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REVIEWS

HeLa Cell Culture: Immortal Heritage of Henrietta Lacks

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Abstract—When we use cell cultures in research, we rarely think about the story behind them, which can be intriguing, providing insight, and sometimes tragic. In the 1950s, the culture of HeLa cells unexpectedly became well known scientifically and became one of the most famous cell cultures. These cells were taken from a woman named Henrietta Lacks, who had cervical cancer and died shortly afterward, and the HeLa cell line proved to be an essential tool for several generations of scientists around the world in developing new treatments and biomedical research. These cells have become unique due to their immortality, endless division, easy cultivation, and adaptation to conservation conditions. At the same time, HeLa cells remain a simplified imitation of the human body.

Keywords: cell cultures, HeLa cell line, Henrietta Lacks, molecular genetics
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INTRODUCTION

One of the most important achievements of the experimental biology of our century is the development of methods for in vitro culturing the animal and plant cells. The application of this method makes it possible to grow the cells of various human tissues on selective nutrient media, similarly to bacteria or other unicellular organisms. Numerous human cell cultures were originally derived from cancer tumors. These cells are capable of endless division in culture and are therefore called "immortal" (immortalitate). Scientists had long been convinced that normal human cells could also go on dividing indefinitely both in vitro and in vivo.

However, in the early 1960s, Leonard Hayflick, professor of anatomy at the University of California, discovered that normal human diploid cells divided for a limited number of times in cell culture. After approximately 50 divisions, hallmarks of aging (senescence) are detected, and, when this limit is reached, cells die (Hayflick limit) [1]. This phenomenon strongly depends on the age of the individual to whom such cells originally belonged: cells of newborn children divide up to 80–90 times in cell culture, and cells of a 70-year-old person divide only 20–30 times. The number of divisions depends on the length of the telomeres: the terminal ends of chromosomes that perform a protective function. Thus, telomeres not only protect chromosomes from deterioration and fusion but also determine the potential capacity for cell replication depending on telomere length. The initial length of human telomeric DNA is from 2 to 20000 bp. With each cell division, the telomere length of normal cells declines by 50–60 bp. In 1984, Carol Grider isolated an enzyme that synthesized (lengthened) telomere DNA. This enzyme was named "telomerase." Artificial induction of gene expression of the catalytic component of telomerase (using genetic engineering methods) makes the cell culture immortal, i.e., able to divide endlessly, revoking the Hayflick limit for this culture [2, 3].

When developing new treatments in biomedical research, scientists often use laboratory-grown human cell cultures. HeLa, the culture of endothelial cells of the uterus of Henrietta Lacks, is among the most famous cell lines. These cells, which adequately simulate a simplified human body under laboratory conditions, show a good example of the immortality of cancer cells [4, 5].

Several tumor cells obtained in 1951 are still proliferating. They can be frozen for decades and divided into different batches. HeLa cells have a rather universal set of cell surface receptors, which can be used to study the effects of various cytokines; they are easily cultured and resistant to conservation. Over the years, tons of these cells have been produced, and all of them are "descendants" of Henrietta Lacks' tumor cells.

These cells made their way into the forefront of science quite unexpectedly. They were taken from a woman named Henrietta Lacks, who died shortly afterward, but the cell population of the tumor that killed her remained alive. All previous attempts to obtain cell cultures from tumor tissues outside the

Fig. 1. Henrietta Lacks, photo by S. Gilgenkrantz [5].

Fig. 2. George Otto Gey (1899–1970), photo by S. Gilgenkrantz [5].

human body had been unsuccessful: after a certain number of divisions, the entire cell line died [5].

But what was unique about this cell line, named "HeLa" after Henrietta Lacks, was that they proliferated in vitro twice as fast as do cells from normal tissues, while the intracellular growth suppression program was completely turned off. The HeLa cell line was the first cell culture. For many years, it remains the only tool essential for several generations of scientists. As a result, scientists obtained the first stable immortal cell culture, which provided it with the status of one of the most popular cell lines used in scientific research. This opens up unprecedented prospects for research in molecular and cellular biology, medicine, and pharmacology.

HENRIETTA LACKS

The beautiful black American woman named Henrietta Lacks (Fig. 1) was a descendant of white planters and their black slaves and one of the daughters in a family with ten children. She lived with her husband and five children in the small town of Turner in southern Virginia. On February 1, 1951, Henrietta Lacks went to the Johns Hopkins Gynecology Clinic with symptoms of strange spotting between her menstrual periods. Examination revealed a 23-cm cervical tumor. A biopsy was performed, and epidermoid cervical carcinoma was diagnosed. Eight months later, despite surgical treatment and radiation therapy, she died at the age of 31 [4, 5].

During the examination, the attending physician sent a biopsy of her tumor to George Gey, who was director of the Tissue Culture Laboratory at Johns Hopkins University (Baltimore, Maryland). He was investigating the problem of cancer treatment and was searching for an immortal human cell line for research (Fig. 2). He was the first to discover the extraordinary properties of these tumor cells, which were destined to become the first human culture. He successfully isolated a single specific cell, grew it, and started a cell line. He initiated the proliferation of Lacks' cells and created an immortal cell line that differed from normal cell populations that had the Hayflick limit. Soon, George Gey discovered that HeLa cells could survive even shipping and sent them to his colleagues across the country. Demand for HeLa cells grew very quickly, and they were replicated in laboratories around the world. They became the first standard cell line, which proliferated unusually rapidly and was even more stable than other cancer cells [5].

On September 1, 1951, George Gey held a test tube of HeLa cell culture and spoke in front of cameras. He announced that the obtained cell line had given rise to a new era in biomedical scientific research that was opening unprecedented prospects in the development of new drugs and that the day when a cure for cancer would be found was not far away. Lacks died at Johns Hopkins Clinic on October 4, 1951, while the population of her cells continued its uncontrollable growth. This took place much earlier than the development of bioethical rules and guidelines for regulating scientific progress.

WHY ARE HER CELLS SO IMPORTANT?

Gey was right. Indeed, HeLa cells became a welcome development for researchers around the world. This cell population, which is identical in all laboratories, allowed scientists to rapidly obtain and confirm new data independently of each other. It can be stated that the giant leap that was taken in molecular biology at the end of the last century was due to the possibility to cultivate cells in vitro. HeLa cells became the first immortal human cells that had ever been grown in a culture medium. They gave scientists an opportunity to cultivate hundreds of other cancer cell lines. Although no conditions for the cultivation of non-transformed cells have yet been found, cancer cells may be considered a rather adequate model for finding answers to questions that are raised by scientists and doctors.

In contrast to a normal population of human cells that divide from 40 to 50 times before they die, HeLa cells can divide indefinitely.

The karyotype of normal human cells contains 46 chromosomes, while HeLa cells have from 76 to 80 chromosomes that are significantly mutated [6]. The appearance of this deviation from the normal karyotype is associated with the human papillomavirus (HPV) HPV18, which is responsible for almost all cases of cervical cancer. HPV inserts its DNA into the host cell. As a result, the host cell begins to synthesize a protein that binds and inactivates the p53 protein, which is known as the "genome keeper" due to its role in preventing mutations and suppressing the tumor. Inactivation of the p53 protein can therefore have disastrous consequences [7].

Even compared to other cancer cells, HeLa cells grow extremely rapidly. Dr. Gey was shocked to see that the cells had doubled their numbers within 24 h of cultivation of his first HeLa sample. This anomaly was caused by the HeLa telomerase enzyme activity. During the division of a normal cell, short repetitive DNA sequences at each end of a chromosome, known as "telomeres," shorten due to a decrease in the activity of this enzyme [8]. This leads to senescence and, ultimately, to apoptosis and cell death. Normal cells divide a maximum number of times before their telomeres are truncated. In HeLa cells, due to high telomerase activity, telomeres lengthen, exhibiting unlimited replicative capacity [9]. This anomaly allows HeLa cells to divide indefinitely, making them now older than Lacks at the time of her death.

Many significant achievements in the world of science have been made thanks to this culture. The creation of a vaccine from inactivated viruses against poliomyelitis by Jonas Salk, a virologist at the National Foundation for Infantile Paralysis, in 1953 would have been impossible without HeLa cells [4]. It was a great and promising scientific success, but, before using the new drug on human beings, it was necessary to test it on living human cells. The population of HeLa cells proved to be an ideal tool. They grew rapidly, which made it possible to assemble the huge number of cells necessary for research sufficiently quickly. Moreover, it also turned out that they were easily infected with the polio virus. In less than a year, the vaccine was ready for use in patients [10].

After the successful use of HeLa cells to obtain a polio virus vaccine, human cell culture lines became essential for the isolation and cultivation of a number of other viruses, as well as the production of antibodies, interferon, and antitumor chemotherapy drugs. Since then, the list of breakthrough technologies and achievements using HeLa cells has been constantly replenished. The cells are commonly used in virology research, to study diseases such as cancer and AIDS, to assess the effects of radiation and toxic substances, to construct genetic maps, to develop cell engineering methods, and to solve a great number of other scientific problems [5].

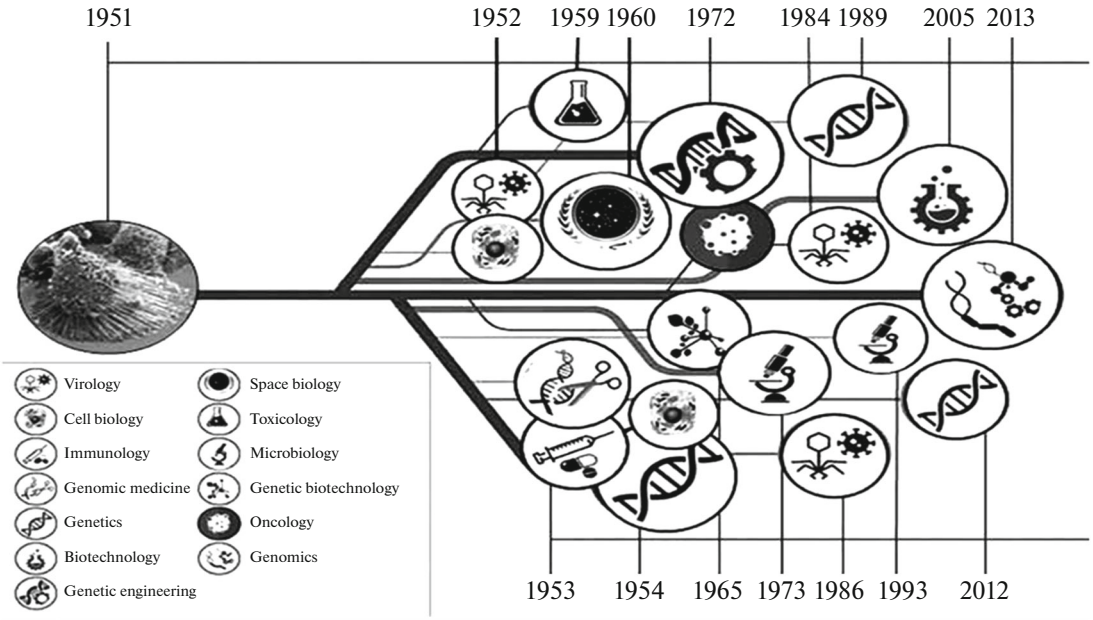
In the late 1960s, HeLa and other cell cultures gave helped the emergence of genetic engineering (generally considered to have begun in 1972), when the first recombinant DNA molecule was created by Paul Naim Berg et al. at Stanford University (United States). Opportunities for targeted construction of artificial genetic programs and the development of numerous essential drugs were created [11].

In December 1960, HeLa cells went into space on board the Soviet satellite *Sputnik 6*, and later they traveled to outer space several times more. The results showed that HeLa cells do well not only on Earth, but also in zero gravity. Since then, HeLa cells have been used for cloning (the famous sheep Dolly, in particular), genetic research, the development of artificial insemination methods, and in thousands of other studies. Since 1972, these cells have been actively used in the international program for the joint fight against cancer, with the participation of physicians from all over the world [5].

Thanks to HeLa cells, a connection between HPV and cervical cancer, as well as the role of telomerase in preventing chromosome degradation, was found. For this, Noble Prizes were awarded to Harald zur Hausen in 2008 and Elizabeth Blackburn, Carol Greider, and Jack Szostak in 2011 [12, 13].

"The mother of virology, cell and tissue technologies, biotechnology, and modern medicine" is far from the only epithets that this cell culture has earned over many decades.

Thus, the involuntary contribution of Henrietta Lacks to medicine is inestimable. For more than half a century of service to science and humanity, the HeLa cell culture has become an invaluable and integral part of biomedical research (Fig. 3).



Year	Research
1951	HeLa cells were first obtained from tissue biopsy of cervical cancer
1952	Birth of cell experimental virology. HeLa cells were used to study the molecular mechanisms of infection of human cells with viruses
1952	The appearance of modern standards in cell biology. Development of techniques of maintaining HeLa cell culture
1952	The emergence of a world standard cell line. First shipping of frozen cells
1953	The birth of genetic medicine. The first experiments on chromosome staining with hematoxylin
1953	Development of polio vaccine by Jonas Salk
1954	The development of commercial standardized cell lines. The first mass production of HeLa cells for sale to research laboratories
1954	The birth of cloning. Due to the viability of HeLa cells, scientists were able to multiply and study clones of individual cells
1959	The first experiments on the effects of toxins on HeLa cells
1960	The birth of space cell biology. The emergence of space biology and medicine: cell growth in zero gravity
1965	First hybrids. Creation of chimeric cells by fusion of HeLa with mouse lymphocytes
1972	Cells are actively used in the international cancer control program with the participation of physicians around the world
1972	The birth of genetic engineering. The first recombinant DNA molecule was created by Berg (Paul Naim Berg et al.)
1973	The emergence of in vitro cellular models of diseases. HeLa was used as a model for the study of salmonellosis
1984	New trends in anticancer research. Using the HeLa model, papillomavirus was shown to cause cancer
1986	A deeper understanding of the biology of AIDS. The HeLa model was used to study the mechanism of cell infection with human immunodeficiency virus
1989	A new trend in the study of life expectancy. A previously unknown telomerase enzyme was discovered in HeLa cells
1993	The study of tuberculosis. The mechanism of tuberculosis infection was investigated using the HeLa model
2005	The study of the action of nanostructures on living tissue. HeLa cells were used to study potential dangers of nanostructures
2012	Steinmetz et al. deposited the sequence of the HeLa cell genome in databases accessible to the scientific community
2013	Individual genomics of cell lines. The results of complete genome sequencing of the HeLa cell line were presented

Fig. 3. The history of the application of the cells in molecular biology and medicine (authors' illustration).

MEANWHILE...

Meanwhile, the identity of Henrietta Lacks was not publicized for a long time. Gey, of course, knew about the origin of HeLa cells, but he believed that confidentiality was a priority in this case. For many years, no one, including the Lacks family, knew that the cells that had become famous worldwide were hers [5].

After the death of Gey in 1970, the mystery was solved. This happened by accident. At the dawn of research technologies using cell cultures, many scientists did not pay sufficient attention to standards of sterility when working with cells and to the possibility of cross contamination of numerous cell lines [4]. The more aggressive and tenacious HeLa cells contaminated weaker cell cultures, floating on dust particles in the air or being carried on nonsterile instruments, unwashed hands, and clothes [4, 5]. After 25 years, scientists found that the purity of the HeLa cell culture was in question: the same cell line in different laboratories had different genetic characteristics [14]. It was decided to solve the problem by genotyping, for which purpose the scientists found Lack relatives and asked them for samples of family DNA for gene mapping. Thus, the secret was revealed.

At the same time, for several decades, no thought was given to the issue of consent to the use of Lacks' cells and those of her relatives. Lack's family has never received compensation for the use of HeLa cells without the donor's consent, and financial assistance to many of her relatives who could not afford health insurance would have been very helpful. However, all inquiries run into a wall, and the defendants are long gone [5, 15]. In 2013, Lack's relatives first obtained a copyright for the use of the cellular material of their great-grandmother in popular science publications. The family refused to take any monetary benefit. At the same time, the National Institutes of Health (NIH) and members of Lack's family agreed to deposit the HeLa genome sequence "in a controlled-access database," the Database of Genotypes and Phenotypes (dbGaP; http://www.ncbi.nlm.nih.gov/gap). Currently, scientists need to contact the NIH to use the controlled-access data in their research, agreeing to their terms and conditions. It is also required by law that the Lacks family be mentioned in any scientific publications [16].

It is worth noting that some scientists have assigned HeLa cells to a new, nonhuman species: *Helacyton gartleri* (*Hela* is in honor of HeLa cells; *cyton* is from the Greek "kutos," which means "cell"; and *gartleri* is in honor of the geneticist Stanley Gartler, who was the first to document the amazing properties of these cells). The evolutionary biologist Leigh van Valen classifies HeLa cells as a new microbial species due to their unlimited division, their own clonal karyotype, chromosomal incompatibility with human beings, different ecological niche, and ability to survive outside the human body. However, many disagree with this, since they consider the survival of HeLa cells to be an artificial phenomenon and claim that evolution in a Petri dish has little bearing on evolution in nature [17]. Van Valen notes that, in parks, squares, and cities created by people, many micro- and macroorganisms live that have adapted to these conditions. Thus, new species have been artificially created by human beings, although not ones born of their flesh. Van Valen claims that, if the HeLa cells had not been obtained from human tissue, there would be no doubt that they would be considered to belong to to a new species [18, 19].

In any case, a specimen of a cancer tumor that had been placed in a nutrient medium out of curiosity began to proliferate rapidly, does not age, and has been used in science for 65 years. At present, the HeLa cell culture is an important scientific tool in many research laboratories. Thanks to it, thousands of studies have been carried out, dissertations have been defended, more than 70 thousand scientific articles have been published, and more than 11 thousand patents have been obtained. Today there are so many cells that, if Lacks were alive, their total weight would be ten times greater than the weight of the woman herself, who, unfortunately, did not find out what invaluable, albeit involuntary, contribution to science she had made.

Therefore, we would like to honor the memory of Henrietta Lacks. Her cells, the immortal heritage left after her, have saved and continue to save more lives than any doctor can do.

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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