

The Hayflick Limit

The Hayflick Limit is a concept that helps to explain the mechanisms behind cellular aging. The concept states that a normal human cell can only replicate and divide forty to sixty times before it cannot divide anymore, and will break down by programmed cell death or apoptosis. The concept of the Hayflick Limit revised Alexis Carrel's earlier theory, which stated that cells can replicate themselves infinitely. Leonard Hayflick developed the concept while at the Wistar Institute in Philadelphia, Pennsylvania, in 1965. In his 1974 book *Intrinsic Mutagenesis*, Frank Macfarlane Burnet named the concept after Hayflick. The concept of the Hayflick Limit helped scientists study the effects of cellular aging on human populations from embryonic development to death, including the discovery of the effects of shortening repetitive sequences of DNA, called telomeres, on the ends of chromosomes. Elizabeth Blackburn, Jack Szostak and Carol Greider received the Nobel Prize in Physiology or Medicine in 2009 for their work on genetic structures related to the Hayflick Limit.

Carrel, a surgeon in the early twentieth century France working on cultures of chick heart tissue, argued that cells can infinitely replicate. Carrel claimed that he had been able to have those heart cells replicate in culture for greater than twenty years. His experiments on chick heart tissue supported the theory of infinite replication. Scientists tried to replicate Carrel's work many times, but these repeated experiments never confirmed Carrel's findings.

Hayflick worked for the Wistar Institute in 1961 where he observed that human cells do not replicate infinitely. Hayflick and Paul Moorhead described the phenomenon in a paper titled "The serial cultivation of human diploid cell strains." Hayflick's job at the Wistar Institute was to provide cell cultures to scientists who conducted experiments at the Institute, but Hayflick pursued his own research on the effects of viruses in cells. In 1965, Hayflick further detailed the concept of the Hayflick Limit in cells in a paper titled "The limited in vitro lifetime of human diploid cell strains."

In that article, Hayflick concluded that a cell could complete mitosis, or cellular duplication and division, only forty to sixty times before undergoing apoptosis and subsequent death. The conclusion held for many cell types, whether they were adult cells or fetal cells. Hayflick hypothesized that the limited replicative capability of the cell related to aging in cells and, consequently, to human aging.

The publication of Hayflick's experiments disconfirmed Carrel's theory about indefinite cellular replication. Some, such as Harry Rubin at the University of California at Berkeley in Berkeley, California, argued in the 1990s that the Hayflick Limit pertained only to damaged cells. Rubin suggested that cellular damage could result from the cells being in an environment that differed from their original environment in the body, or when researchers subjected the cells to laboratory practices.

Regardless of the criticism, other scientists used Hayflick's theory in support of further studies about cellular aging, especially with research in telomeres, which are repetitive sequences of DNA at the ends of chromosomes. Telomeres protect the chromosome from folding in on itself, and they decrease mutations in the DNA. In 1973, Alexey Olovnikov, in Russia, applied Hayflick's theories of cell death to his studies of the ends of chromosomes that did not replicate themselves during mitosis. He said that the process of cell division ends once the cell cannot replicate the ends of their chromosomes.

Although Olovnikov applied Hayflick's theory to his experiments, Olovnikov did not name Hayflick's theory. One year later in 1974, Burnet coined the term Hayflick Limit in his work, *Intrinsic Mutagenesis*. Burnet's work focused on the claim that age was intrinsic to the cells in each species and that they followed the Hayflick Limit, thus establishing a programmed age in which an organism

would die. Elizabeth H. Blackburn at the University of California San Francisco in San Francisco, California, and Jack W. Szostak at Harvard Medical School in Boston, Massachusetts, also applied Hayflick's theory of cellular aging to their research on the structures of telomeres in 1982, when they cloned and isolated telomeres. In 1989, Greider, and Blackburn further developed the theory of cellular aging to discover the enzyme that replicates telomeres, called telomerase. Greider and Blackburn found that the presence of telomerase helps cells escape programmed cell death.

With theories about the biological mechanisms behind aging, scientists expected that they could create a cure for aging. Hayflick helped found the National Institute on Aging in Bethesda, Maryland, in 1974, a branch of the National Institutes of Health in the United States. In 1982, Hayflick also became the president of the Gerontological Society of America, founded in 1945 in New York, New York. Hayflick's role helped to spread the theory of the Hayflick Limit and to further counter the theory of cellular immortality as established by Carrel.

In 2009, Blackburn and Szostak received the Nobel Prize in Physiology or Medicine for their work on telomerase, in which the Hayflick Limit played an essential role.

Sources

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