Regeneration (biology)

In biology, **regeneration** is the process of renewal, restoration, and growth that makes genomes, cells, organisms, and ecosystems resilient to natural fluctuations or events that cause disturbance or damage. Every species is capable of regeneration, from bacteria to humans.[1][2] Regeneration can either be complete[3] where the new tissue is the same as the lost tissue,[3] or incomplete[4] where after the necrotic tissue comes fibrosis.[4] At its most elementary level, regeneration is mediated by the molecular processes of gene regulation.[5][6] Regeneration in biology, however, mainly refers to the morphogenic processes that characterize the phenotypic plasticity of traits allowing multi-cellular organisms to repair and maintain the integrity of their physiological and morphological states. Above the genetic level, regeneration is fundamentally regulated by asexual cellular processes.[7] Regeneration is different from reproduction. For example, hydra perform regeneration but reproduce by the method of budding.

Sun flower sea star regenerates its arms

Dwarf yellow-headed gecko with regenerating tail

The hydra and the planarian flatworm have long served as model organisms for their highly adaptive regenerative capabilities.[8] Once wounded, their cells become activated and start to remodel tissues and organs back to the pre-existing state.[9] The Caudata ("urodeles"; salamanders and newts), an order of tailed amphibians, is possibly the most adept vertebrate group at regeneration, given their capability of regenerating limbs, tails, jaws, eyes and a variety of internal structures.[1] The regeneration of organs is a common and widespread adaptive capability among metazoan creatures.[8] In a related context, some animals are able to reproduce asexually through fragmentation, budding, or fission.[7] A planarian parent, for example, will constrict, split in the middle, and each half generates a new end to form two clones of the original.[10] Echinoderms (such as the starfish), crayfish, many reptiles, and amphibians exhibit remarkable examples of tissue regeneration. The case of autotomy, for example, serves as a defensive function as the animal detaches a limb or tail to avoid capture. After the limb or tail has been autotomized, cells move into action and the tissues will regenerate.[11][12][13]

Contents

Ecosystems

Main article: regeneration (ecology)

Ecosystems can be regenerative. Following a disturbance, such as a fire or pest outbreak in a forest, pioneering species will occupy, compete for space, and establish themselves in the newly opened habitat. The new growth of seedlings and community assembly process is known as regeneration in ecology.[14][15]

Cellular molecular fundamentals

Pattern formation in the morphogenesis of an animal is regulated by genetic induction factors that put cells to work after damage has occurred. Neural cells, for example, express growth-associated proteins, such as GAP-43, tubulin, actin, an array of novel neuropeptides, and cytokines that induce a cellular physiological response to regenerate from the damage.[16] Many of the genes that are involved in the original development of tissues are reinitialized during the regenerative process. Cells in the primordia of zebrafish fins, for example, express four genes from the homeobox *msx* family during development and regeneration.[17]

Tissues

"Strategies include the rearrangement of pre-existing tissue, the use of adult somatic stem cells and the dedifferentiation and/or transdifferentiation of cells, and more than one mode can operate in different tissues of the same animal. All these strategies result in the re-establishment of appropriate tissue polarity, structure and form."[18]:873 During the developmental process, genes are activated that serve to modify the properties of cell as they differentiate into different tissues. Development and regeneration involves the coordination and organization of populations cells into a blastema, which is "a mound of stem cells from which regeneration begins."[19] Dedifferentiation of cells means that they lose their tissue-specific characteristics as tissues remodel during the regeneration process. This should not be confused with the transdifferentiation of cells which is when they lose their tissue-specific characteristics during the regeneration process, and then re-differentiate to a different kind of cell.[18]

In animals

Annelida

Many annelids are capable of regeneration.[20] For example, *Chaetopterus variopedatus* and *Branchiomma nigromaculata* can regenerate both anterior and posterior body parts after latitudinal bisection.[21] The relationship between somatic and germline stem cell regeneration has been studied at the molecular level in the annelid *Capitella teleta*.[22]

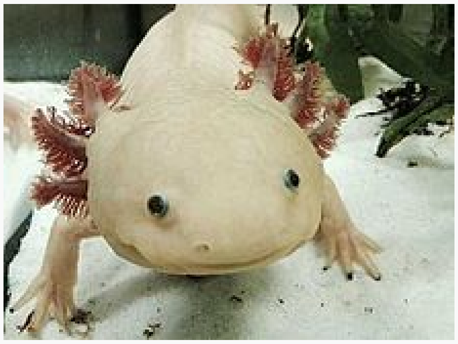
Planaria (Platyhelminthes)

Planarians exhibit an extraordinary ability to regenerate lost body parts. For example, a planarian split lengthwise or crosswise will regenerate into two separate individuals. In one experiment, T. H. Morgan found that a piece corresponding to 1⁄279th of a planarian could successfully regenerate into a new worm. This size (about 10,000 cells) is typically accepted as the smallest fragment that can regrow into a new planarian. Regeneration of planaria is epimorphic regeneration. After amputation, stump cells form blastema.

Amphibians

Simple animals like planarians have an enhanced capacity to regenerate because the adults retain clusters of stem cells (neoblast) within their bodies which migrate to the parts that need healing. They then divide and differentiate to grow the missing tissue and organs back. The process is more complex in vertebrates, but nevertheless, salamanders possess strong powers of regeneration, which begins immediately after amputation. Limb regeneration in the axolotl and newt has been extensively studied and researched.

Limb regeneration in salamanders occurs in two major steps. First, adult cells dedifferentiate into progenitor cells which will replace the tissues they are derived from.[23][24] Second, these progenitor cells then proliferate and differentiate until they have completely replaced the missing structure.[25]



Axolotls can regenerate a variety of structures, including their limbs

After amputation, the epidermis migrates to cover the stump in 1–2 hours, forming a structure called the wound epithelium (WE).[26] Epidermal cells continue to migrate over the WE, resulting in a thickened, specialized signaling center called the apical epithelial cap (AEC).[27] Over the next several days there are changes in the underlying stump tissues that result in the formation of a blastema (a mass of dedifferentiated proliferating cells). As the blastema forms, pattern formation genes – such as HoxA and HoxD – are activated as they were when the limb was formed in the embryo.[28][29] The positional identity of the distal tip of the limb (i.e. the autopod, which is the hand or foot) is formed first in the blastema. Intermediate positional identities between the stump and the distal tip are then filled in through a process called intercalation.[28] Motor neurons, muscle, and blood vessels grow with the regenerated limb, and reestablish the connections that were present prior to amputation. The time that this entire process takes varies according to the age of the animal, ranging from about a month to around three months in the adult and then the limb becomes fully functional.

In spite of the historically few researchers studying limb regeneration, remarkable progress has been made recently in establishing the neotenous amphibian the axolotl (*Ambystoma mexicanum*) as a model genetic organism. This progress has been facilitated by advances in genomics, bioinformatics, and somatic cell transgenesis in other fields, that have created the opportunity to investigate the mechanisms of important biological properties, such as limb regeneration, in the axolotl.[30] The Ambystoma Genetic Stock Center (AGSC) is a self-sustaining, breeding colony of the axolotl supported by the National Science Foundation as a Living Stock Collection. Located at the University of Kentucky, the AGSC is dedicated to supplying genetically well-characterized axolotl embryos, larvae, and adults to laboratories throughout the United States and abroad. An NIH-funded NCRR grant has led to the establishment of the Ambystoma EST database, the Salamander Genome Project (SGP) that has led to the creation of the first amphibian gene map and several annotated molecular data bases, and the creation of the research community web portal.[31]

Researchers at Australian Regenerative Medicine Institute at Monash University, have published that when macrophages, which eat up material debris,[32] were removed, salamanders lost their ability to regenerate and formed scarred tissue instead.[33]

Mammals

The mechanism for regeneration in Murphy Roths Large (MRL) mice has been found, and is related to the deactivation of the p21 gene.[34][35]

At least two species of African Spiny Mice, *Acomys kempi* and *Acomys percivali*, are capable of completely regenerating the autotomically released or otherwise damaged tissue. These species can regrow hair follicles, skin, sweat glands, fur and cartilage.[36]

Adult mammals have limited regenerative capacity compared to most vertebrate embryos/larvae, adult salamanders and fish.[37] But the regeneration therapy approach of Robert O. Becker, using electrical stimulation, has shown promising results for rats [38] and mammals in general.[39]

The MRL mouse is a strain of mouse that exhibits remarkable regenerative abilities for a mammal. Study of the regenerative process in these animals is aimed at discovering how to duplicate them in humans.

By comparing the differential gene expression of scarless healing MRL mice and a poorly-healing C57BL/6 mouse strain, 36 genes have been identified that are good candidates for studying how the healing process differs in MRL mice and other mice.[40][41]

The regenerative ability of MRL mice does not, however, protect them against myocardial infarction; heart regeneration in adult mammals (neocardiogenesis) is limited, because heart muscle cells are nearly all terminally differentiated. MRL mice show the same amount of cardiac injury and scar formation as normal mice after a heart attack.[42] However, recent studies provide evidence that this may not always be the case, and that MRL mice can regenerate after heart damage. [1]

Regeneration in humans

Main article: Regeneration in humans

The regrowth of lost tissues or organs in the human body is being researched. Some tissues such as skin regrow quite readily; others have been thought to have little or no capacity for regeneration, but ongoing research suggests that there is some hope for a variety of tissues and organs.[43] Human organs that have been regenerated include the bladder, vagina and the penis.[44]

See also

- Neuroregeneration
- Epimorphosis
- Morphallaxis
- Polyphyodont

Notes

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External links

Wikisource has the text of a 1920 *Encyclopedia Americana* article about ***Regeneration***.

- Spallanzani's mouse: a model of restoration and regeneration
- Mice that regrow hearts in the news
- DARPA Grant Supports Research Toward Realizing Tissue Regeneration
- The Geniuses Of Regeneration in *BusinessWeek*, May 24, 2004
- UCI Limb Regeneration Lab
- A site dedicated to amputation and regeneration