Paper - Basic Science

Paper Session: Fracture Healing:
Cells and Bone

Discordant Effects of Nonsteroidal Anti-Inflammatory Drugs on Human and Mouse Skeletal Stem Cells From Acute Fractures

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Purpose: Whether nonsteroidal anti-inflammatory drugs (NSAIDs) hinder human fracture healing by direct action on osteoblast differentiation remains unknown. While animal studies suggest NSAIDs are deleterious to osteoblast differentiation in vitro and in vivo, whether NSAID use inhibits fracture healing in humans is controversial. We have prospectively purified bona fide skeletal stem cells from both mice (mSSCs) as well as human fracture sites (hSSCs) and hypothesized that NSAIDs have discordant inhibitory effect on mSSCs but not hSSCs.

Methods: Human SSCs (Podoplanin+CD146-CD73+CD164+) and osteoprogenitors (hOPs; Podoplanin-CD146+) were isolated by fluorescence-activated cell sorting (FACS) from human fractures, and mSSCs (CD51+Thy1-6C3-CD105-) were isolated from complete diaphyseal murine femur fractures 10 days after injury and stabilization. Purified SSCs were cultured in the presence or absence of 3 common NSAIDs, as well as a selective cyclooxygenase (COX)-2 inhibitor, and analyzed subsequently for self-renewal (colony-forming units [CFU-F]) and osteogenic and chondrogenic differentiation capacity. Experiments were performed at least in triplicate for healthy adults (age 44-85 years).

Results: COX-1 and COX-2 messenger RNA and protein was expressed in freshly isolated mSSCs and hSSCs from fractures. NSAIDs inhibited chondrogenic differentiation in mSSCs, while only indomethacin inhibited osteogenic differentiation in mSSCs. In hSSCs, neither NSAIDs at physiologic and supraphysiologic concentrations, with transient or continuous NSAID administration, nor selective COX-2 inhibition, affected hSSC osteochondrogenic differentiation.

Conclusion: NSAIDs differentially affect murine and human SSCs. Caution should be used in extrapolating experimental animal models to clinical practice.

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