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Building a biophysical blueprint for appendage regeneration

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Most human tissues, including the CNS, limbs, and the heart, do not regenerate in response to acute injury. In contrast, amphibians such as frogs can re-grow entire organs, including the tadpole tail and limbs. To understand this dichotomy and develop successful repair therapies for humans, a detailed knowledge of natural regeneration is required. After tail amputation, *Xenopus* tadpoles form a regeneration bud containing stem cells at the injury site. By 7 days, a new tail is re-grown—complete with spinal cord, nerves, vasculature, and muscle. We identified a novel role for voltage-gated sodium channel (NaV)-mediated sodium current in organ repair. While NaVs are known for propagating action potentials in excitable cells, NaV is also required in non-excitable cells to initiate and drive organ regeneration. Expressed early after tail amputation, NaV1.2 induces a strong intracellular Na^+ increase specifically at the injury site. Abolishment of this Na^+ flux blocks regeneration by inhibiting proliferation, altering axonal patterning, and suppressing the downstream genes (Notch and Msx1) that drive regenerative outgrowth. NaV1.2 is absent in non-regenerative conditions, suggesting that this biophysical signal may be harnessed to improve regenerative ability. Indeed, ectopic expression of hNaV1.5 restored regeneration. Demonstrating that Na^+ ions are sufficient to drive regeneration, a transient induction of a 1-hour Na^+ current after the formation of a non-regenerative, scar-like wound epidermis ably restored full regeneration. This reveals that non-regenerative states can be reprogrammed by bioelectrical modulation without molecular technology. In summary, our data demonstrate that non-regenerative tissues may retain an intrinsic repair program that can be activated by relatively simple biophysical signals. Thus the modulation of ion currents is an exciting new strategy for mammalian organ repair.

Biography

Kelly Tseng received her Ph.D. in Genetics from Harvard University and performed her postdoctoral studies on organ regeneration with Dr. Mark T. Keating at Children's Hospital Boston and then with Dr. Michael Levin at Harvard School of Dental Medicine/Forsyth Institute (now at Tufts University). She is an Assistant Professor in the School of Life Sciences at the University of Nevada Las Vegas.

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