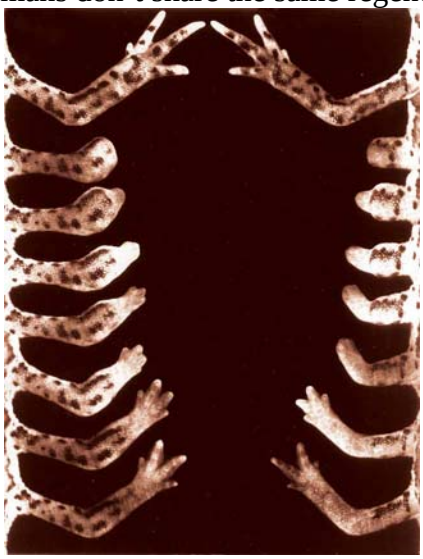
Regeneration - lessons from a salamander

Overview

Mammals possess an efficient but limited regeneration potential, depending on the tissue or organ that is damaged. Even though there are extraordinary examples of mammalian regeneration, they pale in comparison to the abilities displayed by the salamander. Salamanders, belonging to the Urodele amphibian phylum, are capable of regenerating many different body parts. Probably the most incredible is the regeneration of a functional limb. Mammalian regeneration usually relies on tissue specific stem/precursor cells for the repopulation of key tissues. However, most examples of regeneration in these salamanders result from the derivation of precursor cells via the dedifferentiation of terminally differentiated cells. Recent research suggests that tissue specific stem cells, homologous to cells found in mammals, may also contribute to the regeneration process. This begs the question that if mammals share the same cellular compartments as salamanders, why is it that humans don't share the same regenerative abilities?

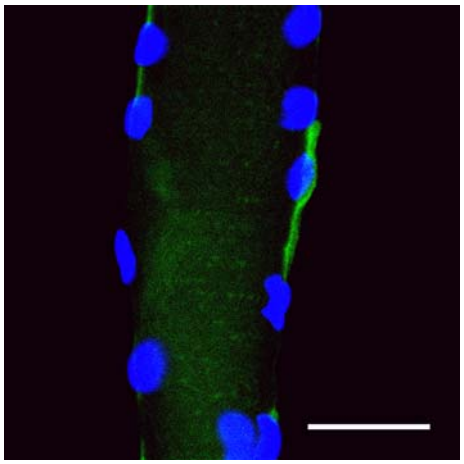


Picture courtesy of How Salamanders Sprout New Limbs (LiveScience 2007-11-01)

Aims

The main aims of my research are to decipher the molecular and cellular properties of salamander heart and limb regeneration.

Limb regeneration studies: Limb regeneration proceeds via the formation of a mesenchymal growth mass known as the blastema. The contribution of different cellular structures to the blastema, like myogenic satellite cells, remains poorly characterized. I intend to focus on the involvement of the skeletal muscle and satellite cells during limb regeneration with the premise of discovering whether muscle or muscle precursor cells give rise to muscle solely, or whether they possess a multipotent plasticity that allows them to contribute to other cells types.



M-cadherin labeled satellite cell on
a newt myofibre

Heart regeneration studies: By contrast with mammals, urodele amphibians display an elevated regenerative capacity in the heart. Previous research has postulated that cardiomyocytes dedifferentiate, proliferate and repopulate a damaged heart. However, even though these salamander studies demonstrated a proliferative response in the cardiomyocytes after injury, it remains unknown as to whether these cells originated from cellular dedifferentiation or from an existing or injury-activated reserve. Recent research in both mammals and zebrafish suggests that cardiac progenitor cells do exist and may have a function in cardiac myocyte turnover in both normal and damaged hearts. I intend to characterize the involvement of the different cell types responsible for heart regeneration in the salamander, with the hope of finding precursor/stem cells comparable to those already described in mammals.

Publications

- **Morrison, J**, Lööf, S, He, P, Aleström, P, Collas, P and Simon, A (2007). Targeted gene delivery to differentiated skeletal muscle; a tool to study dedifferentiation. *Developmental Dynamics*. Vol. 236(2): 481-488.
- **Morrison, J**, Lööf, S, He, P and Simon, A (2006). Salamander limb regeneration involves the activation of a multipotent skeletal muscle satellite cell population. *Journal of Cell Biology*. Vol. 172 (3): 433-440.
- **Morrison, J**, Palmer, D, Cobbold, S, Partridge, T and Bou-Gharios, G (2005). Effects of T lymphocyte depletion on muscle fibrosis in the *mdx* mouse. *American Journal of Pathology*. Vol. 166(6): 1701-1710.
- **Morrison, J**, Partridge, T and Bou-Gharios, G (2005). Nude Mutation Influences Limb Skeletal Muscle Development. *Matrix Biology*. Vol. 23(8): 535-542.
- **Morrison, J**, Lu, Q, Pastoret, C, Partridge, T and Bou-Gharios, G (2000). T-Cell-Dependent Fibrosis in the mdx Dystrophic Mouse. *Laboratory Investigation.* Vol. 80(6): 881-891.

Courses/Examensarbeten

Projects:
Several projects are available to study the regeneration in salamanders.

1. The role of progenitor cells in salamander heart regeneration. The student will be involved with developing a functional heart regeneration model in the salamanders, along with the identification and characterization of the cellular compartments responsible for regeneration.

2. The contribution of skeletal muscle and satellite cells (myogenic precursor cells) to the regenerated tissue of the limb. The student will be involved with developing *ex vivo* experiments to label and lineage-trace myogenic cells, in order to follow them during different regenerative phases in the limb.

3. The pluripotency of blastema cells. The student will be involved with developing a blastema explant cell-culture technique to use as a model system, with a view for using this model to look for specific markers of pluripotency.

All three projects will require a close working relationship with the salamanders, with various surgical techniques needing to be learnt. Along with the *in vivo* studies, techniques such as cell culture, cDNA cloning, PCR, immunohistochemistry and FACS will be some of the techniques commonly used.

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