RIKEN Center for Developmental Biology

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Regeneration

Regeneration is a general term for biological self-repair. There are a number of regenerative mechanisms by which animals are able to replace or restore damaged cells and tissues, ranging from simple wound healing and tissue maintenance to the ability to regenerate limbs, organs and in some cases, entire new bodies.

The study of regenerative phenomena as a field of experimental biology can be traced back to the eighteenth century when scientists in Europe began to investigate patterns of regeneration in animals such as crustaceans, hydras and newts. Labs at the CDB also use highly regenerative model organisms such as planarian flatworms to study regeneration at the cellular and molecular levels. Some of the basic terms and concepts of regeneration research are described below.

Types of regeneration
The processes of animal regeneration were categorized into two main groups by the Nobel Prize-winning geneticist, Thomas Hunt Morgan. The first type he named *morphallaxis* - the regenerative process in which damaged or missing body parts are repaired by the remodeling of existing cells or tissues without cell proliferation. In morphallaxis, which is observed in species such as the hydra, regenerates are smaller than the original structure or organism, and growth takes place subsequent to regeneration.

In contrast to morphallaxis, the form of regeneration known as *epimorphosis* requires the growth of new cells to replace those that have been lost. In many species, including humans, epimorphosis is achieved by the activation of stem cells or progenitor cells in response to injury or disease. Some species, such as newts, actually create new stem or progenitor cells as the first step in epimorphic regeneration.

Epimorphic regeneration is capable of replacing entire missing structures, such as limbs, in certain species. Interestingly, it is also possible for some species to regenerate missing sections of physiological structures through the process of *intercalary regeneration*. By an as-yet unknown mechanism, the injured body recognizes not only the fact that it is damaged but also the specific area of the body that is in need of repair, and regenerates only those parts that are in need of repair. It may be that cells in such systems have unique positional identities similar to coordinates and that when the body senses that cells of a certain identity have been lost, it regenerates only cells of the proper identity for that location in the body. This assures that regeneration only restores structures that have been lost, and does not produce original structures that were not present prior to the injury.

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Reprogramming
Most cells in the body are highly differentiated, having specific identities and roles and unable to give rise to other types of cells. However, in some forms of regeneration, cells de-differentiate and regain the ability to generate cell types other than their own. This is seen in species such as newts and salamanders, in which, for example, pigmented epithelial cells in the iris are capable of transdifferentiating into lens cells when an eye is damaged or lost.

Regeneration and evolution
It is a general, but not universal, rule that less highly evolved species have greater capacities for regeneration. Many simple organisms such as hydra, starfish and flatworm are highly regenerative, even able to regenerate new individual bodies when cut into pieces. However, some relatively highly evolved animals such as crayfish and some amphibians are also able to replace severed limbs, tails and other body parts that have been damaged or lost. Scientists at the CDB are interested in identifying the mechanisms that enable such regeneration, and the evolutionary forces at work in balancing regenerative capacity with organismal complexity.

Regenerative medicine
Although the CDB does not conduct medical research, many mechanisms of development and regeneration are seen as having great potential for application to human medicine, particularly to the emerging field of regenerative medicine. Regenerative medicine is a new, science-based approach to healing that involves using the body's own stem cells and growth factors to repair and restore healthy function to organs, tissues, and physiological systems. The future scope of regenerative medicine spans gene and immunotherapy, cell replacement and tissue engineering - therapies which offer great promise in the treatment of a wide range of diseases that are currently resistant to traditional modes of Western medicine, such as surgery, pharmaceuticals and standard preventive medicine.

Many laboratories at the CDB are engaged in research into the biological processes and mechanisms that characterize stem cells, and it is hoped that in the future the knowledge gained from these studies will play a part in developing cell replacement therapies for a range of diseases and debilitating conditions such as Parkinson's disease, spinal cord injury, diabetes, cardiovascular disease and some forms of cancer.