

Innervation by the sensory nervous system ~~innervation plays a key role in~~ is important for skeletal development and ~~in~~ orchestration of bone remodeling and regeneration. However, ~~it is unclear~~ how and in which bone cells ~~can~~ sensory ~~nerves~~ ~~nerves~~ act ~~to for control~~ ~~regulating~~ these processes ~~remains unclear~~. ~~Here~~ ~~In this study~~, we ~~present~~ ~~show~~ a microfluidic coculture system ~~involving~~ ~~comprising~~ dorsal root ganglion (DRG) neurons and mesenchymal stem cells (MSCs), ~~which~~ ~~that more faithfully~~ represents the in vivo ~~situation~~ ~~scenario~~ of bone sensory innervation ~~more appropriately~~. We report that DRG neurons promote the osteogenic differentiation capacity of MSCs, by ~~mediating the increase~~ ~~increasing~~ of alkaline phosphatase activity and ~~the~~ upregulation ~~of ng~~ osteoblast-specific ~~genes~~ ~~gene~~ expression. ~~Furthermore, we show that~~ ~~Further~~, DRG neurons ~~have a~~ positively impact ~~on~~ Cx43 levels in MSCs during osteoblastogenesis, ~~especially~~ ~~particularly at~~ ~~at~~ an early stage of this process. Conversely, ~~we described a~~ ~~DRG neurons~~ negatively impact ~~of DRG neurons on MSCs~~ N-cadherin expression ~~in MSCs~~ at a later stage ~~of the process~~. Finally, ~~we demonstrate a~~ ~~the~~ cytoplasmic accumulation ~~and nuclear~~ ~~of~~ ~~translocation of~~  $\beta$ -catenin ~~translocation into the~~ ~~nucleus~~, and ~~the~~ subsequently ~~I~~-lymphoid ~~Enhancer-B~~ ~~binding~~ ~~F~~factor 1 ~~—~~ responsive transcriptional activation of downstream genes in cocultured MSCs. ~~Together, o~~ ~~Our~~ study provides ~~strong a robust body of~~ evidence that ~~the osteoblast differentiation potential of MSCs is enhanced~~ ~~the direct interaction of~~ ~~when~~ DRG neurons ~~directly interact~~ with MSCs in a bone-like microenvironment ~~leads to an enhancement of osteoblast differentiation potential of MSCs~~. The osteogenic effect of DRG neurons on MSCs is mediated ~~through the~~ ~~by~~ regulation of Cx43 and N-cadherin expression and activation of the canonical/ $\beta$ -catenin Wnt signaling pathway.

**Comment [A1]:** Here, the sentence has been revised to clearly indicate that accumulation and translocation of  $\beta$ -catenin are being referred to.

**Comment [A2]:** A compound modifier contains 2 or more words, which act together as one adjective and are connected by hyphens. Hyphens are used with these terms so that their meaning is understood clearly.

**Comment [A3]:** The text alongside has been revised to convey the intended meaning in a more concise manner.