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https://www.gesundheitsindustrie-bw.de/en/article/press-release/when-oxygen-determines-if-limb-can-regrow

When oxygen determines if a limb can regrow

Can Aztekin and his team have discovered how oxygen-sensing explains why amphibians regenerate limbs and mammals do not.
Researchers show that mammals briefly activate regenerative programs after injury but shut them down too fast. Altering oxygen sensing keeps cells in a repair-ready state.

Short overview

- **Oxygen acts as a switch for regeneration:** Low oxygen levels trigger the early phase of limb regeneration in mammals by stabilizing the protein HIF1A. This promotes rapid wound healing and primes the activation of genes required for regeneration. At normal atmospheric oxygen levels, HIF1A is destabilized, quickly shutting down this regenerative response.

- **Mammals have hidden regenerative potential:** When oxygen levels are lowered or HIF1A is stabilized, mouse embryos rapidly heal wounds and start showing early signs of rebuilding limbs. This suggests that mammals may not be permanently incapable of limb regeneration, but instead require specific environmental conditions to unlock this potential.

- **The key difference is how cells sense oxygen:** Regeneration-competent animals such as frog tadpoles maintain stable HIF1A activity and remain in a regenerative state even in high oxygen environments. In contrast, mammalian tissues, including humans, respond strongly to oxygen. By manipulating oxygen sensing, this regenerative program can be reactivated, opening the door to testing whether limb regeneration could one day be possible in mammals.

Some animals can regrow lost body parts. Salamanders and frog tadpoles can rebuild entire limbs after amputation. Mammals cannot. For decades, biologists have tried to understand why.

Limb regeneration begins with wound healing. After amputation, cells at the injury site must rapidly seal the wound and switch into regenerative cell types. In amphibians, this process runs smoothly. In mammals, it stalls early. Wound closure is slow and scar formation takes over, blocking regeneration.

One key difference lies in the environment. Amphibian larvae develop in water, where oxygen levels are lower than in air. Moreover, many regeneration-competent species live in aquatic environments. Meanwhile, mammalian tissues are typically exposed to higher oxygen levels after injury.

What is unclear is whether this difference played a direct role in regeneration or was merely a consequence of lifestyle.

A team led by Can Aztekin discovered during his time at the École polytechnique fédérale de Lausanne (EPFL), and now at the Friedrich Miescher Laboratory of the Max Planck Society in Tübingen discovered that oxygen plays a crucial role in limb regeneration. By comparing amputated limbs from frog tadpoles and embryonic mice, the researchers found that the way cells sense oxygen determines if regeneration can even begin.

A latent regenerative capacity

“For a long time, regeneration research focused on amphibians, while mammalian regeneration was rarely examined experimentally side by side in a comparable manner,” says Aztekin. “Although many studies showed that regenerative species such as amphibians and mammals share similar genes, suggesting that mammals may retain a latent regenerative capacity, it remained unclear whether mammalian tissues can indeed activate limb regenerative programs, and what prevents them from doing so.”

The researchers amputated developing limbs from frog tadpoles and mouse embryos and cultured them outside the body

under controlled oxygen conditions. Oxygen levels were lowered to match aquatic environments or raised to levels close to air.

They tracked how cells responded by measuring wound closure, cell movement, gene activity, metabolism, and epigenetic states, including changes to DNA packaging. The work focused on HIF1A, a protein that acts as a cellular oxygen sensor. When oxygen is low, HIF1A becomes stable and activates programs that set the stage for wound healing and regeneration.

A change in cell behavior

Lowering oxygen levels had a clear effect on the limbs of mouse embryos. Under reduced oxygen, mouse cells closed wounds faster and showed signs of entering a regenerative program. Stabilizing HIF1A produced similar effects, even when oxygen levels remained high.

Low oxygen also changed cell behavior, with skin cells becoming more mobile and altering their mechanical properties. Metabolism shifted toward glycolysis, a process that takes place in low-oxygen states. At the same time, chemical marks on DNA-associated proteins shifted to favor the activation of regeneration-related genes.

Frog tadpoles behaved differently. Their limbs regenerated efficiently across a wide range of oxygen levels, including levels well above those normally found in air. Molecular analysis showed that their cells maintain stable HIF1A activity even when oxygen increases, due to low expression of genes that normally shut this pathway down.

By comparing frogs, axolotls, mice, and human datasets, the team found a consistent pattern. Regeneration-competent amphibians show reduced oxygen-sensing capacity, allowing regenerative programs to be initiated and sustained. Mammals show the opposite pattern. Their cells respond strongly to oxygen and switch regenerative programs off soon after injury.

A fresh perspective to centuries-old question

The results suggest that mammalian limbs retain latent regenerative potential at early stages, depending on how cells respond to environmental signals such as oxygen. This means that adjusting oxygen-sensing pathways might one day improve wound healing or regenerative responses in humans.

Importantly, the findings demonstrate the activation of regenerative mechanisms in mammals, not the complete regrowth of a fully formed limb. Although the study does not claim that human limb regrowth is imminent, it does show that differences once thought to be fixed between species may instead hinge on how cells respond to their environment.

“We are very excited about our findings,” says Aztekin. “By directly comparing species that can and cannot regenerate, we bring a fresh perspective to a centuries-old question. Our results show that regenerative programs can be triggered in mammalian tissues and begin to outline a clear, testable path toward promoting limb regeneration in adult mammals.”

Publication:

Georgios Tsissios, Marion Leleu, Kelly Hu, Alp Eren Demirtas, Hanrong Hu, Sabrina Vinzens, Toru Kawanishi, Evangelia Skoufa, Atharva Valanju, Alessandro Valente, Lorenzo Noseda, Haruki Ochi, Antonio Herrera, Selman Sakar, Mikiko Tanaka, Sara A. Wickström, Fides Zenk, Can Aztekin.
Species-specific oxygen sensing governs the initiation of vertebrate limb regeneration.
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