

Innervation ~~by~~ from the sensory nervous system ~~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 ~~nerve~~ nerves act to control these processes ~~remains unclear~~. Here, we ~~present~~ show a microfluidic coculture system comprising dorsal root ganglion (DRG) neurons and mesenchymal stem cells (MSCs), ~~which~~ that ~~more faithfully~~ represents the in vivo scenario of bone sensory innervation more appropriately. We report that DRG neurons promote the osteogenic differentiation capacity of MSCs, by mediating ~~an~~ the increase ~~in of~~ alkaline phosphatase activity and ~~the~~ upregulation ~~of ng~~ osteoblast-specific genes. Furthermore, we show that 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~~ negative 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 ~~of β -catenin~~ and translocation of β -catenin into the nucleus, and the subsequent ly Lymphoid Enhancer - B binding E factor 1 --- responsive transcriptional activation of downstream genes in cocultured MSCs. ~~Together,~~ Our study provides strong a ~~robust body of~~ evidence that the direct interaction of DRG neurons with MSCs in a bone-like microenvironment ~~leads to an enhancement of~~ enhances the osteoblast differentiation potential of MSCs. The osteogenic effect of DRG neurons on MSCs is mediated through the regulation of Cx43 and N-cadherin expression and activation of the canonical/ β -catenin Wnt signaling pathway.

Comment [A1]: Here, the sentence has been revised to clearly indicate that accumulation and translocation of β -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 lowercase as this is not a proper noun.