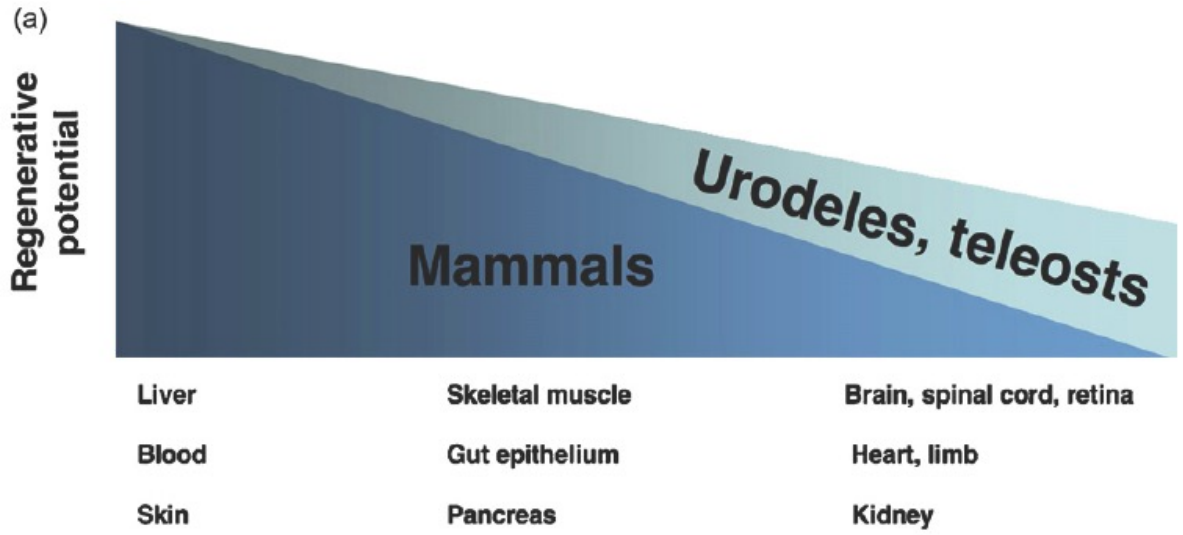
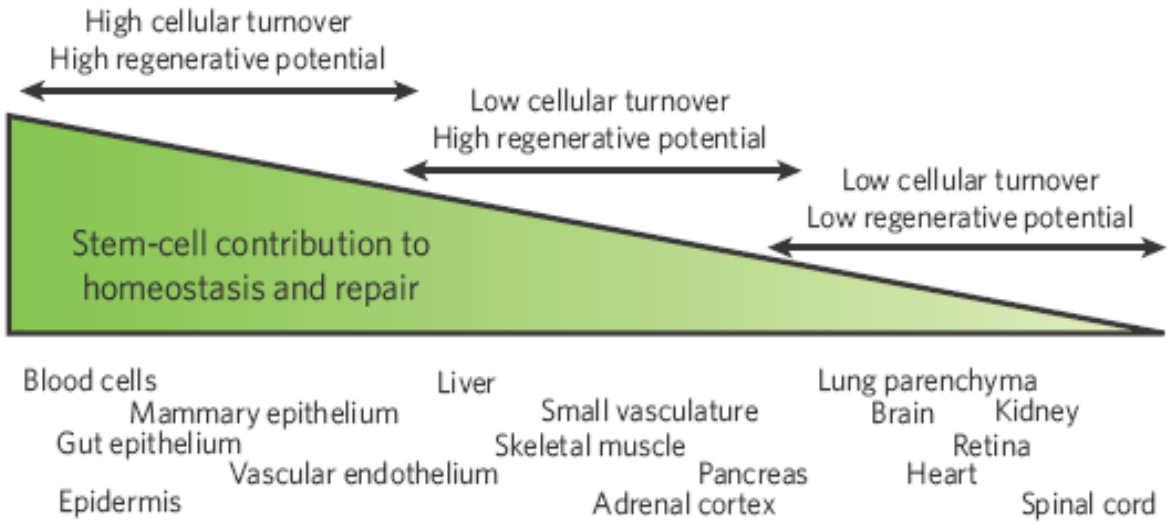
How do species other than mammals regenerate organs?



Species or group	Regenerative capabilities	Microarray	Transgenesis	Knockout/knock down	Genome sequenced
Invertebrates					
Hydra	All tissues and organs	No	Yes	RNAi	No
Planarians	All tissues (neurons, muscles, epithelia) and organs (brain, sensory organs, digestive system, musculature)	Yes	No	RNAi	Yes
Ascidians	All tissues and organs	Yes	Yes	Morpholinos	Yes
Vertebrates					
Newts	Limbs, tail, heart, lens, spinal cord, brain, jaw, retina, hair cells of the inner ear	Yes	Yes	Morpholinos	No
Axolotls	Limbs, tails, heart, spinal cord, brain	Yes	Yes	Morpholinos	No
Frogs	Pre-metamorphic limbs, tail, retina, lens, hair cells of the inner ear	Yes	Yes	Morpholinos	Yes
Zebrafish	Fins, tail, heart, liver, spinal cord, hair cells of inner ear, lateral line	Yes	Yes	Mutagenesis, morpholinos	Yes
Chicks	Hair cell of the inner ear	Yes	Yes	Morpholinos	Yes
Mice	Liver, digit tips	Yes	Yes	Mutagenesis, homologous recombination	Yes

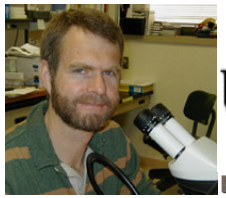
Tissue heterogeneity and stem-cell functionality for homeostasis and repair



The extent to which the effects of ageing on the resident stem cells determine the phenotype of an aged tissue is likely to correlate with the extent to which stem cells are responsible for normal tissue homeostasis and repair. Along this spectrum, tissues generally fall into one of three categories.

1. Tissues with high turnover (such as blood, skin and gut) have a prominent stem-cell compartment and, by definition, have high regenerative capacity.
2. Tissues with low turnover but high regenerative potential might use different strategies to ensure effective repair in the setting of acute injury.
3. Tissues with low turnover and low regenerative potential might have stem cells that mediate only limited tissue repair. Although there has been much interest in harnessing the potential of stem cells in the brain and heart for therapeutic purposes, for example, there is limited endogenous repair capacity of these tissues following acute injuries.

In Urodeles Amphibians:



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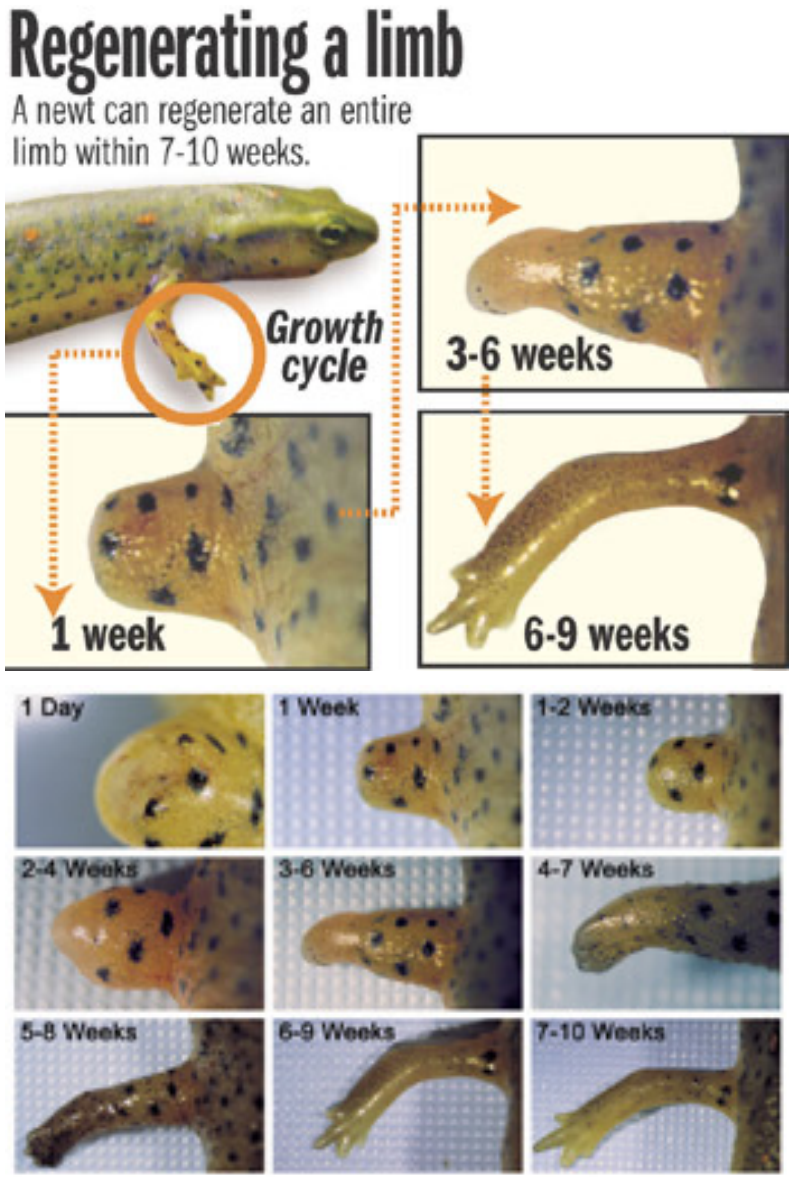
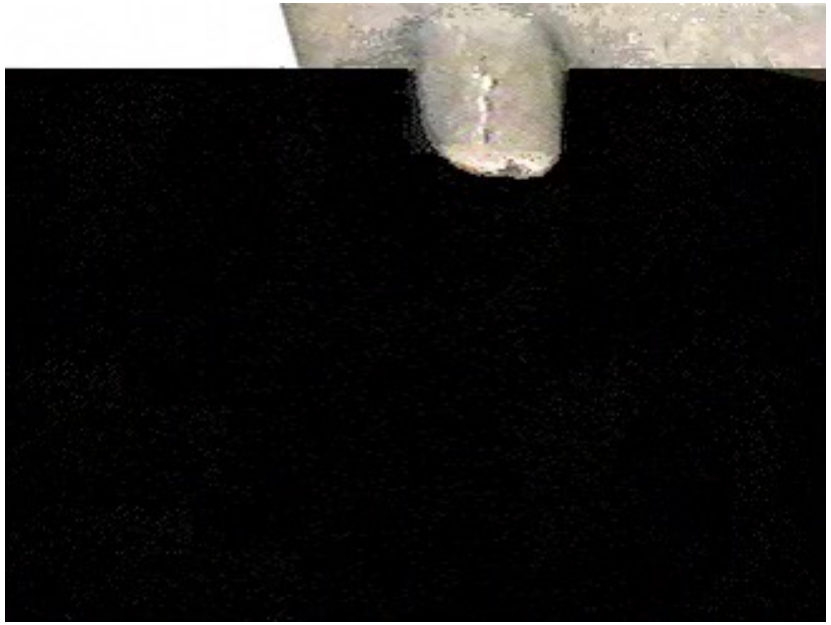


Regenerative potential of *Ambystoma mexicanum* (Axolotl)

Regenerative potential of *Ambystoma mexicanum* (Axolotl)



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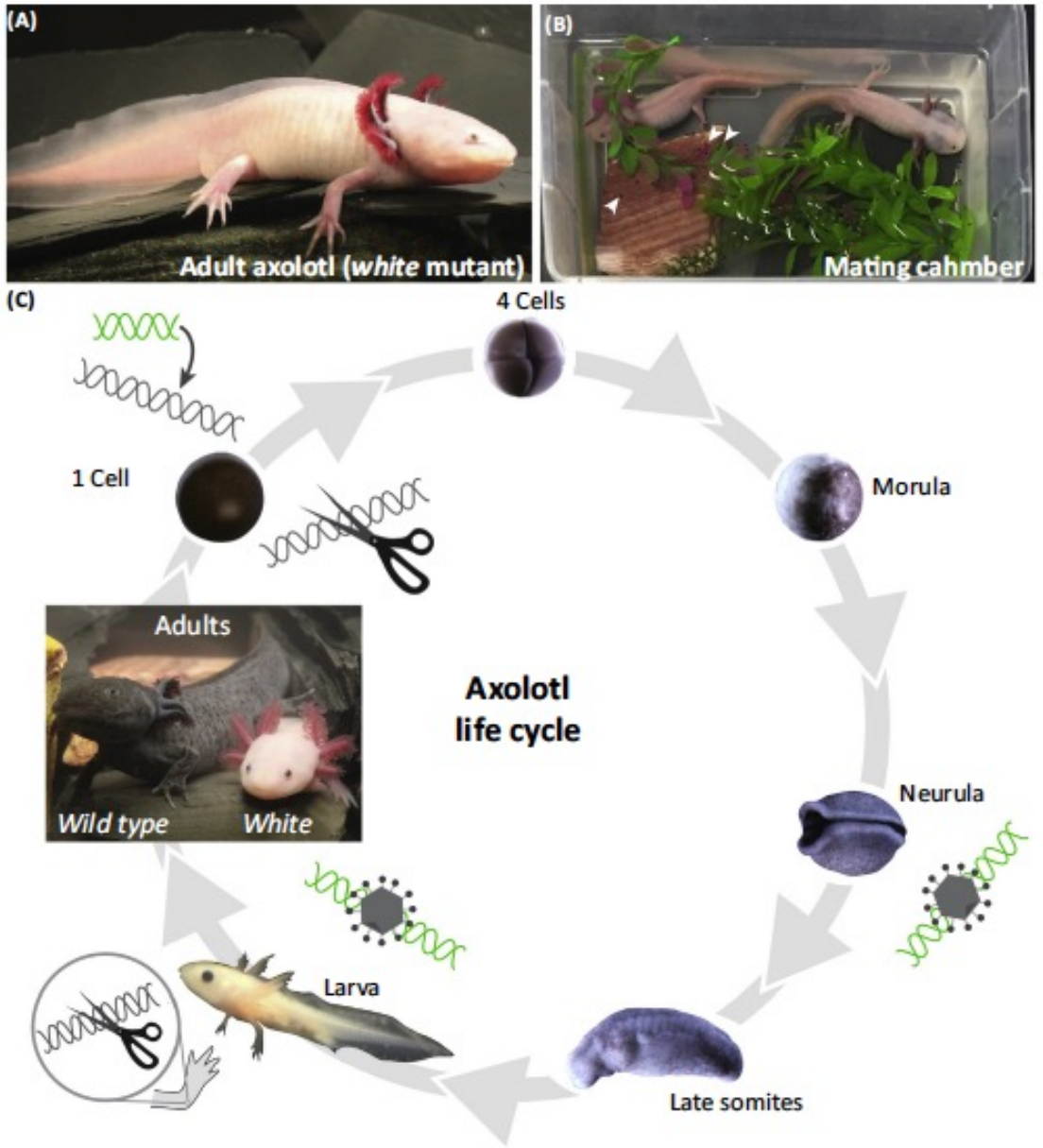
Trends in Genetics, August 2017, Vol. 33, No. 8

Review

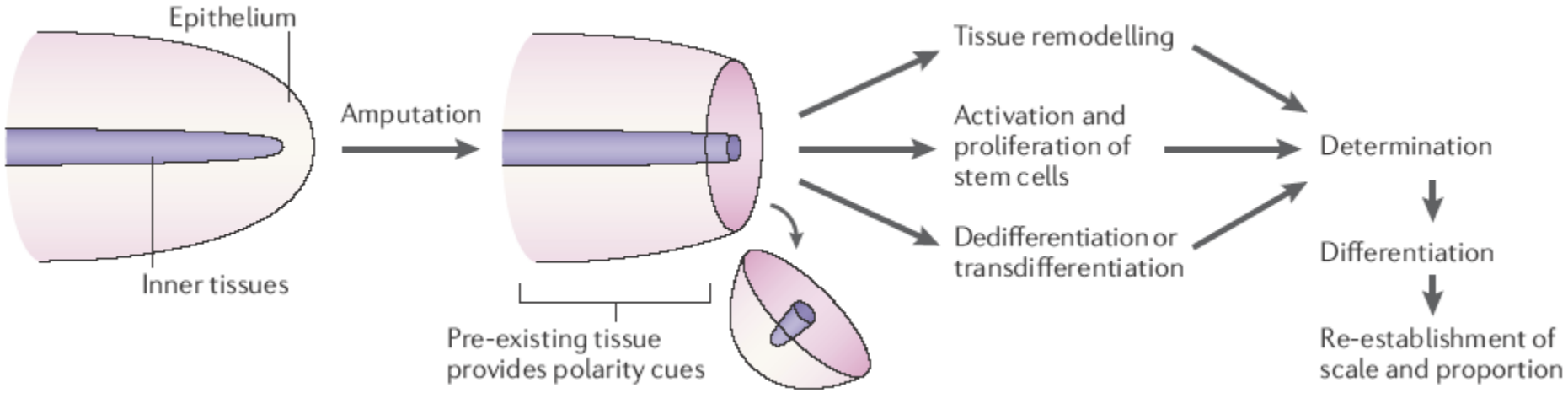
CellPress

Advances in Decoding Axolotl Limb Regeneration

Brian J. Haas[1,*] and Jessica L. Whited[2,*]



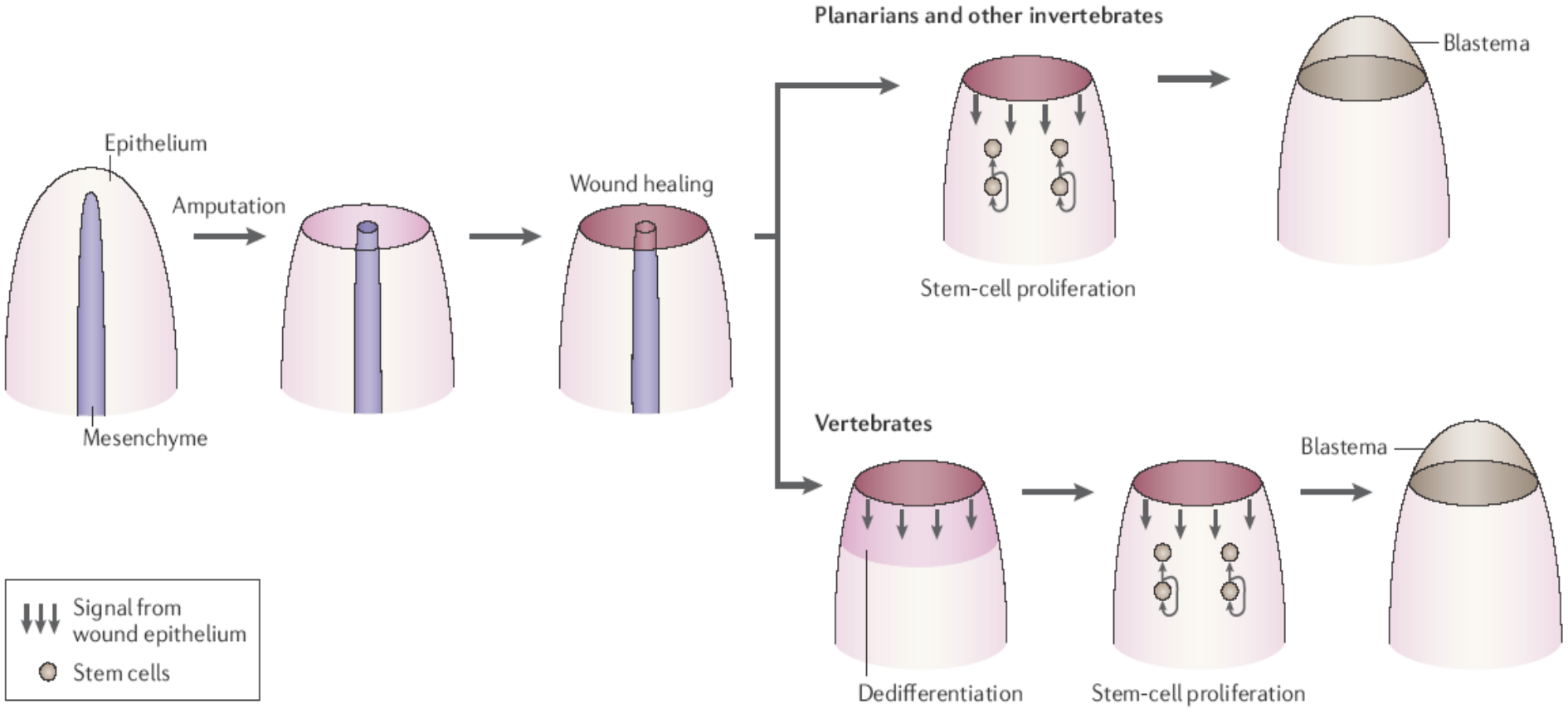
Basic mechanisms of regeneration.



After amputation, wound healing occurs. After wound healing three processes can be activated, either independently or together.

- **Hydra** undergo remodelling of pre-existing tissues to regenerate amputated parts.
- **Planarians** undergo both tissue remodelling and proliferation of resident adult somatic stem cells
- In **Vertebrates**, both stem-cell proliferation and the dedifferentiation of the cells that lie adjacent to the plane of amputation take place. The cells that respond to the stimulus of amputation eventually undergo determination and differentiation, resulting in new tissues that must then functionally integrate with and scale to the size of the pre-existing tissues.

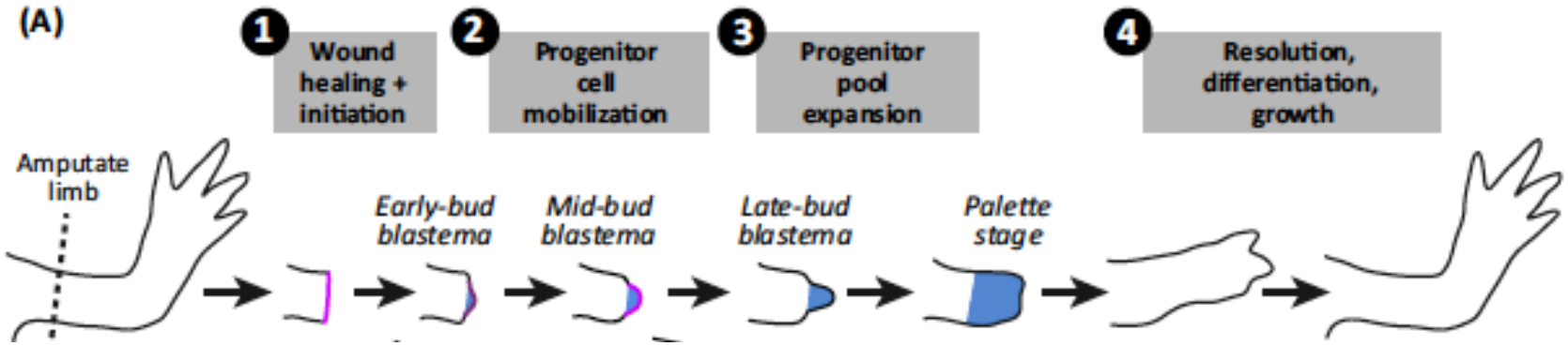
Basic steps in the formation of **blastema** in vertebrates and invertebrates.



In **Vertebrates**, there is evidence that both stem cells and cell-dedifferentiation processes have a role in blastema-mediated regeneration.

In **Invertebrates** such as planarians, stem-cell proliferation seems to have a pivotal role.

Outline of Cellular Events During Limb Regeneration



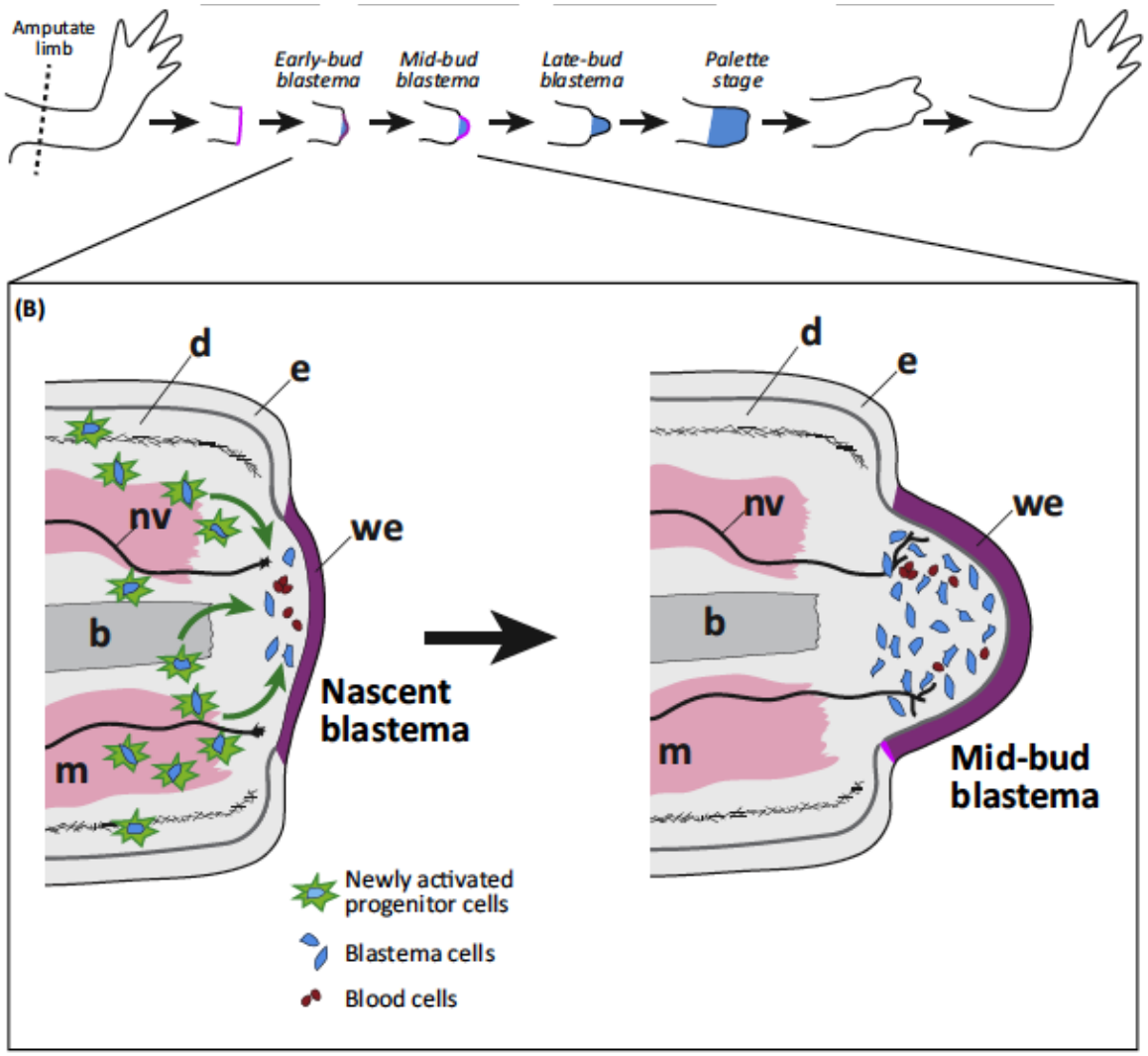
General progression from unamputated to fully regenerated.

(1) Immediately following amputation (within 24 h), a thin wound epidermis (magenta) forms across the cut stump via migration of stump epidermal cells. The wound epidermis thickens as cells within it proliferate.

(2) A visible bump, termed a blastema (blue), forms beneath the wound epidermis. Blastema cells are derived from activated progenitor cells within various stump tissues that migrate to the tip.

(3) Blastema cells proliferate to expand the progenitor pool.

(4) The initial regeneration response resolves, cells begin to undergo differentiation, and the limb continues to grow to the appropriate size



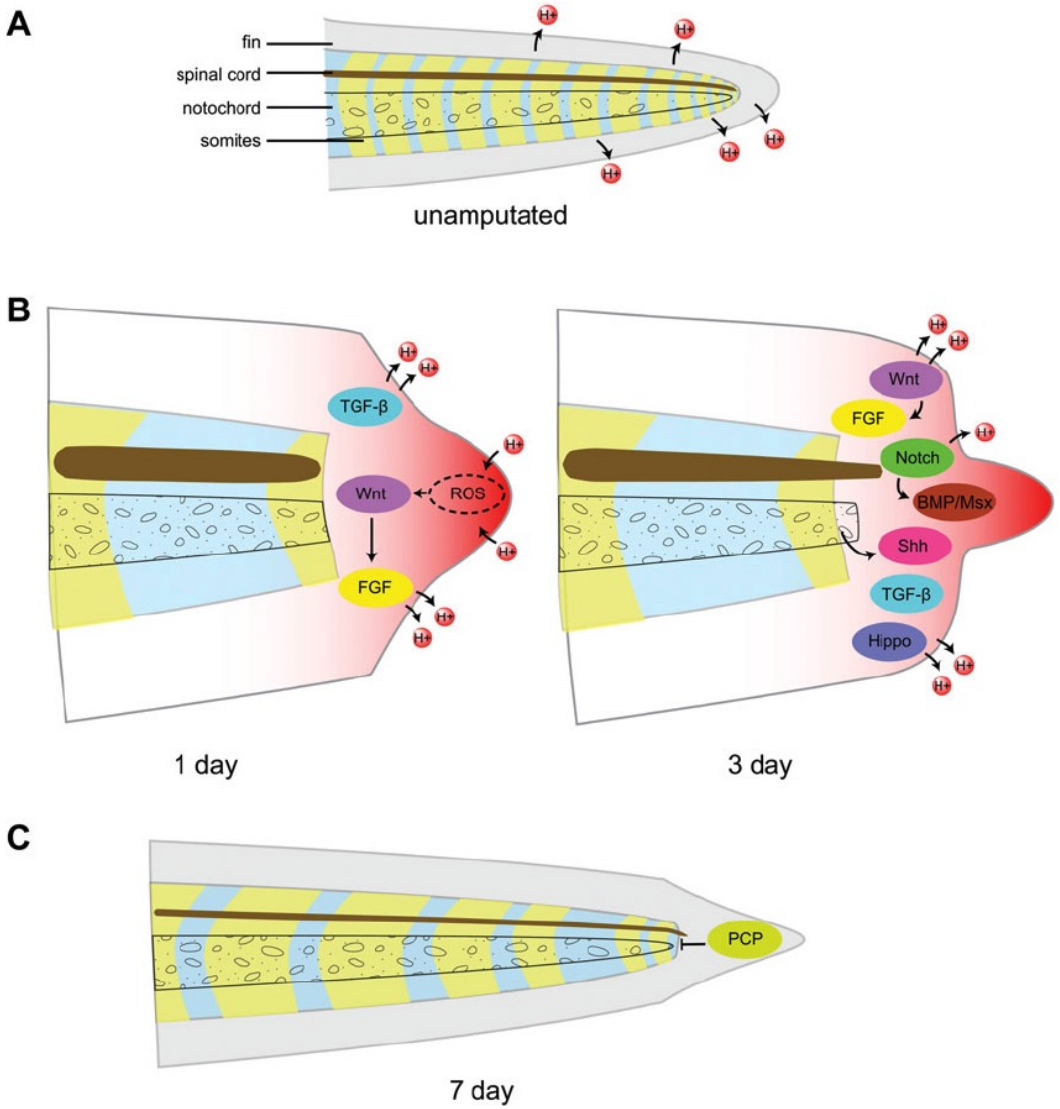
(B) Architectures of tissues such as bone and muscle are locally deconstructed near the amputation plane and are therefore shown as jagged. Newly activated progenitor cells, which give rise to future blastema cells, are cued to re-enter the cell cycle and some fraction of them presumably migrate to the space immediately below the wound epidermis. Blood cells, both red and white, are intermingled with blastema cells.

Received: 22 August 2016 | Revised: 9 September 2016 | Accepted: 12 September 2016
DOI: 10.1002/reg2.69

REVIEW

WILEY Regeneration Open Access

The cellular and molecular mechanisms of tissue repair and regeneration as revealed by studies in *Xenopus*



Stages of tadpole tail regeneration.

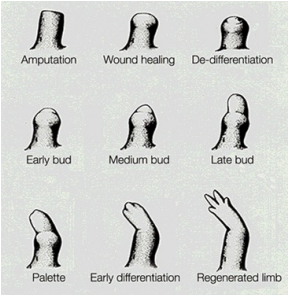
A *Xenopus* tadpole tail is composed of a number of axial structures including the spinal cord, notochord, and somites.

An unamputated tail is in a polarized state, sustained by V-ATPase pumps in the skin.
After amputation, wounded tail is depolarized and simultaneously reactive oxygen species (ROS) are produced at the amputation site.
Downstream targets of the ROS include Wnt, FGF, Shh, TGF-β, BMP, Notch, and Hippo pathways. V-ATPases are also upregulated at this stage to repolarize the skin.
A fully functional tail is regenerated 7 days after amputation.

Limb Regeneration:
A New Development?

Eugen Nacu and Elly M. Tanaka

DFG-Center for Regenerative Therapies Dresden, Technische Universität Dresden, and Max Planck Institute of Molecular Cell Biology and Genetics, 01307 Dresden, Germany; email: eugeniu.nacu@crt-dresden.de, elly.tanaka@crt-dresden.de

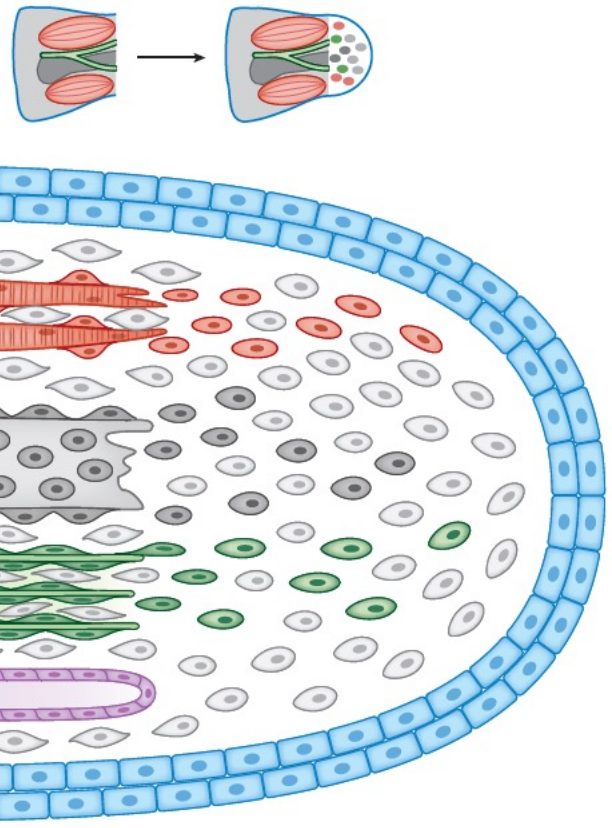


After amputation, cartilage, connective tissue and muscle cells loose their differentiated characteristics and form a blastema.

Blastema: a mesenchymal growth zone that undergo proliferation, differentiation and morphogenesis to regenerate the limb

Does blastema formation involve cellular dedifferentiation or activation of quiescent stem cells?

Cellular dedifferentiation does appear to occur during newt limb blastema formation together with stem cells proliferation.



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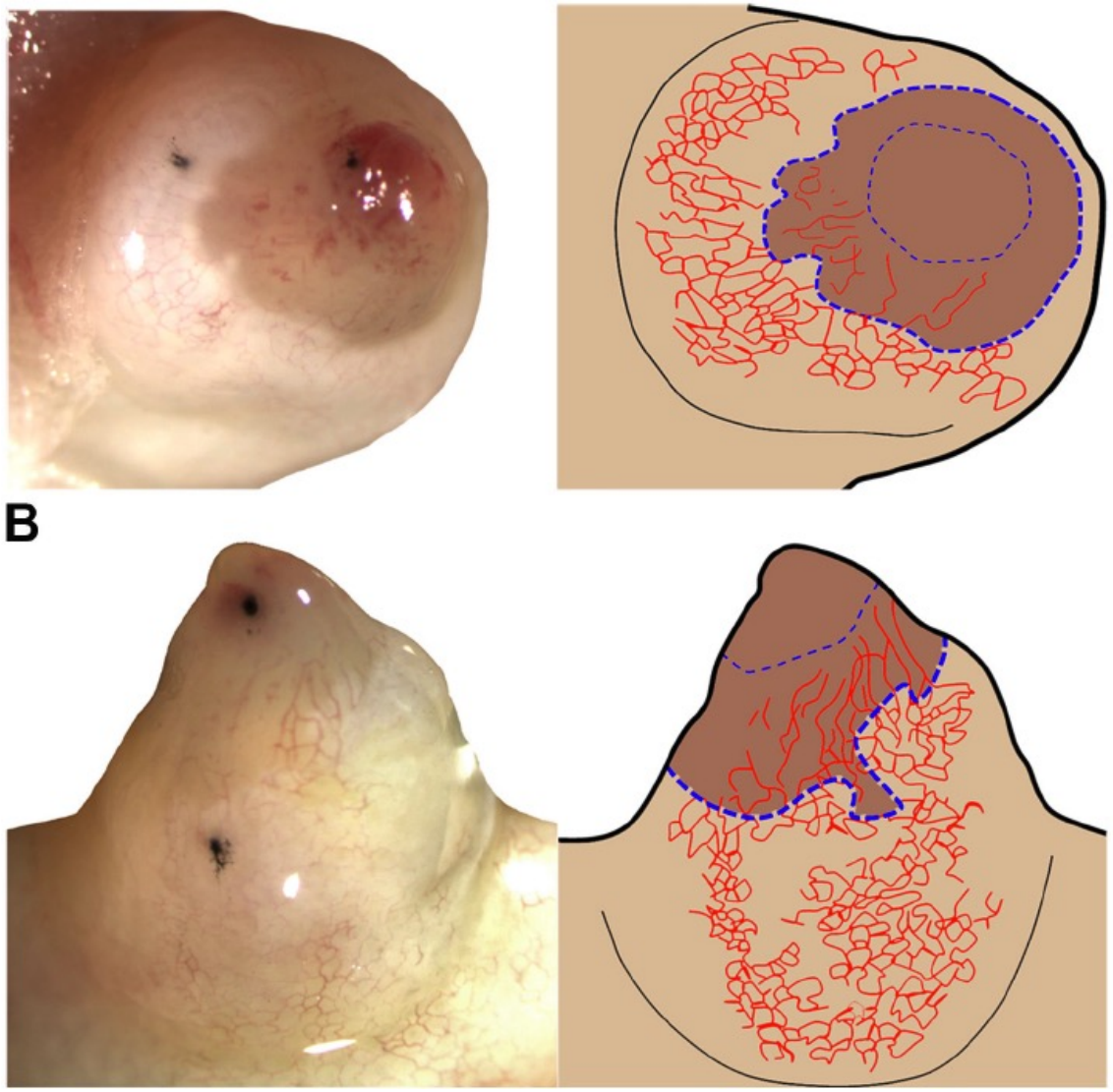
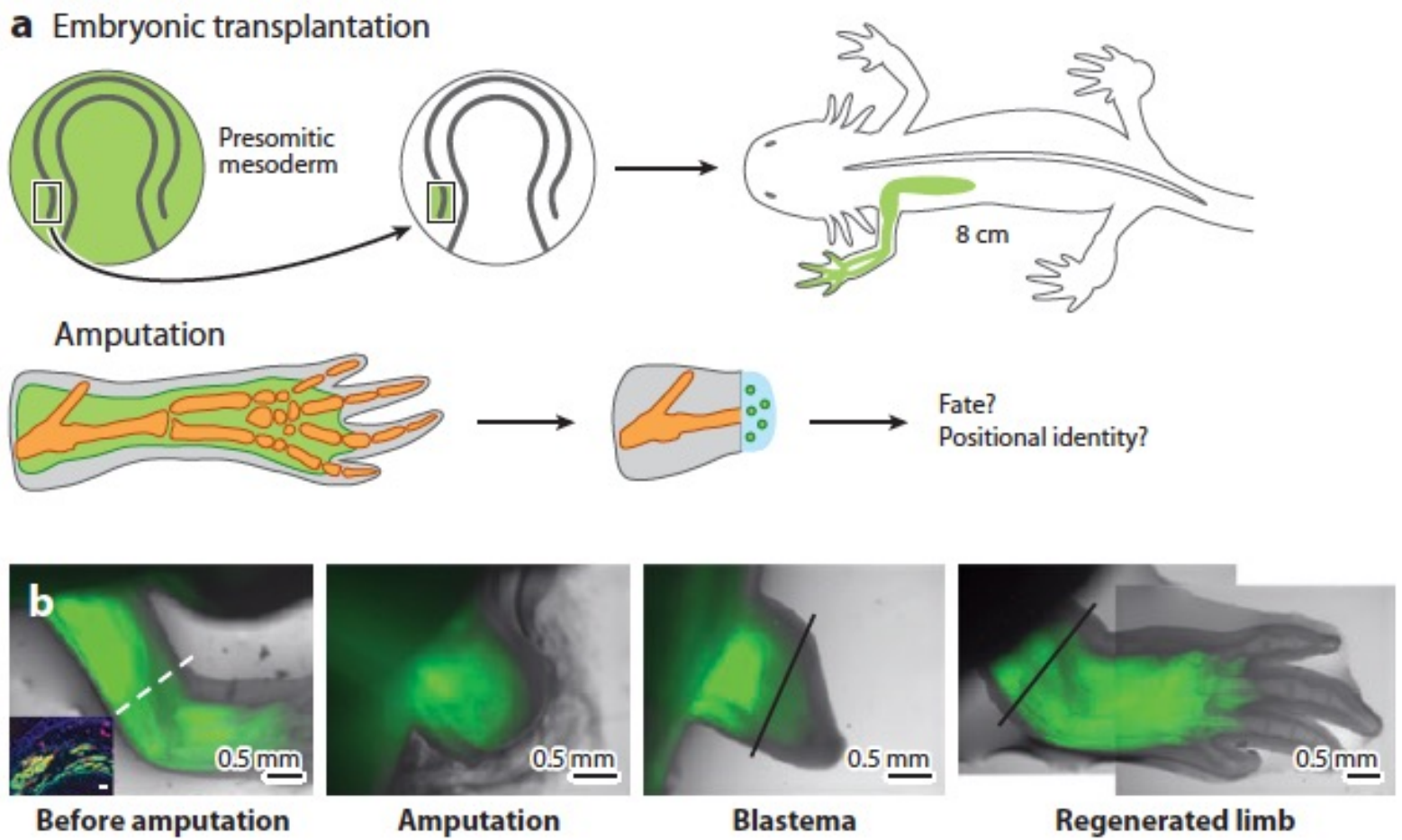
September 2013 | Volume 8 | Issue 9 | e77064 PLOS ONE

Positional Information Is Reprogrammed in Blastema Cells of the Regenerating Limb of the Axolotl (*Ambystoma mexicanum*)

Catherine D. McCusker, David M. Gardiner*



Early bud (EB) blastema (A) and a late bud (LB) blastema (B).



Cells remain restricted to their lineage during axolotl limb regeneration.

(a) Muscle cells, muscle fibers, and satellite cells were labeled by transplanting presomitic mesoderm from transgenic embryos that constitutively express GFP into nontransgenic embryos. Limbs with GFP muscle cells were amputated, and the fate of the muscle cells was followed.
(b) Regeneration of limbs with GFP muscle cells.

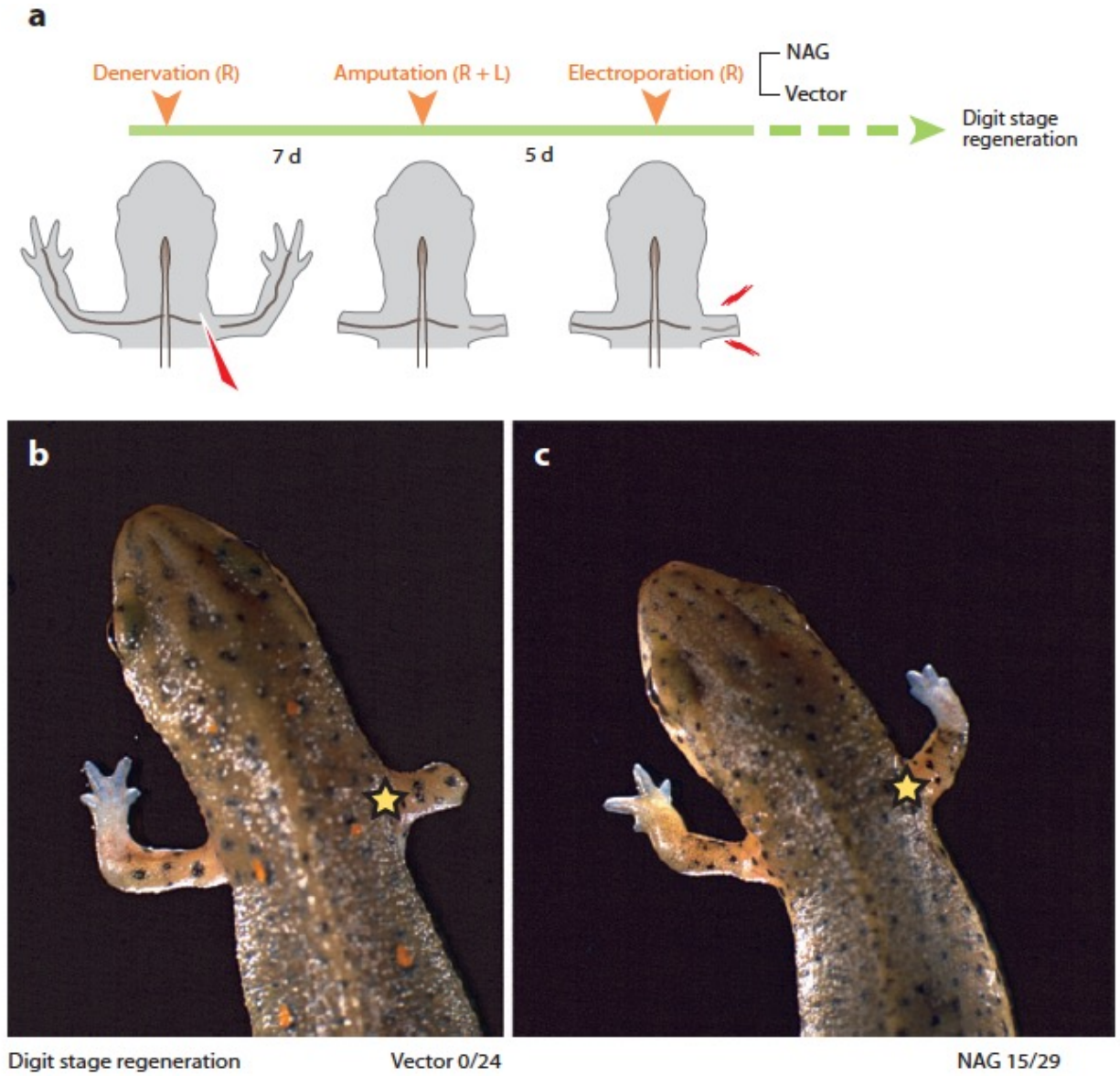
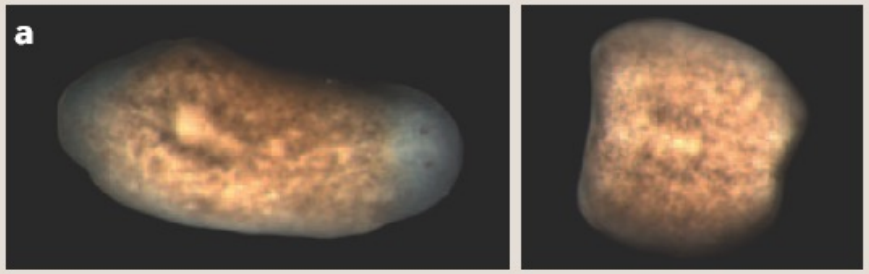


Figure 13

The role of nerves and newt anterior gradient (NAG) in regeneration. (*a*,*b*) A limb that is denervated prior to amputation will not regenerate. (*a*,*c*) The regeneration of the denervated limb is rescued by NAG electroporation after amputation. (*b*,*c*) Stars mark the denervated limbs, and the numbers below the animals show the number of denervated limbs that regenerated out of the total denervated limbs after electroporation of the vector plasmid (control) or NAG. Redrawn from Kumar et al. (2007) with permission from AAAS.

Common signaling pathways inducing regeneration

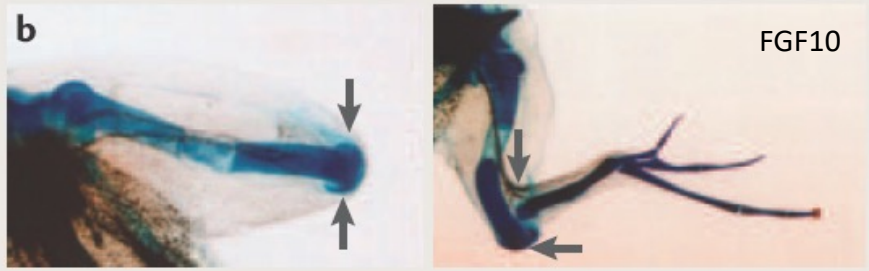
Planaria

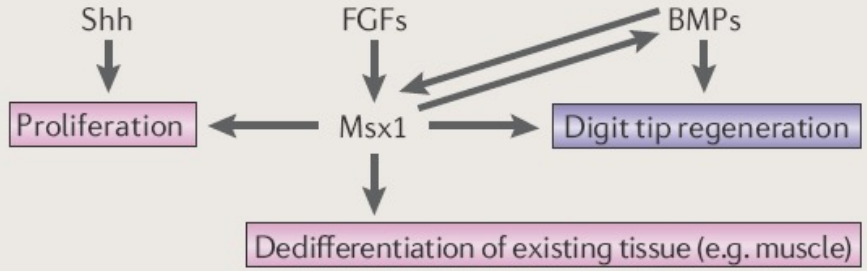


TGFB → TGFBR (?) → SMAD4 → Blastema formation

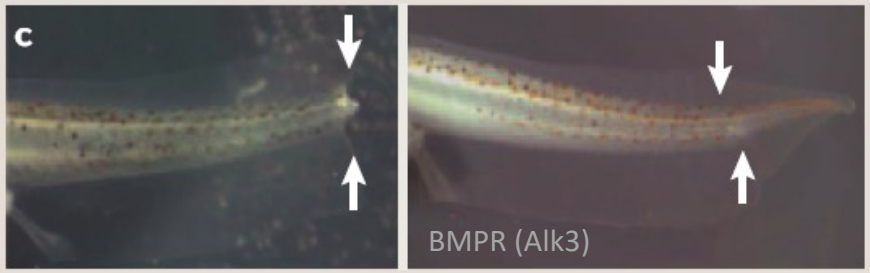
Cephalic and caudal regeneration in planarians is inhibited by the abrogation of the TGF-β pathway (silencing the expression of smad4)

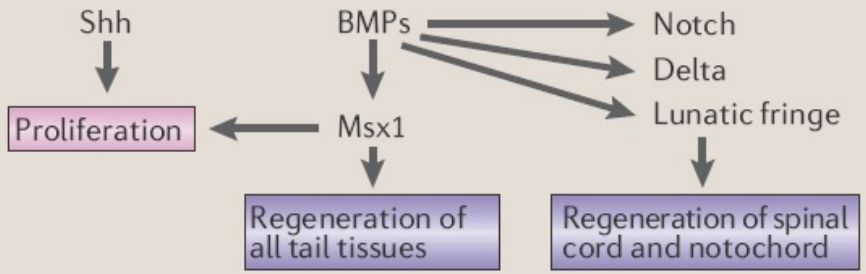
Newt





Zebrafish





Major signaling pathways involved in cellular differentiation are extensively conserved!

Signalling pathway	Species or group		
	Hydra magnipapillata	*Schmidtea mediterranea*	Vertebrates
TGFB	Yes	Yes	Yes
Notch	Yes	Yes	Yes
Wingless	Yes	Yes	Yes
Hedgehog	Yes	Yes	Yes
JAK/STAT	Unknown	Yes	Yes
EGF receptor	Yes	Yes	Yes
FGF receptor	Yes	Yes	Yes
Toll/NFκB	Unknown	Yes	Yes

After amputation, cartilage, connective tissue and muscle cells loose their differentiated characteristics and form a blastema.

Blastema: a mesenchymal growth zone that undergo proliferation, differentiation and morphogenesis to regenerate the limb

Does blastema formation involve cellular dedifferentiation or activation of quiescent stem cells?

Cellular dedifferentiation does appear to occur during newt limb blastema formation together with stem cells proliferation.

Transcription factors msxb and msxc are induced during blastema formation. These data are intriguing, as they are candidates for inducing dedifferentiation in mammalian cells and/or maintaining cells in undifferentiated state.

Limb Regeneration:
A New Development?

Eugen Nacu and Elly M. Tanaka

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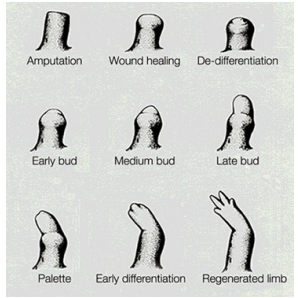
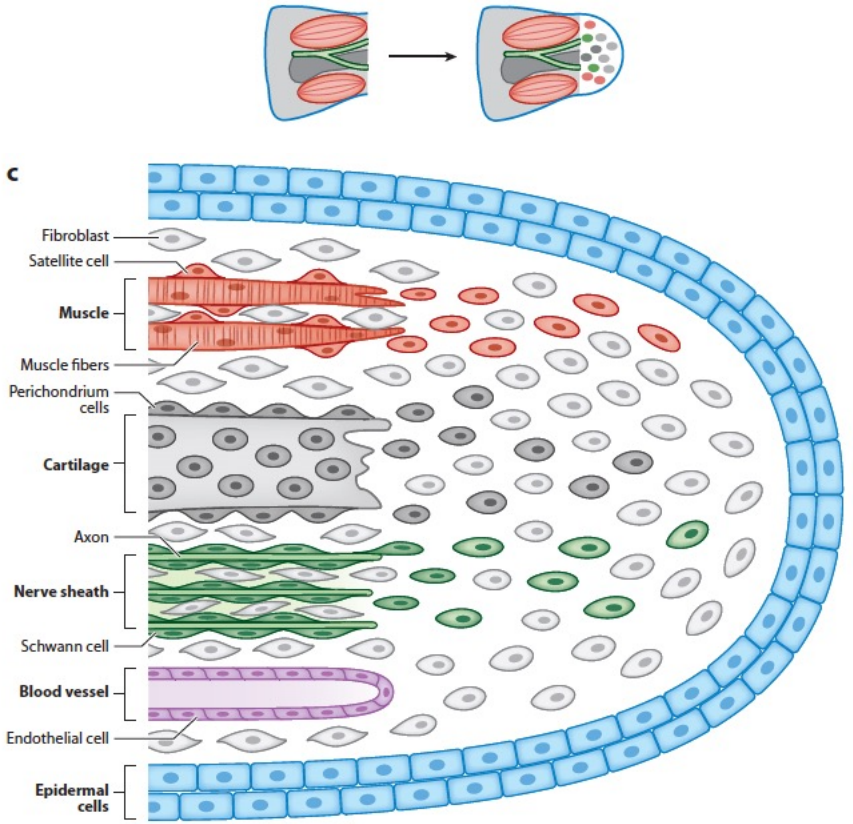
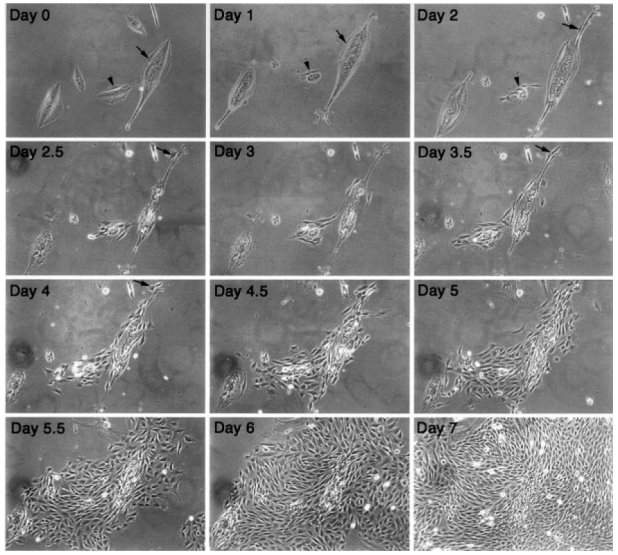


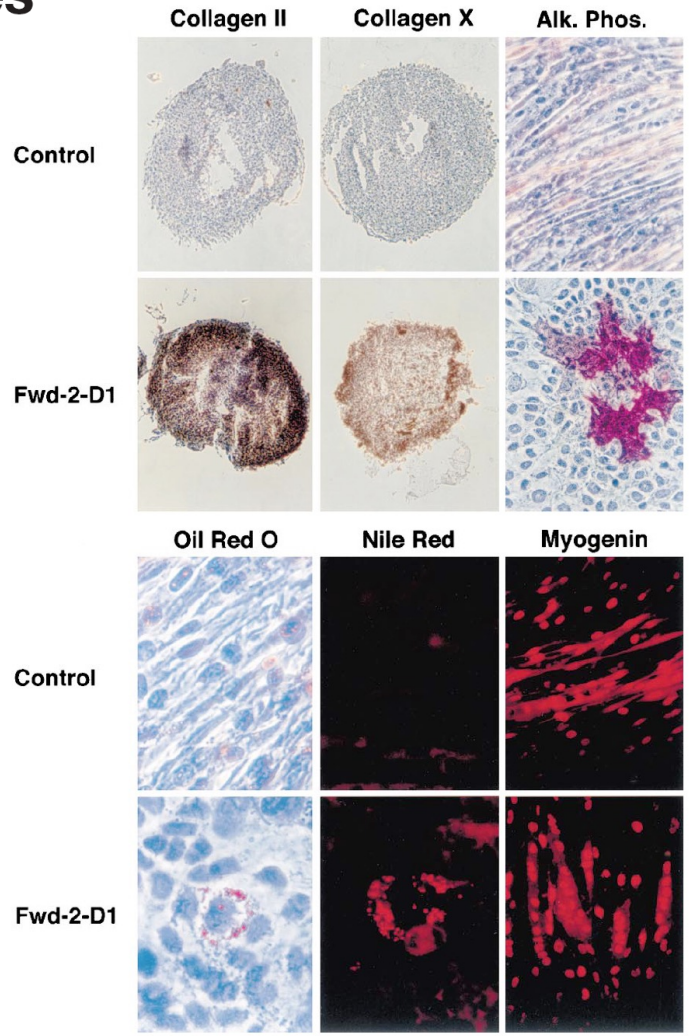


Cell, Vol. 103, 1099–1109, December 22, 2000, Copyright ©2000 by Cell Press

Dedifferentiation of Mammalian Myotubes Induced by msx1

Shannon J. Odelberg,*§‖ Angela Kollhoff,† and Mark T. Keating*†‡‖#
*Division of Cardiology, Department of Internal Medicine





Mononucleated cells from dedifferentiated myotubes exhibit signs of pluripotency (subjected to chondrogenic, osteogenic, adipogenic, and myogenic inducing signals)

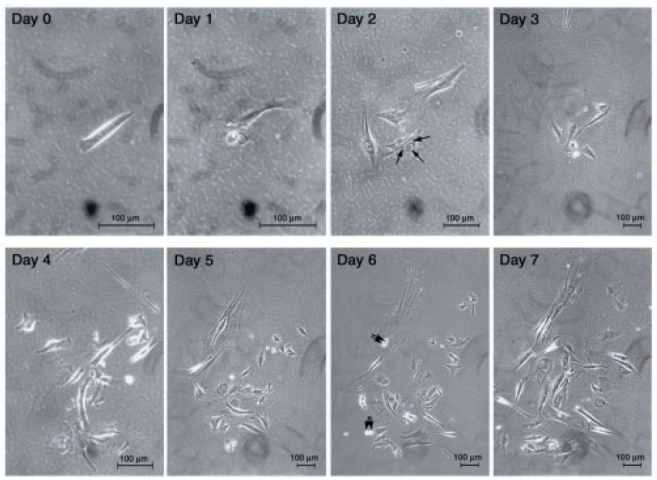
Mammalian cells might maintain the pathways required to respond to the proper “pro-regeneration” signals

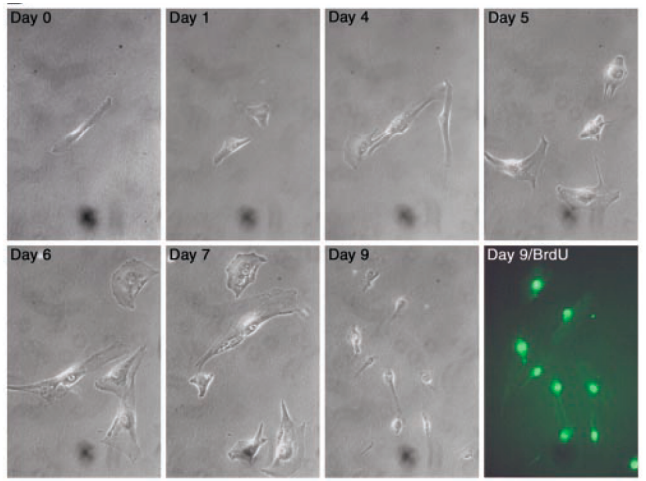
Several factors could explain the absence of cellular dedifferentiation in mammals:

1. The extracellular factors that initiate dedifferentiation are not adequately expressed following amputation
2. The intrinsic cellular signaling pathways for dedifferentiation are absent
3. Differentiation factors are irreversibly expressed in mammalian cells
4. Structural characteristics of mammalian cells make dedifferentiation impossible

Mammalian myotube dedifferentiation induced by newt regeneration extract

Christopher J. McGann*†, Shannon J. Odelberg*†‡, and Mark T. Keating‡§¶||





Mammalian cells retain the intracellular signaling pathways required for dedifferentiation, suggesting that mammals fail to exhibit *in vivo* cellular dedifferentiation because they lack the signals (proteins!) that initiate the process

PNAS | November 20, 2001 | vol. 98 | no. 24 | 13699–13704