

Novel gene in red blood cells may help adult newts regenerate limbs

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Japanese fire-bellied newt. Credit: University of Tsukuba

Newts are the only four-legged vertebrates that can regenerate their body

parts, even as adults. When a newt loses a limb, a mass of cells called a blastema is generated at the stump, from which a new, fully functional limb is eventually regenerated. Can this remarkable ability be explained by genes shared by vertebrates, including humans, or by unique genes that the newt may have evolved?

In a study published in *Scientific Reports*, researchers at several Japanese universities, including the University of Tsukuba, and the University of Dayton, report the discovery of a novel gene, *Newtic1*, from the blastema of an adult newt. This gene is expressed in a subset of red [blood](#) cells and may contribute to limb regeneration in adult newts. Red blood cells, or erythrocytes, function to deliver oxygen around an animal's body. Unlike the other cells in the mammalian body, the erythrocytes lack nuclei, allowing them to carry more oxygen and squeeze into fine [blood vessels](#). In the newt and most other non-mammalian species, however, these cells contain a nucleus. Other than oxygen delivery, the function of these nucleated cells is unknown. This study provides, for the first time, an insight into the roles of these nucleated cells.

In the study, the researchers constructed a database of all the protein-coding genes from the Japanese fire-bellied newt that had been reported in the Japan newt research community. This database contained DNA sequence information of genes from 19 different tissues, including different regenerating organs and limb blastemas. To identify genes related to limb regeneration, they used statistical analyses to look for genes whose expression was increased in association with the formation of the limb blastema. From 694,138 sequences, they found 105,464 expressed in the limb blastema. Further screening of these sequences resulted in the identification of a single gene which was named *Newtic1*. Its existence in newt tissues was confirmed using both DNA- and protein-based methods. Similar genes exist in axolotl and another newt species, but not in any other species. "*Newtic1* is an 'orphan' gene, as it has no

recognizable equivalent in distantly related species," says co-author Fubito Toyama, of Utsunomiya University. "This makes it hard to predict its function."

To understand its function, the researchers investigated where and when the Newtic1 protein is expressed in the newt. They used Newtic1-specific antibodies to look at the expression of Newtic1 in the blastema and in blood. They found that Newtic1 is specifically expressed in a subset of erythrocytes, the premature [red blood cells](#) (termed "PcNobs"). The gene is expressed in some, but not all, the PcNob cells. In normal adult newts, clumps of PcNobs expressing Newtic1 were found in the blood vessels and veins. These clumps were named the erythrocyte clump, EryC. The researchers then analyzed the expression of Newtic1 during adult newt limb regeneration. EryCs were newly generated in the stump region following wound closure five days after the amputation of the forelimb in the middle of the forearm and their number increased with the formation of the blastema. The EryCs were transported from the stump region to the blastema through regenerating blood vessels/capillaries that extend from the stump to the blastema. As the digits appeared in the regenerating forearm, the number of EryCs decreased.

By looking at the expression of Newtic1 in larval newt tissues and limb blastemas, the researchers determined that Newtic1-expressing erythrocytes do not contribute to the limb blastema in the larval stage. "The contribution of EryCs to the limb blastema, at least in this species, is specific to the terrestrial adult life-stage," concludes co-author Chikafumi Chiba, a professor at the University of Tsukuba.

The researchers suspected that PcNobs contained actively expressing genes, so they examined gene expression in normal blood. The results suggested the expression of many [genes](#) encoding secretory molecules, including growth factors and matrix metalloproteases. Most of the

secretory molecules identified are known to be involved in the development and remodeling of blood vessels, events also involved in limb regeneration. The expression of two of the identified growth factors, for which the reagents were available (TGFβ1 and BMP2), was confirmed in purified PcNobs and EryCs.

Expression of TGFβ1 and BMP2 in regenerating limbs shows that EryCs appear to release these factors into the regenerating blood vessels and capillaries as they enter the growing blastema. "Our hypothesis is that EryCs may work toward the regeneration of blood vessels and capillaries," says lead author Roman Casco-Robles, a Ph.D. candidate at the University of Tsukuba.

"Our findings show, for the first time, the complex behavior of nucleated erythrocytes in normal blood and during [limb regeneration](#)," says Chikafumi Chiba. "Our results suggest that PcNobs, a dominant nucleated erythrocyte in circulating blood, carry various secretory molecules throughout the body."

While the unique regenerative ability of the [newt](#) cannot be explained completely by the presence of the *Newtic1* gene, its discovery has helped identify PcNobs and EryCs as likely candidates that provide important molecules to an injured region or to the emerging blastema of a [limb](#). These findings may provide insight into wound healing, tissue regeneration and repair in other animal species.

More information: Roman M. Casco-Robles et al, Novel erythrocyte clumps revealed by an orphan gene *Newtic1* in circulating blood and regenerating limbs of the adult newt, *Scientific Reports* (2018). [DOI: 10.1038/s41598-018-25867-x](https://doi.org/10.1038/s41598-018-25867-x)

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