BONE

Reversal of age-related decline in fracture repair —the benefits of a youthful circulation

Bone repair and osteogenic potential diminish with ageing, with corresponding implications for fracture repair in elderly individuals. A new study published in *Nature Communications* shows that young haematopoietic cells can rejuvenate fracture repair in old mice via modulation of β -catenin levels. “Fracture healing in mice is very similar to that in humans,” explains lead investigator Benjamin Alman. “Many interventions in the repair process in mice are applicable in humans and, as such, drugs that are successful in mice have a high likelihood of being effective treatments for rejuvenation of bone repair in elderly patients.” Although preliminary, the findings have potential implications for fracture repair and even osseointegration of implants (dental and orthopaedic) in elderly patients.

Following on from their previous work in mice, which identified a role for β -catenin in normal fracture healing, the researchers examined the role of β -catenin in ageing, a situation in which fracture healing is less than optimal. To their surprise, the researchers found that levels of β -catenin increased during fracture repair in aged mice, contrary to what would have been predicted from their studies on normal bone healing. This preliminary finding, together with other studies showing that a youthful circulation can rejuvenate the repair of aged muscle, led Alman and colleagues to investigate the effects of the age of the haematopoietic system on bone regeneration and osteoblast differentiation.

Using heterochronic parabiosis—the surgical joining of old and young animals to test for circulating cells or factors in one animal that affect the other animal—the researchers studied the effect of a youthful circulation on the rate and efficiency of tibial fracture repair in old mice. Heterochronic parabiosis resulted in rejuvenation of *in vivo* bone repair and osteogenic potential (assessed by *in vitro* osteoblast differentiation) in old parabionts

(aged 20 months) of the heterochronic pairings. Fracture calluses in these mice contained twofold more bone tissue and markedly less fibrotic tissue than fracture calluses in old mice in isochronic (old–old) pairings. Reversal of the aged phenotype occurred even when osteoblasts were depleted from the young parabionts (aged 3 months) of the heterochronic pairings. Conversely, ablation of osteoblasts in old parabionts prevented fracture repair and osteoblastic differentiation. These findings demonstrated the importance of endogenous, aged osteoblasts in fracture repair and ruled out osteoblasts residing in the young parabionts from contributing to rejuvenation. The findings also indicate that a circulating cell or factor exists in young parabionts that is capable of stimulating endogenous, aged osteoblasts in the repair process.

The researchers next used bone marrow transplantation to determine if the rejuvenation factor originated from a haematopoietic cell. Engraftment of young bone marrow rescued fracture repair and osteogenic potential in aged mice, with results similar to those seen in old parabionts of heterochronic pairings. Similarly, ablation of osteoblasts in host mice prevented fracture repair, whereas depletion of donor osteoblasts had no effect. Interestingly, in bone-marrow-derived rejuvenation, only CD45⁺ haematopoietic cells engrafted into the bone marrow space, which indicates that these cells (which have circulatory capacity but lack the potential to become osteoblasts) are responsible for rejuvenation of fracture repair in aged mice. Furthermore, conditioned media from young bone marrow stromal cells (BMSCs), of which 50% were CD45⁺, rescued osteogenic potential in old BMSCs, which suggests that CD45⁺ cells secrete a factor capable of rejuvenating aged osteoblastic differentiation. Confirmation that modulation of levels of β -catenin by the CD45⁺-secreted factor is required for

wildpixel/istock/Thinkstock

rejuvenation was obtained by genetically decreasing levels of β -catenin in old fracture calluses early in the fracture repair process. Radiography and histological analysis of calluses 21 days after the fracture was sustained revealed better fracture healing, higher bone content and less fibrotic tissue in treated mice than in wild-type littermates.

“The most significant conclusion is that bone healing cells (osteoblasts) do not wear out with age, but given the right stimuli can behave as young cells,” comments Alman. “Rejuvenation in fracture repair can be achieved by providing the right environmental cues and it is very likely that a pharmacological approach can be developed to successfully rejuvenate fracture repair.” The researchers plan to test whether drugs that modulate β -catenin levels can improve fracture healing in elderly patients.

David Holmes

Original article Baht, G. S. et al. Exposure to a youthful circulation rejuvenates bone repair through modulation of β -catenin. *Nat. Commun.* doi:10.1038/ncomms8131