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BONE

Cranking fracture repair up a notch

> The findings might lead to new treatments for the 10–20% of bone fractures that do not heal

Bone marrow stem cells (BMSCs) are important for skeletal development, but their role in bone repair after fracture is unclear. In new data presented in *The Journal of Clinical Investigation*, Notch signalling within BMSCs is shown to be required for the complete repair of fractures.

"We provide the first evidence demonstrating in mice that a particular type of cell signalling (Notch) is required for normal fracture repair by maintaining a specific type of skeletal stem/progenitor cell," explains study investigator Matthew Hilton.

The investigators generated a mouse line lacking *Rbpj*, which encodes a transcriptional regulator of Notch signalling, specifically in skeletal cell lineages. Compared with wild-type mice, *Rbpj* knockout mice had no evidence of fracture union even up to 42 days after fracture. Instead, an undifferentiated mass of mesenchymal tissues developed within the fracture gap of *Rbpj* knockout mice, which expressed high amounts of collagen α-1 (III) chain compared with fractures in wild-type mice and ultimately caused the failure of fracture reunion.

Building on previous work showing that loss of Notch signalling can deplete the BMSC pool in adolescent mice, the team investigated whether a loss of these cells is responsible for the failed fracture repair. Isolating bone marrow-associated cells from wild-type and *Rbpj* knockout fracture, Hilton and his team performed colony forming unit (CFU) assays for fibroblastic (CFU-F) and osteoblastic (CFU-OB) cell frequency to quantify the BMSCs. Overall, fewer CFU-F and CFU-OB cells were observed, and the ratio of CFU-OB to CFU-F cells was higher, in the fracture site of *Rbpj* knockout mice than in wild-type controls. These results indicate that the BMSC pool in *Rbpj* knockout mice is depleted and the remaining BMSCs are more differentiated than those in wild-type mice with a fracture.

"Our study not only implicates Notch signalling within BMSCs, but also BMSCs themselves as a critical or requisite cell population in normal fracture repair," says Hilton. "Our data demonstrate that if Notch signalling is defective specifically within BMSCs, the BMSC population is depleted and/or defective, resulting in severely compromised healing and fracture non-unions."

The findings might lead to new treatments for the 10–20% of bone fractures that do not heal. "We are now working on methods to use activators of the Notch signalling pathway to enhance the 'stemness' of BMSCs and expand these populations to have a sufficient quality and quantity of BMSCs for therapeutics aimed at enhancing bone repair and regeneration," outlines Hilton.

Tim Geach

ORIGINAL ARTICLE Cuicui, W. *et al.* Notch signaling in skeletal progenitors is critical for fracture repair. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI80672 (2016)