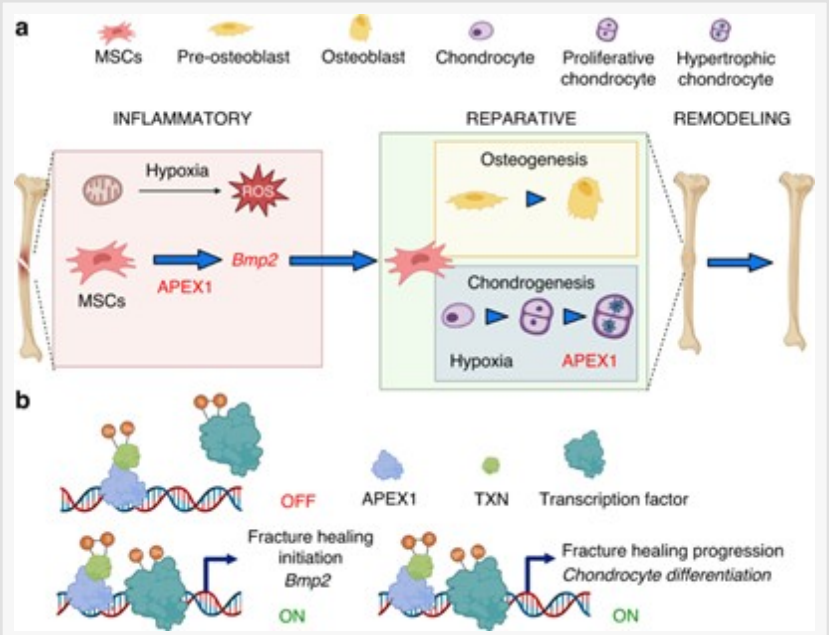
# Why Some Broken Bones Fail to Heal: Scientists Reveal a Critical Molecular Trigger

*Researchers uncover a redox-regulated mechanism that determines whether bone fractures heal or progress to nonunion*




Cellular and molecular role of Apex1 in fracture healing. (a) Apex1 regulates Bmp2 expression in mesenchymal progenitors during inflammation and promotes chondrocyte differentiation during repair. (b) Apex1 and thioredoxin (TXN) enable redox-dependent act

BEIJING, BEIJING, CHINA, February 2, 2026 /EINPresswire.com/ -- Bone fractures usually heal efficiently, but in some patients this process fails, causing nonunion. A recent study identifies Apex1 as a redox-regulated driver of fracture repair. Using genetic mouse models, researchers show Apex1 controls early Bmp2 activation and later chondrocyte maturation, coordinating callus formation, vascularization, and cartilage-to-bone transition. These findings highlight oxidative stress regulation as a promising therapeutic strategy to improve bone healing and reduce the risk of fracture nonunion.

Bone has an extraordinary capacity to heal after injury, restoring its structure and mechanical function without leaving a scar. Yet for a clinically significant number of patients, this regenerative process fails, resulting in fracture nonunion—a condition associated with chronic pain, prolonged disability, and repeated surgical interventions. Despite advances in orthopedic techniques, the biological reasons why some fractures fail to heal remain poorly understood. New research now identifies a key molecular mechanism that determines whether bone repair is successfully initiated or derails early in the process.

Fracture healing begins immediately after injury, when disrupted blood supply creates a hypoxic microenvironment at the fracture site. This low-oxygen state promotes the production of reactive oxygen species (ROS), which serve as signaling molecules that activate genes required for tissue

repair. While tightly regulated ROS signaling is essential for healing, excessive oxidative stress can damage cells and impair regeneration. In this study, researchers identify apurinic/apyrimidinic endonuclease 1 (Apex1), a redox-sensitive protein, as a central mediator that translates hypoxia-driven ROS signals into transcriptional activation required for bone repair. The findings were published on January 16, 2026, in Volume 14 of the journal Bone Research.

The study was led by Dr. Emma Muiños-López, a researcher at the Instituto de Investigación Sanitaria de Navarra (IdiSNA), Spain. Their work focused on understanding how redox biology integrates environmental stress signals with the molecular programs that guide skeletal regeneration.

To investigate the role of Apex1, the team generated genetically engineered mouse models in which Apex1 was selectively silenced in mesenchymal progenitor cells—the early precursor cells that give rise to cartilage and bone. The researchers analyzed both skeletal development and fracture repair using a combination of imaging techniques, histological analysis, gene expression profiling, and transcriptomic approaches. This comprehensive strategy allowed them to follow the effects of Apex1 loss across multiple stages of bone healing, from early inflammation to later cartilage maturation and bone formation.

The results revealed that Apex1 plays an indispensable role at two distinct phases of fracture repair. During the initial inflammatory phase, Apex1 is required for activation of Bmp2, a master regulatory gene that initiates healing by stimulating periosteal expansion and callus formation. When Apex1 was absent, Bmp2 expression was markedly reduced, periosteal activation was blunted, and early fracture healing was delayed. As a consequence, the initial callus that serves as the biological scaffold for repair was significantly smaller. “Apex1 acts like a molecular switch at the very start of healing, translating oxidative signals into the gene programs that tell cells to build new bone,” explains Dr. Muiños-López.

Apex1 was also found to be critical during the reparative phase, when cartilage must mature and be replaced by bone through endochondral ossification. In mice lacking Apex1, chondrocytes failed to progress beyond a pre-hypertrophic state and did not express key markers such as type X collagen and matrix metalloproteinases necessary for cartilage breakdown. This defect impaired vascular invasion and subsequent bone formation, leading to persistent fracture gaps characteristic of nonunion-like healing defects.

Importantly, the researchers showed that these healing defects could be reversed. Restoring Bmp2 signaling—either through genetic overexpression or localized delivery of recombinant Bmp-2—rescued callus formation and improved fracture repair. This finding confirms that Apex1 functions upstream of Bmp2 and identifies redox-regulated transcription as a decisive control point in bone regeneration. “By restoring Bmp2, we can essentially bypass the missing Apex1 signal and get healing back on track, which opens exciting therapeutic possibilities,” notes Dr. Muiños-López.

Beyond fracture repair, the study also provides broader insight into skeletal biology. Transient growth plate abnormalities observed during development in Apex1-deficient mice closely resembled human metaphyseal dysplasias that resolve with age, reinforcing the protein's role in chondrocyte maturation. Together, these findings address a longstanding challenge in orthopaedics: understanding why some fractures fail to heal despite appropriate stabilization.

By identifying Apex1 as a master regulator of fracture healing initiation and progression, the study highlights redox-modulating strategies as a potential avenue to enhance bone repair, particularly in patients at high risk of nonunion, such as older adults, smokers, and individuals with diabetes.

Reference

Titles of original papers: Apex1, a transcriptional hub for endochondral ossification and fracture repair
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About Dr. Emma Muiños-López from Clínica Universidad de Navarra, Spain
Dr. Emma Muiños-López is a researcher at Clínica Universidad de Navarra, Spain, and an active member of the Instituto de Investigación Sanitaria de Navarra (IdiSNA). Her research focuses on tissue regeneration, redox biology, and the molecular mechanisms governing skeletal repair and disease. Through interdisciplinary and collaborative research, her work advances the understanding of biological processes underlying musculoskeletal regeneration and fracture healing, with potential implications for future therapeutic strategies.

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