

Knee joint signals bones to grow

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Scientists from the Memorial Sloan Kettering Cancer Center, US, have revealed a communication system between the knee joint and developing bones in mice, which controls bone growth during early development



and after injury.

Writing in the journal *eLife*, the authors suggest that bone growth is controlled not only from within the bone itself, but by neighboring <u>cells</u> situated in nearby joints. These cells 'talk' to developing bone cells using different communication channels, instructing them to grow and mature. A better understanding of these communication channels could be used to improve treatment for correcting bone growth defects.

Bone growth is an intricately controlled process which begins with an initial temporary cartilage structure—the growth plate—and involves many types of cell and signaling molecules. Previous studies have shown that growth follows a specific genetic programme orchestrated within the growth plate. However, classic experiments where the position of different growth plates was interchanged suggested that the local environment can modulate this genetic programme.

"The identification of local signals coming from elsewhere and their contribution to the growth plate are only just beginning to emerge," explains lead author Alberto Roselló-Díez, Postdoctoral Research Fellow at Sloan Kettering. "A major obstacle is the lack of models where only cells outside of the growth plate can be altered, so we developed a mouse model to study the contribution of individual communication pathways outside the plate."

They first tested whether damage to cells surrounding the growth plate would affect bone growth in the left leg of mice. The growth plate itself was left intact, as was the right leg for comparison to the left. Consistent with the expected role of neighboring signals, damaging these surrounding tissues impaired growth plate function and stunted bone growth.

Further investigation revealed that loss of surrounding cells causes



multiple changes in cell communication, which impairs <u>bone cells'</u> ability to multiply and increase in size. One pathway—the insulin-like signaling pathway—was much less active in the left <u>knee</u> joint of the mice. A closer look showed that immune cells were suppressing this pathway, leaving the growth plate without this vital signal. However, replenishing the signal didn't completely reverse the effect, suggesting insulin-like signaling is one of several important pathways.

The team next looked at whether classic damage response signals were activated in the knee joint after injury. They found similar patterns in the left mouse leg to those seen in osteoarthritis, not only in the knee structures but also in the cartilage that wraps the bones' ends, suggesting that the injury response is a further mechanism that triggers altered signaling from the knee joint to the growth plate.

At later stages of development, the insulin-like <u>pathway</u> was no longer active in the knee joint of either limb, showing that bone growth eventually becomes independent of this external influence. The authors suggest this fits with the idea that local signals from outside the growth plate are important in establishing body proportions early on in development.

"We have identified two components of the knee joint that control bone growth, at least following injury, and we've shown that signals from these components influence distinct growth plate signaling pathways and lead to reduced bone growth," concludes Alexandra Joyner, PhD, senior author and Developmental Biologist at Sloan Kettering. "Further studies are needed to confirm and expand the repertoire of local regulators of bone growth, adding valuable insights to evolutionary studies and providing avenues for therapies that can correct long bone growth defects."

More information: Alberto Roselló-Díez et al, Altered paracrine



signaling from the injured knee joint impairs postnatal long bone growth, *eLife* (2017). DOI: 10.7554/eLife.27210

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