New genomic tool for salamander biology could spur deeper understanding of tissue regeneration

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A research team led by scientists at Brigham and Women's Hospital has assembled a catalogue of every active gene in a variety of tissues in the axolotl, a type of salamander known for its striking ability to fully regenerate limbs following amputation. The catalogue, known as a "transcriptome," provides a important resource for the community of researchers who study axolotls—a model organism that promises to shed light not only on the molecular mechanisms that underlie limb regeneration but also how on potential ways to repair and replace human tissues that are damaged or lost as a result of injury, illness, or even congenital disorders.

Despite the promise of axolotl research for human regenerative medicine, the genomic resources currently available for axolotls remain quite limited. This is due in part to the large size and highly repetitive nature of the organism's genome—indeed, it is roughly 10 times the size of the human genome. Propelled by recent advances in genomic sequencing and bioinformatics, researchers have found an alternative for identifying and studying axolotl genes: transcriptomes.

"Our hope is that this new resource will help make axolotls accessible not only to researchers who already work on the organism, but also to those in other fields who wish to explore it," said Jessica Whited, PhD, a senior author of the study and an assistant professor in the Department of Orthopedic Surgery at BWH. "Unfortunately, the axolotl has been

largely impenetrable for the majority of scientists." To help accomplish this goal, Whited and her collaborators, led by Brian Haas, Senior Computational Biologist at the Broad Institute, are making their data available through an easily navigable web portal, https://portals.broadinstitute.org/axolotlomics/.

In the last few years, a handful of axolotl transcriptome studies have been published. What distinguishes the latest study is its near-completeness, in terms of represented genes, and its coverage of diverse tissues involved in limb regeneration, including bone and cartilage, skeletal muscle, heart, and blood vessels. The researchers also included different portions of the blastema, a cluster of cells that forms shortly after limb amputation and directs the formation of a complete new limb.

In addition to developing this valuable resource, Whited and her colleagues also mined it to uncover important axolotl genes and investigate the genes' potential functions. One interesting gene is kazald1, which is very highly enriched in blastema cells. Although it has been identified in mammals and has even been found in certain types of tumors, virtually nothing is known about kazald1's function.

Because of the axolotl's relatively long generation time—it takes 9 months for a newly-fertilized embryo to develop, grow, and become sexually mature— traditional methods for deleting genes to understand their effects are labor-intensive and daunting at large scale. Therefore, the study's first author, graduate student Donald Bryant, developed an innovative approach to modify, or "edit" genes solely in the axolotl limb. Although the efficiency of the method needs to be improved, future work in this area could help accelerate efforts to elucidate the functions of scores of axolotl genes and, in turn, help reveal the molecular steps required for limb regeneration.

More information: Bryant DM et al. "A tissue-mapped axolotl de

novo transcriptome enables identification of limb regeneration factors." *Cell Reports*. DOI: 10.1016/j.celrep.2016.12.063

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