By cutting out one gene, researchers remove a tadpole's ability to regenerate

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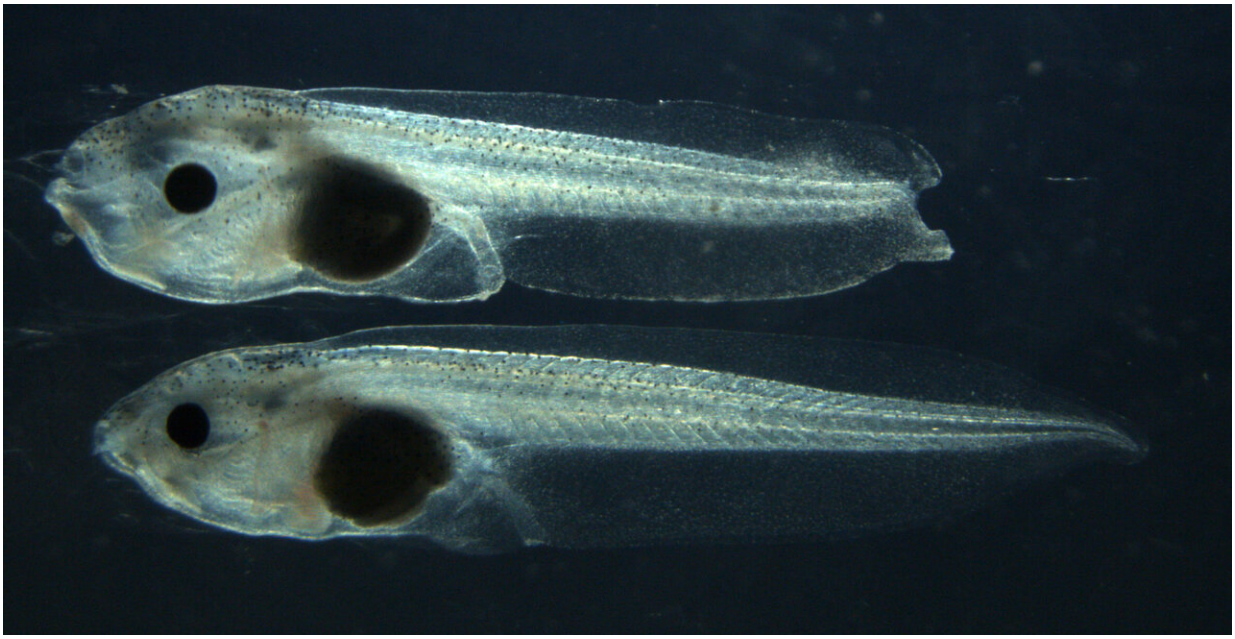


This picture shows how c-Answer inhibits tail regeneration after amputation in Xenopus tadpoles (top: c-Answer, bottom: control) Credit: Andrey G. Zaraisky and Daria D. Korotkova

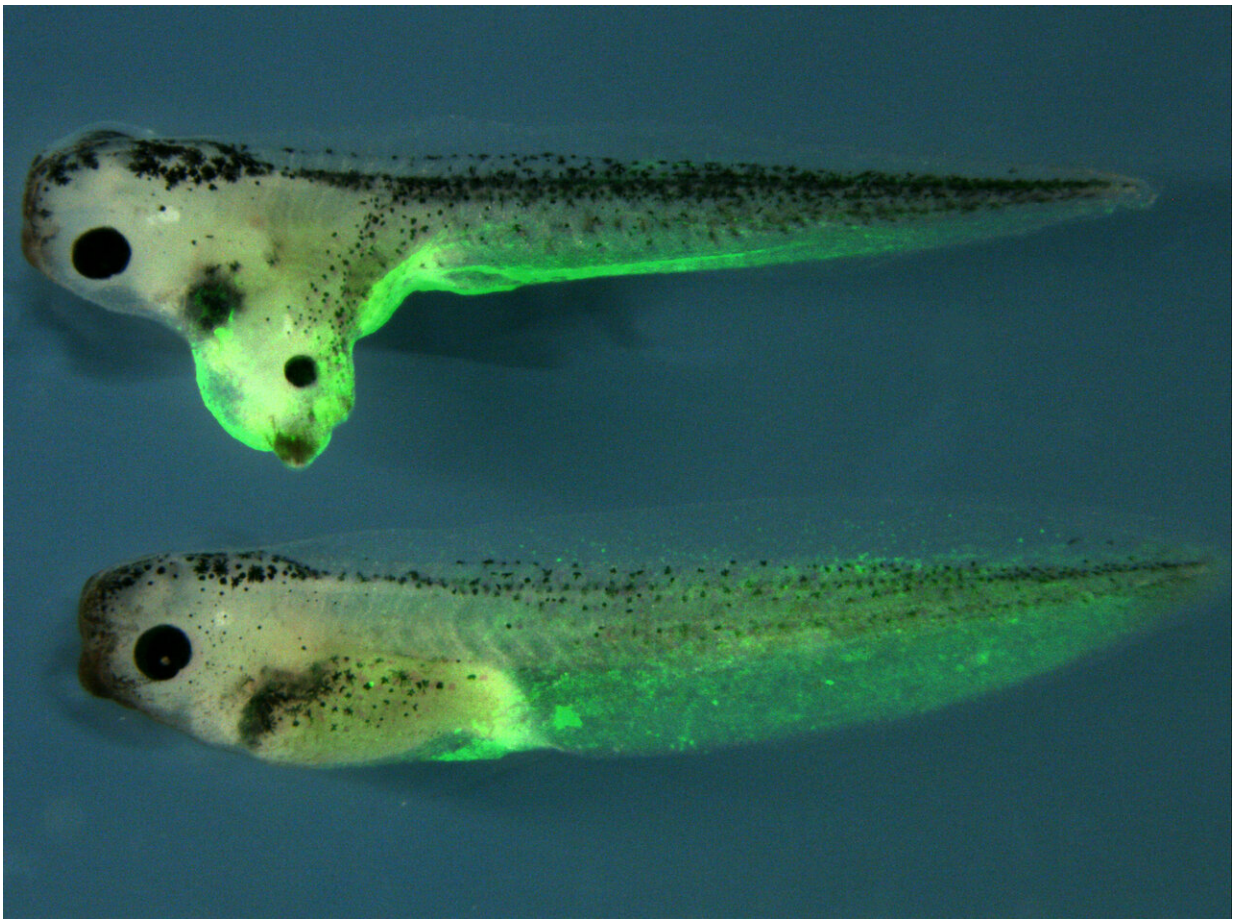
Tadpoles of frogs that can typically regrow amputated tails or limbs lost their ability to regenerate after researchers blocked the expression of a newly identified gene that is one of the drivers for this regrowth. Furthermore, scientists hypothesize that the loss of appendage regeneration in warm-blooded animals might have been caused by the

gain or loss of this gene, dubbed c-Answer, in an ancestor's genome during evolution. The work appears October 22 in the journal *Cell Reports*.

"We suppose that genes can only disappear if removing them has advantages for the animal," says first author Daria Korotkova of the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry in Moscow. "So, we suggest that when this gene disappeared from warm-blooded species it was by a mutation, acting as a trade-off for the loss of appendage regeneration."

Using a computer algorithm, the researchers identified several genes that disappeared in the genomes of warm-blooded vertebrates, including humans, but are present in cold-blooded ones. They did this by searching the DNA of African clawed frogs, *Xenopus laevis*, to determine which genes code for regeneration. They then looked for similar DNA patterns in warm-blooded species, such as chicks, and noted anywhere a gene differed. They then selected one of the identified cold-blooded specific genes, encoding for previously unknown transmembrane protein, and named it c-Answer (cold-blooded animals specific wound epithelium receptor-like).

The research team, including Korotkova, Andrey Zaraisky, Vassily Lyubetsky, Anastasiya Ivanova, Lev Rubanov, Alexander Seliverstov, Oleg Zverkov, Natalia Martynova, Alexey Nesterenko, Maria Tereshina, and Leonid Peshkin, then overexpressed or blocked c-Answer in tadpole embryos. They discovered that enhancing c-Answer allowed tadpoles to regenerate lost tails earlier in their life than those that hatched naturally, whereas tadpoles with c-Answer blocked could transition into frogs but could not regenerate amputated appendages.



This picture shows how c-Answer over expression induces formation of ectopic head with the forebrain and cyclopic eye. (Overlay: green fluorescence serves as a tracer that shows the distribution of the injected material (c-answer mRNA) Credit: Andrey G. Zaraisky and Daria D. Korotkova

"C-Answer modulates at least two important molecular pathways that are common to all vertebrates," says senior author Zaraisky, head of the laboratory of molecular bases of embryogenesis at the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry. "Its loss in evolution might alter the functioning of these pathways and, accordingly, lead to major physiological transformations."

"We also found that over expression of c-Answer causes advanced brain growth and larger eyes, which surprised us, since it means c-Answer modulates for regeneration and brain development," says Korotkova. "However, it was observed that when c-Answer is blocked, *Xenopus laevis* tadpoles had smaller brains, so there is still work to be done in order to better understand this relationship."

More information: Daria D. Korotkova et al, Bioinformatics Screening of Genes Specific for Well-Regenerating Vertebrates Reveals c-answer, a Regulator of Brain Development and Regeneration, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.09.038

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