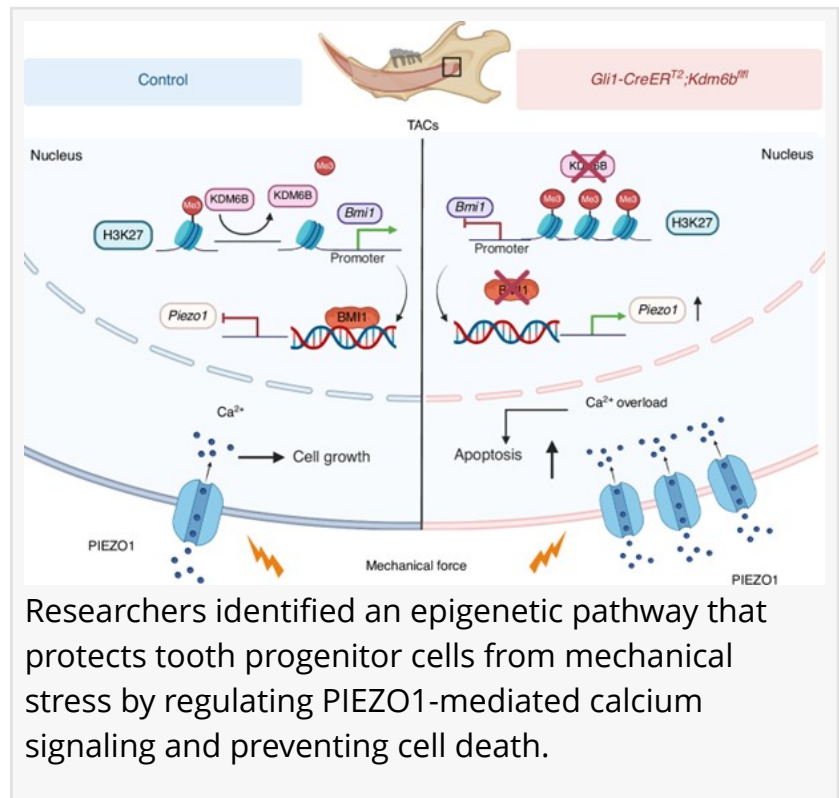


Epigenetic 'Mechanostat' Protects Tooth Progenitor Cells from Mechanical Stress

Researchers uncovered an epigenetic pathway that shields tooth-forming cells from force-induced damage and preserves tissue renewal

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/EINPresswire.com/ -- An epigenetic “mechanostat” has been discovered that protects tooth-forming progenitor cells from mechanical stress and supports lifelong tissue renewal. Using mouse incisors, the study shows that KDM6B restrains force-induced calcium signaling by regulating the mechanosensitive channel PIEZO1 through a chromatin-based pathway. The findings reveal how mineralized tissues adapt to constant mechanical loading and identify potential therapeutic targets for skeletal and dental degeneration, while providing new insights into tissue regeneration and mechanobiology overall.



Mineralized tissues such as teeth and bones experience continuous mechanical forces throughout life. Everyday activities, including chewing, biting, and movement, generate physical stresses that are essential for maintaining tissue health, yet excessive mechanical stimulation can damage cells and contribute to degeneration. Scientists have long understood that cells can sense and respond to mechanical cues, but the molecular mechanisms that protect regenerative tissues from the harmful effects of persistent forces have remained largely unknown. Understanding how tissues maintain this balance is a central challenge in regenerative biology and skeletal health research.

Addressing this challenge, a research team led by Professor Yang Chai from the Center for Craniofacial Molecular Biology, Herman Ostrow School of Dentistry at the University of Southern California, USA. Using continuously growing mouse incisors as a model system, the researchers

investigated how dental progenitor cells adapt to mechanical loading. The mouse incisor is particularly well suited for this purpose because it undergoes lifelong renewal while experiencing substantial forces during gnawing and chewing. By combining genetic mouse models, transcriptomic analyses, chromatin profiling, calcium imaging, and mechanical loading experiments, the team systematically examined how epigenetic regulation influences cellular responses to force. Their findings were published in Volume 14 of the journal *Bone Research* on May 28, 2026.

The researchers focused on KDM6B, an enzyme that removes repressive chromatin marks and regulates gene activity. They found that KDM6B is highly expressed in transit-amplifying cells, a rapidly dividing progenitor population responsible for generating new tooth-forming cells. When *Kdm6b* was selectively deleted in the dental stem cell lineage, normal tooth growth became impaired under mechanical loading conditions. The affected incisors exhibited reduced growth, thinner dentin, enlarged pulp cavities, and defective differentiation of odontoblasts, the specialized cells responsible for dentin formation.

Further investigation revealed that the absence of KDM6B made progenitor cells unusually sensitive to mechanical stress. The loss of *Kdm6b* triggered excessive activation of PIEZO1, a mechanosensitive ion channel that converts physical force into intracellular calcium signals. Elevated PIEZO1 activity caused abnormal calcium influx and increased cell death within the progenitor cell compartment. Importantly, reducing mechanical load substantially alleviated these defects, demonstrating that KDM6B specifically protects cells against force-induced damage rather than supporting growth under all conditions.

The team uncovered the molecular pathway underlying this protective effect. KDM6B normally removes the repressive histone mark H3K27me3 from the promoter of the gene *Bmi1*, allowing BMI1 expression to remain active. BMI1, in turn, directly suppresses Piezo1 expression. Without KDM6B, H3K27me3 accumulates, *Bmi1* becomes silenced, PIEZO1 levels rise, and calcium signaling becomes excessive. Genetic experiments confirmed this mechanism: reducing either H3K27me3 levels or PIEZO1 expression restored calcium balance, rescued progenitor cell survival, and largely restored normal tissue architecture.

“Our study shows that KDM6B acts as an epigenetic safeguard that prevents mechanical forces from overwhelming regenerative cells,” said Prof. Chai. “By limiting PIEZO1-dependent signaling, this pathway allows tissues to benefit from mechanical stimulation while avoiding cellular damage.”

The findings establish a direct link between chromatin regulation and mechanotransduction, two fields that have traditionally been studied separately. Because PIEZO1 signaling is involved in many mechanically active tissues throughout the body, the newly identified KDM6B–H3K27me3–BMI1–PIEZO1 pathway may have implications extending far beyond dental biology. The work provides a framework for investigating how stem and progenitor cells adapt to forces in skeletal tissues, cartilage, and other mechanically dynamic organs.

“This discovery suggests that epigenetic regulators can function as molecular mechanostats that tune cellular sensitivity to force,” said Prof. Chai. “Understanding these mechanisms may help us develop strategies to protect regenerative cells and improve tissue repair.”

Overall, the study reveals a previously unrecognized mechanism that enables mineralized tissues to withstand lifelong mechanical stress while maintaining regeneration. In the short term, the findings provide new targets for studying mechanically induced tissue damage and degeneration. Looking ahead, therapies aimed at modulating the KDM6B–BMI1–PIEZO1 pathway could potentially enhance tissue regeneration and help prevent disorders associated with excessive mechanical loading, including conditions affecting the musculoskeletal and craniofacial systems.

Reference

Titles of original paper: KDM6B safeguards mineralized tissue homeostasis from mechanical stress through epigenetic control of PIEZO1-mediated mechanotransduction in the mouse incisor

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Yang Chai is Dean and the G. Donald and Marian James Montgomery Professor of Dentistry at the Herman Ostrow School of Dentistry of the University of Southern California (USC), and a University Professor of Otolaryngology–Head and Neck Surgery at the Keck School of Medicine. Internationally recognized for his research on craniofacial development, genetics, and cellular signaling, he investigates the causes and prevention of craniofacial disorders. Prof. Chai chairs the National Institute of Dental and Craniofacial Research Board of Scientific Counselors and was elected to the National Academy of Inventors in 2024.

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