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 ~~nerves~~ 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~~ upregulati~~on 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 describe~~d~~ 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~~ ~~L~~lymphoid ~~E~~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 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.

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