YAP and TAZ: Protein partners identified as potential key for fetal bone development

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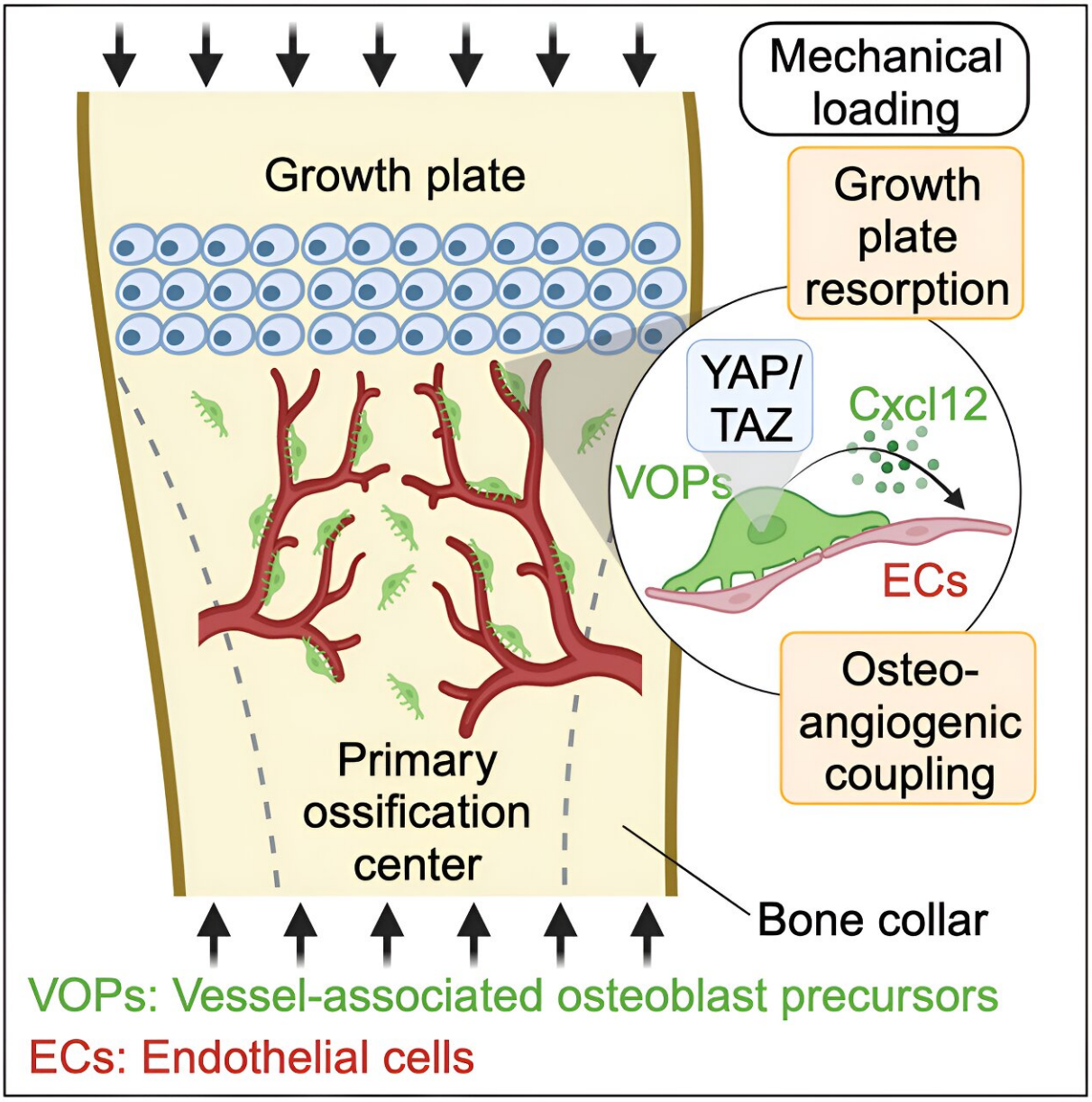

Graphical abstract. Credit: *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.11.029

A pair of proteins, YAP and TAZ, has been identified as conductors of bone development in the womb and could provide insight into genetic diseases such as osteogenesis imperfecta, known commonly as "brittle bone disease."

This small animal-based research, published in *Developmental Cell* and led by members of the McKay Orthopaedic Research Laboratory of the Perelman School of Medicine at the University of Pennsylvania, adds understanding to the field of mechanobiology, which studies how mechanical forces influence biology.

"Despite more than a century of study on the mechanobiology of bone development, the cellular and molecular basis largely has remained a mystery," said the study's senior author, Joel Boerckel, Ph.D., an associate professor of Orthopaedic Surgery. "Here, we identify a new population of cells that are key to turning the body's early cartilage template into bone, guided by the force-activated gene-regulating proteins, YAP and TAZ."

By combing through the genes expressed by individual cells in developing mouse limbs, through single-cell sequencing, Boerckel and the study's first author, former Penn Bioengineering doctoral student Joseph Collins, Ph.D., along with their colleagues, found and described a class of cells that they named "'vessel-associated osteoblast precursors (VOPs)," which "invade" early cartilage alongside blood vessels.

Since osteoblasts are the cells required to form (and fix) bones, these cells would essentially be the grandparents to bones, with osteoblasts

being bones' parents.

And, importantly, a pair of proteins called YAP and TAZ that are sensitive to the natural movement of the body—which the team's previous work has shown is crucial to early bone development and regeneration—serve as guides to the VOPs, passing on signals they glean from the body's mechanobiology.

The researchers found that YAP and TAZ help direct blood vessel integration into the cartilage, a vital aspect of bone development. They were able to demonstrate this role by first genetically removing YAP and TAZ from human cell models, which appeared to stop angiogenesis, the process by which new blood vessels form. Then, the researchers treated those human cell models with a special variety of protein called CXCL12, which restored YAP and TAZ and restarted normal angiogenesis.

The study is a result of a long-time collaboration with Dr. Niamh Nowlan of University College Dublin, whose laboratory focuses on how mechanical forces direct skeletal development in animal models and in human patients.

It's also appropriate that Boerckel, Collins, and their team are using their exploration of bone development as a lens to further the understanding of mechanobiology.

"The study of bone development is the birthplace of mechanobiology," Boerckel said. "For example, Wolff's Law of Bone Transformation, says that trabecular—spongy—bone adapts in a manner depending on the stresses placed on it, but Julius Wolff spent more time in his 1894 book focused on bone development than on trabecular bone."

With the information the Penn researchers gleaned from their study on

both bone development and mechanobiology, they believe they can now inform some of the knowledge and, hopefully, treatment of genetic and congenital musculo-skeletal conditions. That includes brittle bone disease—in which the body doesn't make collagen correctly, causing bones that can break easily—or arthrogryposis—a condition in which joints develop improperly due to limited fetal movement.

"We are now working on using these findings to target these cells and pathways, either by direct mechanical or pharmacologic means, to restore cellular function and proper bone development in utero, potentially preventing these types of conditions," Boerckel said.

More information: Joseph M. Collins et al, YAP and TAZ couple osteoblast precursor mobilization to angiogenesis and mechanoregulation in murine bone development, *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.11.029

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