# Breakthroughs in blood stem cells and axolotl genetics pave way for new regenerative therapies



Recent breakthroughs in regenerative medicine reveal significant insights into the biological processes that underpin both human ageing and tissue regeneration, with implications that could herald a new era of therapies aimed at extending healthy lifespans. Two pivotal studies have captured the scientific community's attention by highlighting the mechanisms through which blood cells age in humans and how Mexican axolotl salamanders regenerate lost limbs.

One group of international researchers, collaborating under the auspices of the Centre for Genomic Regulation and the Institute for Research in Biomedicine in Barcelona, conducted comprehensive research into the ways human blood stem cells change over time. Their findings, published in a recent issue of Nature, indicate that as individuals age, particularly past 50, these stem cells become increasingly dominated by a narrow subset known as “clones.” This shift is significant because the clones produce myeloid cells associated with chronic inflammation, which can fuel a variety of age-related diseases. Indranil Singh, a co-first author of the study, noted, “The change from diversity to dominance isn’t random,” emphasising that the onset of this transformation can begin even in individuals as young as 50, becoming almost inevitable by 60.

The researchers employed a novel method to trace chemical “bar codes” imprinted by stem cells as they divide, allowing them to track changes over an individual's lifespan. This innovative approach may eventually equip scientists with the tools to predict acute myeloid leukaemia and offer potential avenues for rejuvenation therapies. Dusko Ilic, a professor of stem cell sciences at King’s College London, highlighted that the technique holds promise for early disease detection and might guide future treatments aimed at reversing negative trends in blood cell production. Nevertheless, significant hurdles remain in refining these predictive tools, accentuated by a lack of comprehensive knowledge about the various clones identified.

In tandem with this study, researchers explored the regenerative capabilities of axolotls and how they manage to regrow limbs lost through injury. This investigation also appeared in Nature and found that a specific gene, Hand2, plays a pivotal role in directing limb regrowth. Elly Tanaka, senior author of the axolotl study, remarked on the exciting prospect that similar genetic circuits exist in humans, suggesting a possible pathway towards unlocking enhanced regenerative abilities. This line of research posits that if human cells can tap into analogous “memories” of their positions and functions, it may open doors to innovative methods for engineering replacement tissues.

The regenerative phenomena observed in axolotls are not merely anecdotal; extensive studies have identified various biological mechanisms that facilitate their remarkable healing abilities. Research focusing on the mTORC1 pathway reveals that rapid activation of protein synthesis is crucial for limb regeneration, a trait not seen in non-regenerative species like mice. Specific amino acid sequences unique to urodele amphibians, including axolotls, allow for heightened sensitivity to tissue damage and responsive repair processes. This underscores the intricate molecular adaptations these creatures possess—adaptations that may hold valuable lessons for human regenerative medicine.

Further investigations have demonstrated that macrophages—cells vital to the immune response—play an essential role during the limb regeneration process in axolotls. Their timely infiltration is critical; researchers found that without them, while the wound may close, the limb growth fails, leading to fibrosis rather than successful regeneration. This dynamic interplay of inflammatory and anti-inflammatory signals showcases a sophisticated orchestration of the immune response that aids regeneration.

These twin studies on blood ageing and axolotl regeneration not only deepen our understanding of biological ageing and tissue restoration but also hint at future therapies that might one day enable humans to mimic the extraordinary regenerative abilities found in nature. As Lars Velten, a co-author of the blood research, succinctly stated, “If we want to move beyond generic anti-ageing treatments and into real precision medicine for ageing, this is exactly the kind of tool we need.” Together, these findings represent a significant stride toward unlocking the secrets of longevity and regeneration, with the potential to transform therapeutic approaches in regenerative medicine.

### Reference Map

1. Paragraphs 1, 2, 3, 4, 5, 6, 7, 8
2. Paragraphs 5, 6, 7
3. Paragraphs 5, 6
4. Paragraphs 7
5. Paragraphs 7
6. Paragraphs 6
7. Paragraphs 6

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## Bibliography

1. <https://www.ft.com/content/a1f83886-fb29-4f5f-9577-bec61dfd31d2> - Please view link - unable to able to access data
2. <https://www.nature.com/articles/s41586-023-06365-1> - This study investigates the role of the mTORC1 pathway in tissue regeneration in axolotls. It demonstrates that rapid activation of protein synthesis is crucial for limb regeneration in axolotls, a feature not observed in non-regenerative species like mice. The research identifies unique expansions in mTOR protein sequences among urodele amphibians, suggesting that these adaptations enable axolotls to maintain a highly sensitive state primed for rapid activation, facilitating efficient tissue regeneration. The findings provide insights into the molecular mechanisms underlying regenerative potential in vertebrates.
3. <https://www.nature.com/articles/489477c> - This article explores how the Mexican axolotl salamander regenerates lost limbs by reprogramming cells in the amputated limb stumps to mimic developing embryonic cells. Researchers found that limb amputation in axolotls triggers the expression of genes PL1 and PL2, which are active in sperm, egg cells, and developing embryos. Suppressing these proteins led to increased cell death and slowed limb growth, suggesting that these genes play a critical role in limb regeneration. The study offers insights into potential strategies for regenerating tissue in humans.
4. <https://www.pnas.org/doi/10.1073/pnas.1300290110> - This research examines the role of macrophages in limb regeneration in axolotls. It reveals that macrophage infiltration is essential for successful limb regeneration, as their depletion during the early stages of regeneration leads to wound closure but permanent failure of limb regrowth, associated with extensive fibrosis. The study highlights the dynamic immune response in axolotls, with simultaneous induction of inflammatory and anti-inflammatory markers within the first 24 hours after limb amputation, underscoring the importance of macrophages in orchestrating the regenerative process.
5. <https://www.mdpi.com/1422-0067/25/22/11904> - This article discusses the regenerative pathways in axolotls, polychaetes, and planarians, focusing on the Wnt/β-catenin, FGF, BMP, and Shh signaling pathways. It highlights how these pathways are essential in the regeneration process, particularly in blastema formation. The study also examines the role of Hox genes in the development and regeneration of axolotls, noting their expression patterns during limb bud development and regeneration. The findings provide insights into the molecular mechanisms underlying regeneration and potential therapeutic targets for human regenerative medicine.
6. <https://elifesciences.org/articles/48511> - This study presents methods for a multiplex CRISPR/Cas9 haploid screen in chimeric axolotls, a novel platform for haploid genetic screening in animals to identify genes essential for limb regeneration. The research demonstrates that limb regeneration in axolotls is a high-fidelity process, with the contributions of small cell populations to the original limb being replicated in the regenerated limb. The findings provide a valuable resource for understanding the genetic basis of limb regeneration and potential applications in regenerative medicine.
7. <https://phys.org/news/2023-07-ultra-sensitive-on-off-axolotls-regrow-limbs.html> - This article discusses research on how an ultra-sensitive on-off switch in axolotls helps them regrow limbs. The study focuses on the mTORC1 pathway and its role in tissue regeneration. Researchers found that axolotls possess a unique variant of the mTOR protein, which allows for rapid activation of protein synthesis in response to injury, facilitating efficient limb regeneration. The findings suggest that understanding this mechanism could lead to advancements in regenerative medicine and improve wound healing in humans.