How to grow a new limb

Salamanders are commonly used as regeneration models because they can grow new limbs after amputation. At the amputation site, a clump of undifferentiated progenitor cells called the blastema forms and then regenerates the missing tissues. A fully formed limb is comprised of multiple tissue types (including dermis, muscle, nerve and skeletal elements) that must coordinate in order for the limb to function properly. How the blastema is formed from these distinct tissue types and then goes on to regenerate them is not well understood, but new research from Elly Tanaka and colleagues (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany) is starting to clarify this complex process.

Previous work led many scientists to believe that blastema cells are pluripotent, or capable of differentiating into any type of cell. To establish this as fact, however, the different limb cell types would need to be tagged and then tracked during blastema formation and eventual limb regeneration. Tanaka's group developed a

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method of labeling different limb tissues in the axolotl (*Ambystoma mexicanum*, a member of the salamander group) with green fluorescent protein in order to monitor the tissues during limb regeneration. They found that each tissue type produced progenitor cells with restricted potential; cells kept a 'memory' of their tissue origin and were not pluripotent (*Nature* **460**, 60–65; 2009). Dermis was the most plastic of the tissues tested and formed both cartilage and tendons, but not muscle, in addition to dermis. On the other hand, muscle and

Schwann progenitor cells formed only muscle and Schwann cells, respectively, despite going through the blastema stage.

These results led to the conclusion that the blastema is a heterogeneous group of restricted progenitor cells rather than a homogeneous group of pluripotent cells. This means that limb regeneration in the axolotl occurs without complete de-differentiation of cells to a pluripotent state. In addition, the work suggests that, in terms of tissue specificity, blastema cells are similar to limb bud progenitors, the embryonic cells that go on to form limbs during vertebrate development. It isn't known yet how salamander cells at the site of amputation restart this normally embryonic program of tissue formation. Future research will examine gene activation and expression during regeneration in order to help clarify the molecular signals that control blastema cells and trigger the regeneration process. Tanaka believes that such research may lead to the possibility of limb regeneration in mammals.

Monica Harrington

MINICELLS MITIGATE TUMOR GROWTH

To develop therapies that stop the spread of cancer, researchers face a host of challenges, ranging from drug-resistant cancer cells to dangerously toxic drugs. To try to overcome drug resistance, researchers have harnessed a natural phenomenon called RNA interference to silence, or destroy, specific RNA in cancer cells. For example, researchers can use a small interfering RNA (siRNA) to silence a gene responsible for chemotherapy resistance. Although scientists have found several promising strategies for delivering siRNAs into cancer cells, several challenges still remain.

Now, researchers have created a new technique for delivering both gene silencing agents and cytotoxic drugs to cancer cells (*Nat. Biotechnol.* published online 28 June 2009; doi:10.1038/nbt.1547). When tested in animals with cancer, this treatment method has been particularly effective at halting tumor growth and, in some cases, even eliminating tumors altogether.

Himanshu Brahmbhatt of EnGeneIC (Sydney, Australia) and colleagues used bacteria to create lifeless minicells, each of which is about 1/250th the width of a human hair. The team loaded the minicells with either a gene silencing agent or a cytotoxic drug. To direct the minicells to cancer, the researchers coated the surface of the cells with antibodies. The research team gave mice with cancer two sequential treatments with minicells. In the first treatment round, the researchers injected minicells filled with a gene silencing agent that turned off production of a protein pump that expels toxins and causes drug resistance in cancer cells. Next, to kill the tumor cells that were no longer drug-resistant, they gave the mice minicells filled with a chemotherapy drug.

This treatment regimen stopped the progression of tumors in mice with human breast cancer and those with human colon cancer. For mice with a drug-resistant strain of human uterine tumors, the dual-wave treatment completely eliminated the tumors. The differences in survival rates of these mice were even more striking: all of the mice that received dual-wave minicell treatment survived for at least 110 d with no signs of tumors, whereas mice from all the other groups died early (usually within 30–40 d).

Though the dual-minicell treatment inhibited or diminished cancer in mice, the safety and effectiveness of such treatments in human cancer patients remains to be seen. According to the *New York Times*, the team was planning to start testing the treatment regimen in people who have solid tumors in July. **Kirsten Dorans**