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# Reawakening dormant potential: Overcoming the evolutionary blockade to mammalian regeneration

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Regeneration, the process of replacing lost or damaged tissue, is a remarkable ability common in vertebrates like fish and salamanders but severely limited in most mammals. A key question in biology is why this seemingly beneficial trait was lost during evolution. Unraveling the evolutionary drivers behind the gain or loss of regeneration promises to shed new light on regenerative medicine.

A recent study from Lin et al. team reframes our understanding of how regenerative capacity evolves, proposing a new framework centered on a reversible "evolutionary blockade" rather than the outright loss of genetic material. They demonstrated that this blockade could be lifted, successfully restoring complex ear pinna regeneration in mice by either reactivating the expression of *Aldehyde Dehydrogenase 1 Family Member A2 (Aldh1a2)* or by directly supplementing its product, Retinoic Acid (RA).[1] This breakthrough not only provides a clear genetic explanation for the evolutionary divergence in regenerative abilities but also unveils a highly promising therapeutic strategy: repairing damaged tissues by awakening the body's own dormant, endogenous regenerative programs (Figure 1).

## RA IS A CRITICAL REGULATORY SIGNAL IN REGENERATION

Identifying the mechanisms behind mammals' limited regenerative ability is often complicated by the large phylogenetic distance between them and highly regenerative species, such as lower vertebrates. To overcome this challenge, this study employed a more effective research strategy that minimizes "evolutionary noise" by comparing closely related mammals with differing regenerative capacities.

The authors leveraged the natural diversity in ear pinna regeneration among placental mammals, contrasting highly regenerative species with non-regenerative ones. Through single-cell and spatial transcriptomics, they discovered that the failure to regenerate in mice stems from a critical divergence in the molecular program of a key cell population known as wound-induced fibroblasts (WIFs). The team traced this divergence to insufficient production of RA, a potent developmental morphogen. This deficiency prevents WIFs from engaging the proper morphogenetic program, causing the blastema to collapse into a fibrotic scar instead of proceeding with regeneration. Remarkably, simply restoring this pathway by either supplementing with RA or re-expressing *Aldh1a2* is sufficient to rescue the complex regenerative process. This finding suggests that the downstream "molecular machinery" required to execute regeneration remains largely intact within the mouse cells, albeit in a dormant state.

## EVOLUTIONARY DECAY OF CIS-REGULATORY ELEMENTS

Investigations of gene expression and function have led to the development of molecular models for regeneration in multiple contexts; however, a gap remains in the understanding of the regulatory events that activate tissue regeneration programs. Lin et al. elucidate that although the *Aldh1a2* gene in mice is structurally intact, it remains transcriptionally silent due to the evolutionary decay of its cis-regulatory elements. In the genome of the regenerative rabbit, the *Aldh1a2* locus is governed by a suite of injury-inducible enhancers (*AE1-AE6*); conversely, the regulatory potential of these elements has been abrogated at the orthologous locus in mice. This regulatory decay is mechanistically linked to the AP-1 transcription factor complex. The AP-1 complex, a heterodimer composed of Jun, Fos, Maf, and ATF family proteins, is essential for activating regeneration-responsive enhancers and initiating the downstream gene network that drives tissue regeneration.

This "cis-regulatory decay" theory aligns with recent findings in other regeneration models. The theory indicates that the regenerative program relies on the precise synergistic coupling between specific DNA regulatory sequences known as Tissue Regeneration Enhancer Elements (TREEs) or Regeneration-Responsive Enhancers (RREs) and their cognate promoters, which are activated upon injury to initiate downstream gene expression and drive the regenerative process.[2] This theory is grounded in the principle of evolutionary constraints. Protein-coding genes, such as *Aldh1a2*, are highly conserved due to their pivotal roles in fundamental processes, including embryonic development, where mutations are often lethal. In contrast, mutations in non-coding regulatory elements usually only affect gene expression in specific contexts, such as tissue injury, without disrupting the gene's primary functions.

## A NEW PARADIGM FOR AWAKENING ENDOGENOUS REGENERATIVE POTENTIAL

A key insight of the study is that the barrier to mammalian regeneration is specific and reversible, a conclusion supported by a decisive functional "rescue" experiment. Researchers reintroduced functional, rabbit-derived regulatory elements into mice, separately testing a key promoter (*Apr*) and enhancer (*AE1*). The results unequivocally showed that the rabbit-derived enhancer, but not the promoter, significantly promoted ear pinna regeneration in mice. However, the partial rescue achieved by the enhancer alone contrasts with the robust regeneration from AAV-mediated Aldh1a2 overexpression, highlighting the gap between restoring fine-tuned endogenous regulation and forcing gene expression. This result implies that complete regeneration relies not on a single hierarchical switch but on the synergistic interplay of multiple regulatory elements—including enhancers, promoters, and the AP-1 complex—to drive precise spatiotemporal gene expression. Consequently, future research into how these elements cooperatively regulate *Aldh1a2* will be central to fully understanding and reconstructing the regeneration program. Crucially, despite the complexity, the successful reactivation demonstrates that the molecular machinery for tissue repair is not lost in mammals, but merely silenced. Thus, this "reawakening" strategy has broad therapeutic implications that extend beyond simple wound healing: it bridges the gap between promoting regeneration after acute injury and restoring the diminished repair capacity associated with aging. By targeting the epigenetic root of these silenced programs, this approach holds the potential to reconstruct functional tissue architecture in both injured and senescent organisms.

## FUTURE DIRECTIONS AND CHALLENGES

While this study represents a landmark achievement in regenerative biology, any pioneering work simultaneously uncovers new challenges. Primarily, the core discovery must be tested for its generalizability. Is the decline of the retinoic acid pathway a ubiquitous principle underlying the loss of regenerative capacity in mammals, or is it a phenomenon restricted to the specific context of the rodent auricle? Secondly, it is necessary to understand how the activity of these control regions is attenuated as the regenerative event concludes, to mitigate the risk of tissue overgrowth or tumorigenesis.


**Figure 1. Reawakening dormant regenerative potential by overcoming an evolutionary blockade** Drawing from the classical Chinese novel *Journey to the West*, this allegory illustrates mammalian regenerative potential as the Monkey King (Sun Wukong)—a powerful immortal being trapped beneath a mountain by a magical seal. In this biological parallel, the mountain and seal represent an evolutionary blockade: the silencing of the key regenerative gene *Aldh1a2* (encoding retinaldehyde dehydrogenase, the rate-limiting enzyme for endogenous retinoic acid biosynthesis) due to degenerated or epigenetically repressed regulatory enhancers, resulting in the disruption of retinoic acid signaling required for tissue regeneration. The Tang Monk symbolizes modern therapeutic interventions—including epigenetic editors that restore enhancer function to reactivate endogenous *Aldh1a2* expression, and exogenous retinoic acid that bypasses the enzymatic blockade—that break this biological seal. The liberation of the Monkey King thus mirrors the restoration of retinoic acid signaling and the subsequent unleashing of functional regenerative programs.

Furthermore, despite the immense potential demonstrated by this research, its path to clinical translation remains fraught with challenges. As a potent regenerative regulator, RA acts through multifaceted mechanisms: it not only guides WIFs to restore damaged tissue, but also acts as a critical stem cell niche signal that resolves the state of "lineage plasticity" which stem cells enter after injury.[3,4] Future investigations should dissect RA-driven crosstalk, specifically determining how WIFs modulate immune polarization to suppress fibrosis and how RA resolves stem cell plasticity to guide recommitment to chondrogenic or dermal lineages. Unraveling these mechanisms provides the basis for precise regenerative control.

However, the severe toxic side effects of RA, particularly its teratogenicity and its narrow therapeutic window, render systemic administration strategies clinically unfeasible. To circumvent these limitations, immediate efforts should focus on localized and controllable intervention strategies, such as bioscaffolds with optimized release kinetics, to strictly confine RA activity to the target tissue. Moreover, therapeutic success relies on RA metabolic stability, requiring a tight balance between its synthesis and the prevention of its degradation. Simultaneously, and more fundamentally, research must trace the upstream mechanisms. It is essential to map the complete regulatory network of the *Aldh1a2* gene, delving into the synergistic interplay between enhancers and promoters. The ultimate goal is to engineer gene therapies capable of precisely and safely activating endogenous *Aldh1a2* expression specifically at the injury site, thereby mimicking the natural regenerative program without systemic risks.

## CONCLUSION

In summary, the research by Lin et al. represents a breakthrough that fundamentally reframes our understanding of the loss of regenerative capacity in mammals. Research indicates that mammals may have made an evolutionary trade-off, sacrificing the high metabolic cost of tissue regeneration in exchange for more robust immune defense systems and stricter tumor suppression mechanisms to adapt to their environment.[5] However, this research reveals that this capacity was not completely lost, but exists in a dormant state that can be reawakened, opening up entirely new theoretical and practical pathways to unlock the intrinsic regenerative potential within mammals. Furthermore, the "comparative evolutionary multi-omics" framework established by this study provides a blueprint extending beyond the ear. While WIFs drive regeneration in the ear, complex organs like the heart or spinal cord likely rely on distinct cellular engines due to their unique tissue architectures. By applying this comparative paradigm to such organs, researchers can systematically identify tissue-specific key cell populations and their silenced regulatory elements. This strategy promises to uncover unique "evolutionary locks" in myocardial or neural tissues, broadening the clinical scope of regenerative medicine.

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## AUTHOR CONTRIBUTIONS

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## DECLARATION OF INTERESTS

The authors declare no competing interests.