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An Introduction to Aging and Regeneration

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Abstract

Tissues are maintained through a balance of cellular aging and regeneration. Aging refers to the gradual loss of cellular function, and regeneration is the repair of damaged tissue generally mediated by preexisting adult or somatic stem cells. Scientists are interested in understanding the biological mechanisms behind these two complex processes. By doing so, researchers may be able to use somatic stem cells to treat degenerative diseases and develop therapies that could delay the effects of aging.

In this video, we provide a brief history of the field of aging and regeneration, touching upon observations made in ancient Greece, as well as modern-day experiments. Some of the questions being asked in this field, and the prominent methods being used by biologists to answer them, are then explored. Finally, we look at a few specific experiments being conducted in today\'s aging and regeneration research laboratories.

Transcript

Biologists in the field of aging and regeneration aim to understand the mechanisms of these two complex processes that are implicated in maintenance of tissue homeostasis.

Aging, or "senescence," involves deterioration of cell morphology and loss of functions over time, whereas regeneration refers to replacement of aged or damaged cells. The tissues in our bodies are maintained in a delicate balance between senescence and regeneration. Although most of our tissues have a finite lifespan, some of them do have the capacity to fully regenerate following an injury.

This video will briefly discuss the history, highlighting the key discoveries in the field, some of the important questions that are currently being investigated, some assays being used to answer these questions, and a few specific laboratory applications of these concepts.

Before talking about the current experiments being conducted, let's take a look at some of the important discoveries in the history of aging and regeneration research.

The first observations of tissue regeneration occurred around 350 B.C., when Aristotle noted that lizards were able to regenerate their tails after they'd been severed.

In the 18th century, tissue regeneration became a hot topic of research, and three scientists - R. A. Ferchault de Réaumur, Abraham Trembley, and Lazzaro Spallanzani-independently carried out detailed tissue regeneration studies in crayfish, hydra, and newts, respectively.

Mainstream scientist became less interested in the regeneration phenomenon over the next century, but in the early 1900s interest started to buildup in the related field of aging. Alexis Carrel, a French surgeon and biologist, suggested that cells grown in culture were immortal and could divide indefinitely. However, other scientists could not replicate his claims.

In 1961, Leonard Hayflick and Paul Moorhead demonstrated that, contrary to what Carrel claimed, normal cells grown in culture undergo division for a finite number of times, about 40 to 60, after which they enter the senescence phase. This phenomenon of limited cell division became known as the "Hayflick limit."

The first hints of a mechanism for this limit came in 1973, when Soviet biologist Alexey Olovnikov recognized that the DNA replication machinery couldn't fully replicate the ends of chromosomes, called telomeres. He predicted the existence of a mechanism to maintain telomere length in healthy and cancer cells.

Later in 1984, Elizabeth Blackburn, Carol Greider, and Jack Szostak discovered that this mechanism involved an enzyme called telomerase. They demonstrated that telomerase is responsible for addition of repetitive sequences to the 3' end of the chromosome, which would then allow DNA polymerase to fully replicate the chromosome ends. Blackburn, Greider, and Szostak shared the Nobel Prize for this discovery in 2009.

Now that we have reviewed some of the discoveries related to aging and regeneration, let's look at a few key questions being asked in the field today.

One important question being investigated is: how do cells age? A prevailing theory of cell aging is called the Free Radical Theory. The idea is that, when cell organelles called mitochondria carry out oxidative respiration, byproducts known as reactive oxygen species, or ROS, are formed. Overproduction of these molecules induces oxidative stress, which alters the function of organelles, such as the mitochondria themselves and the endoplasmic reticulum, and can also cause damage to the nuclear DNA. Scientists are interested in discovering the mechanisms behind these occurrences.

Another question that's being asked is: what are the physiological and environmental factors affecting an organism's lifespan? Some researchers seek to analyze the effects of environmental changes, for example caloric restriction, on an organism's lifespan. Other researchers are interested in identifying genes and biochemical pathways that regulate the process of aging.

Finally, scientists are also trying to understand how tissues undergo spontaneous regeneration following injury. Special cells known as adult stem cells have been found to be instrumental in this process, and some researchers are curious about the dynamics of these cells following injury. From a clinical perspective, scientists are interested in investigating how these cells can be employed in therapies for degenerative disorders.

Now that you know some of the questions being asked in the field, let's look at different research tools that scientists employ to answer these questions.

One of the ways to measure cells' age is by determining the telomere length and telomerase activity. Both these parameters can be measured using polymerase chain reaction, or PCR.

Scientists also examine the established markers of senescent cells, like β-galactosidase. This can be done by staining the cells using biochemical assays and observing them under the microscope.

For examining the factors affecting organism's lifespan, scientists often use invertebrate model organisms, such as worms or flies. The advantages with these models organisms are their relatively short generation times, and their ability to be grown in simple laboratory setups. In addition, genetic manipulations can be easily performed in these organisms, which help scientists to examine the roles of genes in the process of aging and longevity.

Finally, the role of adult stem cells in tissue regeneration can be studied using several approaches. For example, scientists can label adult stem cells in the target tissue with specific markers, which enable them to trace these cells as tissue regenerates. Sometimes, researchers directly inject these multipotent stem cells into the damaged tissue to study their role in repair following injury.

Since you now know some of the methods used in the field of aging and tissue regeneration, let's look at a few specific applications of these methods.

The roundworm *Caenorhabditis elegans* has been used as a screening platform to identify gene mutations that can prolong lifespan. Here, after age synchronization with the help of a timed egg-laying protocol, scientists analyzed the effect of a gene mutation on an organism's lifespan.

To study the mechanisms of tissue regeneration, many models are available that involve initial injury followed by analysis of regenerative mechanisms. In this example, scientists examined tissue regeneration following ablation of the lateral line, a key sensory component of the zebrafish peripheral nervous system.

In order to induce ablation, scientists treated fish with gentamicin. After the designated recovery time, the fish were poured into the fluorescent vital dye solution, which stains the neural stem cells. These stained cells were then quantified using fluorescence microscopy.

Lastly, researchers often inject adult stem cells to induce repair of damaged tissue. Here, scientists used multipotent stem cells to induce regeneration of damaged muscle tissues. In order to do that, scientists generated mouse models with damaged hind limb muscles. Then, multipotent stem cells were injected directly into the damaged muscles. Following injection, the cells were given time to proliferate and differentiate, and their contribution to functional amelioration was analyzed.

You've just watched JoVE's introduction to the field of aging and regeneration. This video reviewed historical highlights of the field, some key questions being asked by biologists, a few prominent assays being used to answer those questions, and current experiments being conducted to understand the biology of senescence and regeneration. As always, thanks for watching!