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STEM CELLS

An ageing decline

The regenerative and self-renewal capacity of stem cells decline with age. A study published in *Nature* now shows that an age-dependent change in fibroblast growth factor (FGF) signalling in the muscle stem cell niche affects stem cell quiescence and is responsible for the decline in stem cell function.

Satellite cells have the capacity to self-renew and function as a stem cell population that is essential for the repair and homeostatic maintenance of skeletal muscle. They are located along the length of muscle fibres, and this close association maintains satellite cell quiescence and function. Thus, the muscle fibre is considered to be a component of the satellite stem cell niche. During ageing, the regenerative capacity of muscle cells declines because of a decrease in satellite cell function and also because of a reduction in satellite cell numbers. Brack and colleagues set out to investigate how ageing affects the satellite cell niche and how this might have an impact on satellite cell function.

As the quiescent state (a reversible state of proliferation arrest) is known to be important for the maintenance of adult stem cell numbers and function, the authors first investigated whether this state is disrupted in aged satellite cells. When analysing transgenic mice in which a histone H2B–GFP reporter that marks dividing cells was transiently induced, they found that the GFP signal diluted more rapidly in satellite cells of aged mice compared with cells from adult mice. This suggested that aged satellite cells spend less time in a quiescent state. This was confirmed by lower expression levels of sprouty 1 (*Spry1*), a quiescence marker, and higher expression levels of *MyoD*, a marker for cycling satellite cells, in these cells.

> “an increase in FGF2 signalling from the ageing niche … causes a decline in satellite cell function”

Next, the authors investigated how loss of quiescence might affect satellite cell function. Interestingly, when transplanted into adult wild-type mice, aged satellite cells were gradually lost from the satellite cell compartment. Aged cells also progressively lost markers of self-renewal and gained differentiation markers such as myogenin. Thus, aged satellite cells seem to lose their self-renewal capacity after cell cycle entry in a cell-autonomous manner.

The authors then determined whether the loss of quiescence and progressive loss of satellite cells were due to changes in the ageing niche. FGF ligands are potent stimulators of satellite cell mitogenic activity, and expression of *Fgf2* was substantially increased in aged muscle fibres. Furthermore, FGF2 accumulated in close proximity to aged satellite cells but was not detected within satellite cells themselves, which suggests that the aged niche is a main source of FGF2. Importantly, the authors showed that soluble extracts from aged fibres induced cell cycle entry in satellite cells, and that this was abolished in the presence of a blocking antibody against FGF2. Thus, increased levels of FGF2 in aged muscle fibres lead to a loss of satellite cell quiescence.

Spry genes are downstream targets and negative feedback regulators of FGF signalling. The authors found that FGF2 specifically inhibited the expression of *Spry1* in satellite cells. Moreover, in an aged niche only non-dividing satellite cells were enriched in *Spry1* expression, indicating that SPRY1 inhibits FGF signalling from the niche and thereby maintains satellite cell quiescence. Indeed, deletion of *Spry1* led to loss of quiescent cells and, conversely, *Spry1* overexpression prevented satellite cell depletion.

On the basis of their results, the authors propose a model in which an increase in FGF2 signalling from the ageing niche downregulates *Spry1* expression and causes a decline in satellite cell function. Ultimately, this impairs the regenerative capacity of muscle cells, as was seen in injured mice that lacked *Spry1*. However, what causes the FGF2 increase during ageing remains to be determined.

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ORIGINAL RESEARCH PAPER Chakkalakal, J. V. *et al.* The aged niche disrupts muscle stem cell quiescence. *Nature* 26 Sep 2012 (doi: 10.1038/nature11438)

FURTHER READING Wang, Y. X. & Rudnicki, M. A. Satellite cells, the engines of muscle repair. *Nature Rev. Mol. Cell Biol.* **13**, 127–133 (2012)