Jones, K. M., Basson, M. A. & Brack, A. S. *Nature* **490,** 355–360 (2012).
9. Cousin, W. *et al. PLoS ONE* **8,** e63528 (2013).
10. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. *Cell* **153,** 1194–1217 (2013).
11. Baker, D. J. *et al. Nature* **479,** 232–236 (2011).
12. Li, H. *et al. Nature* **460,** 1136–1139 (2009).
13. Menendez, S. *et al. Aging Cell* **11,** 41–50 (2012).
14. Pajcini, K. V., Corbel, S. Y., Sage, J., Pomerantz, J. H. & Blau, H. M. *Cell Stem Cell* **7,** 198–213 (2010).
15. Shyh-Chang, N. *et al. Cell* **155,** 778–792 (2013).

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CORRECTION

In the News & Views article 'Conservation: Making marine protected areas work' by Benjamin S. Halpern (*Nature* **506,** 167–168; 2014), Figure 1 was published with the wrong caption. The correct caption can be seen in the online version at go.nature.com/pssric.