



When broken bones need air: Erythrocytes step in to heal

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The human skeleton fulfills multiple critical roles: it provides biomechanical stability and posture, enables motion, protects vital organs and neural structures, and houses the bone marrow, which is essential for the production of white and red blood cells. Fractures, described as early as the 17th century BC in the Edwin Smith papyrus, are among the most common traumatic events affecting humans (1). As such, they can compromise several of these skeletal functions, leading to substantial morbidity and even mortality.

A key process crucial for successful fracture healing is revascularization of the fracture site, which supplies the callus with oxygen, nutrients, inflammatory cells, and progenitor cells necessary for repair (2, 3). Classically, angiogenesis at the fracture site is thought to be initiated by hypoxia following vascular disruption (4). In this canonical model, vascular damage leads to local hypoxia, stabilizing the hypoxia-inducible factor (HIF) transcriptional heterodimer under low oxygen tension, which in turn increases vascular endothelial growth factor (VEGF) expression and drives angiogenesis (5, 6). This cascade has long underpinned the conceptual framework for vascular regeneration in bone repair.

A new study by Lang et al. (7) provides intriguing insights into the early stages of fracture repair, prompting a reassessment of these long-standing assumptions. The authors report that surprisingly, immediately after fracture, the local microenvironment is not hypoxic. Instead, oxygen tension in the injured bone marrow is elevated, and this elevated state persists for over a week following injury.

This unexpected finding raises several important questions and invites a reexamination of fundamental concepts in fracture repair. The first set of questions relates directly to the absence of early hypoxia at the fracture site. How is oxygen maintained at high levels despite disruption of the marrow vasculature? In search of the answer, Lang et al. systematically rule out both early angiogenesis and systemic erythropoietin (EPO) elevation as drivers of increased oxygen. Instead, they identify a local expansion and activation of erythroid precursor cells (EPCs) within the marrow at the injury site. These cells synthesize hemoglobin *in situ*, which is sufficient to elevate and maintain oxygen levels. This emphasis on local erythropoiesis echoes recent findings that chondrocytes in the growth plate can produce substantial hemoglobin to buffer hypoxia and survive in a low-oxygen niche (8). In both scenarios, high concentrations of hemoglobin, whether in erythrocytes or in chondrocytes, act as an “oxygen battery,” stabilizing oxygen availability within otherwise hypoxic microenvironments.

These insights, which introduce bone marrow EPCs as a new cellular player in fracture repair, raise further compelling questions. Which mechanism senses the fracture and triggers the rapid activation of erythropoiesis and hemoglobin synthesis at the injury site? Another important question concerns scalability: is this mechanism sufficient in larger

organisms with substantially larger bones, such as humans? If so, what adaptations might be required to sustain effective local oxygen buffering across a much greater tissue volume?

Another important open question concerns the functional consequences of the absence of hypoxia during the initial phase of fracture repair. According to classical dogma, hypoxia is required to initiate regeneration. If hypoxia does not occur, as shown by Lang et al., the early phases of regeneration may be attenuated or delayed, which likely reflects a purposeful biological strategy.

The authors propose that elevated oxygen may provide an antimicrobial buffer, reducing infection risk immediately after injury. This may be particularly relevant in evolutionary contexts, where fractures often occurred in contaminated environments. Temporary hyperoxia could thus act as a protective mechanism, prioritizing survival over immediate regenerative efficiency.

A second explanation relates to mechanical and morphological considerations. In the absence of orthopedic intervention, fractures can undergo a spontaneous, proprioception-mediated realignment of the bone fragments during the early repair period (9). Rapid induction of hypoxia and callus formation could mechanically “lock in” a misaligned configuration. By delaying callus deposition, a transient hyperoxic phase may allow the fracture ends to settle into a more anatomically favorable alignment before structural stabilization begins, an evolutionary advantage that could improve long-term function.

While the study by Lang et al. does not directly disprove a role for hypoxia in fracture repair, the observation that the initial fracture site is not hypoxic provides a powerful opportunity to revisit this enduring notion. Several previous studies have reported that *in vivo* hyperoxia, rather than hypoxia, can be beneficial or even essential for revascularization and bone repair, challenging the view that hypoxia is the primary trigger of early healing (10, 11). One of the strongest arguments supporting hypoxia has been its ability to induce angiogenesis through the HIF-1/VEGF pathway. However, substantial evidence indicates that HIF-1 can also be activated by nonhypoxic stimuli,

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including metabolic and redox cues, which can likewise upregulate VEGF and initiate angiogenesis through hypoxia-independent mechanisms (12, 13). Clinically, evidence supporting the use of hyperbaric oxygen (HBO) to promote fracture healing remains inconclusive and, in many cases, unconvincing (14), further illustrating the complexity of oxygen biology in bone repair.

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Overall, the work of Lang et al. reopens fundamental questions about oxygen levels and their diverse roles during fracture repair. It calls for new studies to dissect not only the presence or absence of hypoxia but also the timing,

localization, and cellular handling of oxygen at each stages of healing processes. In particular, the identification of bone marrow EPCs as a novel cellular player in early fracture repair may have important consequences. Understanding the clinical significance of EPC-driven local erythropoiesis, as well as the upstream mechanisms that regulate hemoglobin synthesis and oxygen buffering at the fracture site, will open new avenues into the molecular control of oxygen handling during bone healing. Thus, in addition to reshaping our conceptual understanding of fracture repair, these findings may also support future therapeutic strategies that will harness oxygen dynamics more effectively to optimize skeletal regeneration.

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