Bone or cartilage? Presence of fatty acids determines skeletal stem cell development

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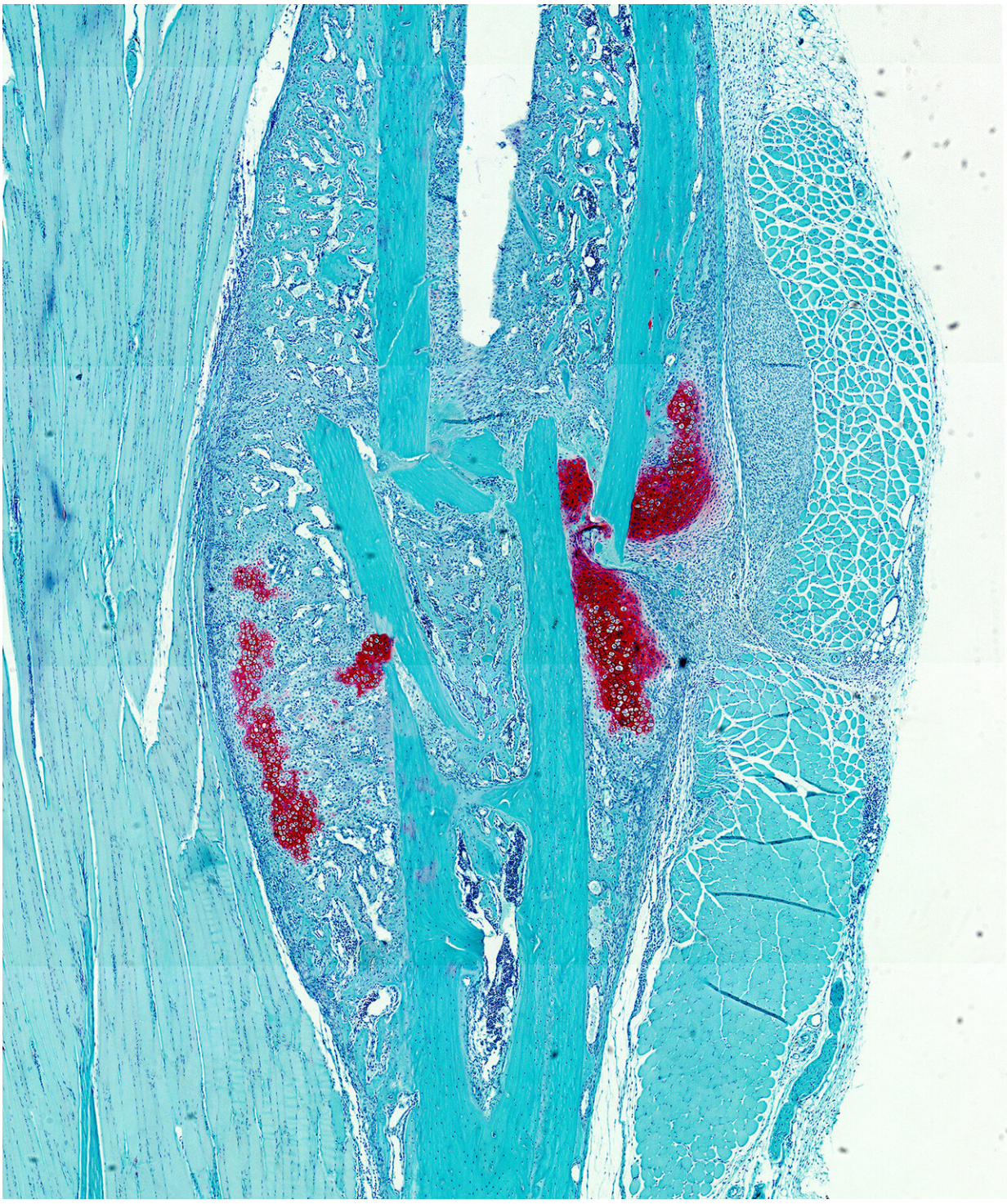

A histologic section of a mouse bone fracture. Safranin O has been used to colour the cartilage cells red (specifically the proteins produced by cartilage cells); all other tissues are blue. Credit: Nick van Gastel.

In the event of a bone fracture, fatty acids in the blood signal to stem cells that they have to develop into bone-forming cells. If there are no blood vessels nearby, the stem cells end up forming cartilage. The finding that specific nutrients directly influence the development of stem cells opens new avenues for stem cell research. Biomedical scientists from KU Leuven and Harvard University published these results in *Nature*.

Bone fractures heal through the action of skeletal progenitor cells: stem cells that have evolved further but can still develop into different types of cells. Bone healing occurs in one of two ways: The progenitor cells evolve into bone-forming cells when the fracture is small, and into cartilage cells when the fracture is bigger. This cartilage is later replaced by bone. Until now, scientists did not know how progenitor cells decide whether to become bone or cartilage cells.

"Our hypothesis was that the presence of blood vessels plays a role," explains first author Nick van Gastel. "Despite what many people think, our bones are full of blood vessels, while cartilage does not have any." This new study on mice confirmed the team's assumption: when blood vessels surrounding a fracture were blocked, cartilage was formed. When they were not, new bone was created immediately.

In a second phase of the study, the researchers tried to find out which signal the blood vessels actually send to the progenitor cells to make them evolve into either a bone or a cartilage cell. "Our previous research had already shown that nutrients play a role in the biology of progenitor cells," explains Professor Geert Carmeliet from the Clinical and Experimental Endocrinology Unit at KU Leuven, who led the study. For the current study, the team tested how the presence of different nutrients influences progenitor cell fate. Their results show that the fatty acids present in blood cause progenitor cells to grow into bone-forming cells.

If there are no fatty acids nearby, progenitor cells activate the SOX9 gene, which plays an important role in skeletal development. This is the signal for the cell to become a cartilage cell. Cartilage cells do not need fatty acids to survive and form cartilage.

"This study is useful for researchers in regenerative medicine, since we still know little about cartilage formation," says Professor Carmeliet. "Research into cartilage disorders such as osteoarthritis may also benefit from these findings. There are indications that cartilage cells receive more fatty acid signals and don't produce enough of the SOX9 gene in patients with such disorders, which can have adverse effects on the joints. Finally, our study shows for the first time that specific nutrients can inform stem cells which type of cell they should become. That is an important step forward in stem cell research." Eventually, the researchers hope to map out the effects of different nutrients on different types of progenitor cells.

More information: Lipid availability determines fate of skeletal progenitor cells via SOX9 , *Nature* (2020). DOI: 10.1038/s41586-020-2050-1 , nature.com/articles/s41586-020-2050-1

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