TISSUE REGENERATION

Mechanical waves help zebrafish regrow their tails

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Regenerative animals accurately regrow lost appendages. Now research suggests that mechanical waves propagating from the amputation edge play a key role in this process.

Animals such as lizards, salamanders, and zebrafish regenerate lost tails, limbs and fins. This ability has fascinated broad audiences for centuries, prompting extensive investigation into the underlying mechanisms[1]. Although many of the genetic and biochemical factors involved have been identified, how physical interactions between cells affect tissue reconstruction is less understood. Now, writing in *Nature Physics*, Marco P. De Leon and co-workers reported that mechanical signalling around the wound edge enables the precise regrowth of amputated zebrafish tailfin[2].

When an appendage of a regenerative animal is amputated, the lost portion is accurately reconstructed. For example, zebrafish fins can precisely regenerate the correct structure given a particular amputation position (Fig. 1). However, it is not yet fully understood[1] how the regenerating tissues sense where the fin was cut off.

There are two stages in the regeneration process. During the wound healing stage, the cut is re-sealed by the epithelium. Then, the lost structures, such as bones and muscles, are rebuilt.

During the first phase, epithelial cells around the amputation edge collectively migrate into the wound. *In vitro* studies have shown that physical forces play an important role in the coordination of the movement of multiple cells[3,4]. However, the dynamics and functions of collective cell migration *in vivo* are less understood.

De Leon and co-workers analysed the collective migration of epithelial cells during the wound healing stage of zebrafish tailfin regeneration. Their live imaging revealed that immediately after amputation, epithelial cells located within approximately 100 μm from the amputation edge started to migrate into the wound. They were then closely followed by the cells behind them[2]. Thus, the changes in cell motility propagated as 'mechanical waves' in the epithelium starting from the edge of the wound. Similar waves of collective cell migration were previously observed *in vitro*, either by tracking single cells[5] or by computationally highlighting cell mobilisation with the 'white wave' method[6], which was also used by De Leon and co-workers' *in vivo* assay[2].

The *in vivo* analysis of collective cell migration showed that the more proximal, i.e., closer to the trunk, the amputation position was, the further the mechanical waves propagated (Fig. 1)[2]. The authors designed a mathematical model that explained the wave behaviour in terms of tissue tension and recapitulated *in vivo* results. Moreover, when tissue tension was experimentally

altered, cell migration waves changed as the model predicted. Hydrogen peroxide (H_2O_2) was identified as a regulator of the mechanical waves. The more proximal the amputation level was, the more H_2O_2 was produced by the wound tissue (Fig. 1). On the other hand, damping H_2O_2 production reduced the distance of mechanical wave propagation and slowed down fin regeneration.

Based on these results, the authors proposed the following mechanism: H_2O_2 triggered the mechanical waves; the level of H_2O_2 was dependent on amputation position and determined the distance of mechanical wave propagation, which in turn dictated the rate of subsequent tissue regeneration.

It is technically challenging to test the specific effects of tissue mechanics and H_2O_2 on tissue regeneration. Nevertheless, the mathematical modelling results and multiple lines of correlative evidence helped to support the authors' hypothesis. Future work could test whether an increase of the H_2O_2 signal and/or mechanical wave propagation causes excess regeneration.

The authors speculated that the same physical signalling may be at work in other regenerative animals and in embryonic gastrulation, and could perhaps be exploited in medicine[2]. One interesting question is whether this mechanism also regulates regeneration in other organs such as the heart or the brain[7]. It would also be intriguing to investigate how the mechanical signal interacts with known biochemical signals regulating collective cell migration, wound healing, and tissue regeneration, such as those mediated by the ERK1/2 MAP kinase, calcium ions, and retinoic acid[1,8,9].

By applying knowledge and methods from *in vitro* collective cell migration studies [3,4,6], De Leon and co-workers shed light on the role of mechanical signalling in tissue regeneration *in vivo*, which could open a new avenue in regenerative biology research.

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Competing interests

The author declares no competing interests.

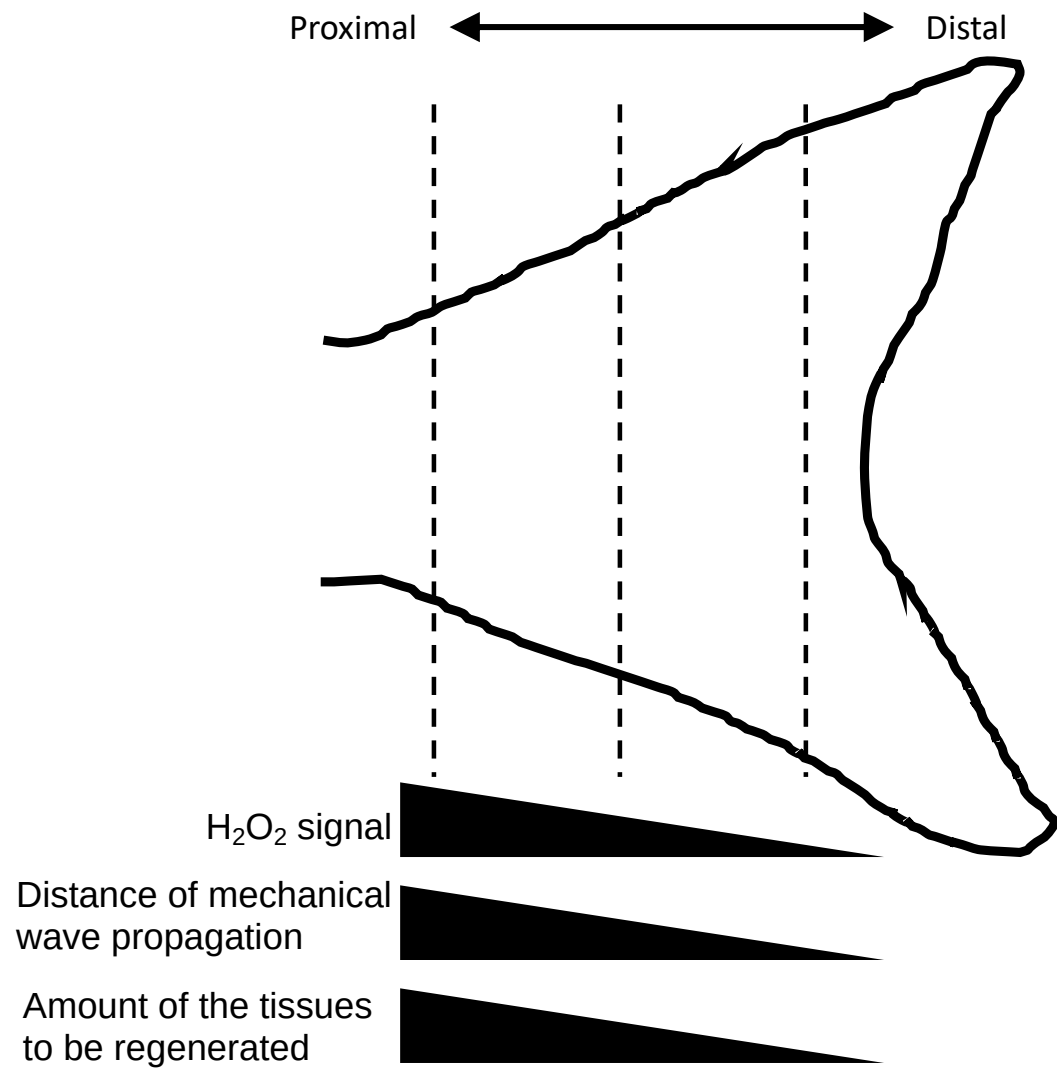

Fig.1: H_2O_2 signalling and the mechanical wave of collective cell migration during zebrafish tailfin regeneration.
Schematic of the regeneration process. The zebrafish tailfin cut off at different levels (dashed lines) precisely regenerates the structure. The more proximal the cut, the more H_2O_2 is produced, the further the mechanical waves of collective cell migration propagate, and the more tissues are regenerated.