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Review Article

Dolly and the History of Cloning

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Abstract

Cloning is the term broadly meaning natural or artificial development of two or more genetically identical cells or organisms. In defining the term cloning, one starts from one side in zoology and botany and the other in reproductive medicine and cell biology from different starting points.

Cloning is a form of asexually propagation of different one cell and multi cell organisms which produce offsprings that are identical to the parent organism and to each other, but for science it is, however, more interesting to studying mammal cloning. Cloning is a term that dates back to 1963 and, apparently, is not particularly complicated. In 1962, British scientist John Gurdon managed to create a single frog. He successfully transplanted the core from a frog stem cell into an unopened egg in which he had previously destroyed the nucleus with UV radiation. Although the resulting egg cell managed to develop only to tadpole, this core transfer technique has shown the way for a new successful cloning.

Keywords: *Dolly; Embryo; Technology*

Introduction

The announcement, in February 1997, of the birth of Dolly, the first mammal cloned from an adult cell, marked a clear dividing line in the history of cloning research [1]. Before Dolly, cloning was a complex technique of limited use. It might have worked occasionally in lower organisms such as frogs; it might even have been possible to clone some mammals using cells taken from early embryos but most scientists viewed the cloning of mammals from adult cells as impossible.

The birth of a mammal cloned from an adult cell was a big deal because it meant that, for the first time, scientists could produce a genetic copy of another living animal [1]. The donor could be a known quantity, chosen for its specific qualities or desirable attributes. Cloning from embryonic cells was less exciting because you were, by definition, creating a genetic duplicate of an embryo whose abilities and attributes were unknown.

These scientific advances were intertwined with public concern and controversy over the proper scope of biomedical research and shaped by allegations of fraud, both in the public sphere and within the close-knit scientific community [1]. This story will set the stage for understanding not just the cloning of Dolly but also current cloning research.

Dolly is a clone

Dolly was born on 5 July 1996. She was named after the country singer Dolly Parton, partly to reflect her genetic origins as a mammary gland cell [1].

You might be wondering just how scientists can be so sure that Dolly was a clone [1]. In Dolly's case, only one animal survived out of 277 attempts. Maybe the surrogate ewe was already pregnant or perhaps Dolly resulted not from a differentiated cell but a stray immature cell accidentally picked up in the laboratory.

To show definitively that two animals are genetically identical, scientists use a technique known as DNA fingerprinting [1]. This is the same method used in paternity tests and by police forces around the world to match evidence collected from crime scenes with particular suspects. It works by comparing highly variable DNA segments across samples. If a large number of typically variable segments match, scientists can conclude that the samples are genetically identical. Dolly's genetic fingerprint matched the donor cells precisely. Using statistics, the scientists concluded the probability that a second sheep would share, by chance, this same profile was about one in two billion. In short, it is more likely that you will win the lottery or get struck by lightning than it is that Dolly was born from a stray contaminating cell.

Scientists also use simple techniques to help verify that a clone is truly a clone [1]. Dolly, for instance, was cloned from a Finn Dorset sheep, which has a white face but developed in a Scottish Blackface surrogate. Because Dolly had a white face, scientists know she was not the offspring of her surrogate.

When Dolly's birth was announced the following February, it stunned the world [1]. She made headlines from New York to New Zealand and everywhere in between. Scientifically, she was significant because she proved that cloning using a differentiated adult donor cell was possible. She answered, once and for all, the question Weismann had posed a century before. Her birth also set off a flurry of follow-up research, repeating and extending the technique. But Dolly's impact extended well beyond the scientific world. She gained lasting fame not because of the scientific doors she opened but because she brought the specter of human cloning once again to the fore.

Revolutionary event

A revolutionary event in biology and medicine occurred in 1996 when scientists at the Roslin Institute in Scotland succeeded in cloning animals from cultured cells taken from a mature ewe [2]. Dolly is the first mammalian clone created by transferring the nucleus from an adult cell to an unfertilized egg (with its own nucleus already been removed). Clones have since been produced from adult cells of mice, cattle, goats, pigs and other animals.

The major breakthrough that set the stage for creating Dolly came when scientists at the Roslin Institute successfully produced lambs by nuclear transfer from cells taken from early embryos that had been cultured for several months in the laboratory [2]. The experiment using cultured embryonic cells led to the cloning of Dolly using adult (differentiated) cells, which sets it apart from all previous cloning attempts of employing embryonic (undifferentiated) cells. The success of cloning adult cells proves that cell differentiation is reversible, and the hands of time in the developmental process can be manipulated to reprogram its course. This sets the beginning of the technique of somatic cell nuclear transfer (SCNT), more commonly referred to as cloning, to generate transgenic livestock.

If we should not underestimate the significance of human cloning, neither should we exaggerate its imminence or misunderstand just what is involved [3]. The procedure is conceptually simple. The nucleus of a mature but unfertilized egg is removed and replaced with a nucleus obtained from a specialized cell of an adult (or fetal) organism (in Dolly's case, the donor nucleus came from mammary gland epithelium). Since almost all the hereditary material of a cell is contained within its nucleus, the renucleated egg and the individual into which that egg develops are genetically identical to the organism that was the source of the transferred nucleus. An unlimited number of genetically identical individuals-clones-could be produced by nuclear transfer. In principle, any person, male or female, newborn or adult, could be cloned, and in any quantity. With laboratory cultivation and storage of tissues, cells outliving their sources make it possible even to clone the dead.

Cow

Following Dolly's birth, a top priority for scientists was extending the cloning technique to work with other species [1]. Although most mammals are similar, and scientists often assume a technique will transfer from species to species, it was not certain that the protocol

used to clone Dolly would work with other animals. Sheep seemed particularly amenable to cloning, while other animals, including mice, had proven more challenging. With great anticipation, scientists awaited the first reports of cloning from differentiated adult cells in other species.

The wait was not long. Before 1998 was over, two groups had cloned cattle from differentiated cells and the first extension of the technique to work with mice was reported [1]. These results proved that Dolly was not a fluke and thus legitimized the field. Furthermore, the successful cloning of cows suggested that the vision of producing therapeutic compounds in milk might well be feasible, while the successful cloning of mice verified the utility of the technique as a basic biomedical research tool.

Mice

Mice are the workhorses of mammalian developmental biology labs [1]. Over the years, scientists have devised a host of procedures for working with these small rodents and manipulating their genes. They have also bred countless varieties, or strains. Today, you can open a catalog and order a mouse tailored to answer a specific research question. Mice that are predisposed to tumor development, heart attacks, or insulin resistance are merely a phone call away. Thus, the successful cloning of mice was a critical step if the technology was to develop into a truly useful developmental biology research tool.

Although earlier attempts had proven unsuccessful, using the template provided by Dolly's cloning, scientists were able successfully to clone mice.

Dogs

Dogs have an unusually complex reproductive system, in which eggs develop significantly after ovulation but before fertilization [1]. This necessitates modification of the standard cloning procedure and has hindered attempts to clone this most popular of house pets. Finally in 2005, after several years of trying, one research group reported successfully cloning a dog. This cloned dog, named Snuppy or "Seoul National University puppy" after the institution where it was created, quickly gained worldwide fame and is perhaps the second most famous cloned animal ever. Snuppy was even named the "2005 Invention of the Year" by Time magazine. Following reports of fraud in other cloning experiments carried out by the laboratory that created Snuppy, some scientists wondered if Snuppy was truly a clone. An investigation completed in early 2006 into Snuppy's pedigree verified that the dog was indeed a clone and deserves his place in history.

Embryo

The process of embryo splitting can be used in farm animals to produce genetically identical offspring [4]. The process is of little practical interest or significance since the numbers are limited and since the offspring has to be produced before knowledge about the exact properties of the developing animal can be ascertained.

These limitations changed dramatically with the successful introduction of nuclear transplantation technologies, exemplified by the birth of the sheep "Dolly" in July 1996 [4]. Nuclear transplantation is defined as the introduction of a cell nucleus from an adult donor cell (a somatic cell with a full chromosomal complement) into an enucleated egg cell (oocyte). The process had been tried prior to "Dolly", in particular in the frog system, in order to prove the hypothesis that every cell of a mammalian organism carries a full chromosomal complement. These early experiments never resulted in the development of adult animals, but rather stopped at the tadpole stage.

Since "Dolly", nuclear transplantation (NT) experiments have been repeated successfully with many species, lately even with rats, but never with primates [4]. Common to all of these efforts is the observation that the process is and remains extremely inefficient and error-prone. The proportion of live offspring per NT embryo transferred can reach 50 % and more in cows, but, in general, does not exceed 1 - 2%. In addition, those few animals that live to birth suffer from various abnormal phenotypes, i.e. placental abnormalities, fetal overgrowth and overweight, respiratory diseases, liver fibrosis, cardiac myopathies and many other defects. Even the sheep "Dolly" died prematurely after six years with symptoms of arthritis. The observed abnormalities can depend on the donor cell type used in the NT experiments. It has, for example, been shown that animals derived from cumulus cell nuclei tend to be obese, or that, in the pig system, there are no placental abnormalities.

Interestingly enough, in cases where offspring could be produced from cloned animals, the observed deficiencies are not heritable, indicating that other than pure genetic mechanisms are at work in nuclear transplantation.

Dangerous technology

The first safety argument is that cloning is an inefficient and dangerous technology [5]. According to this argument, animal experiments show that many eggs, embryos, fetuses, newborns, and mothers must die to generate a handful of live clones. Reasoning by analogy, opponents argue that human reproductive cloning is also likely to be inefficient and dangerous to embryos, fetuses, babies, egg donors and gestational mothers. This charge amounts to a half-truth. Yes, mammalian cloning is a new science, it has not been perfected yet, and success rates are low at present. Opponents, however, have painted a picture that is darker and more disturbing than the reality by presenting data in manner that is one-sided and often erroneous.

The Dolly experiment is often cited as proof of just how inefficient and dangerous cloning can be [5]. In 1996, Dr. Ian Wilmut and his associates at the Roslin Institute injected the nuclei of cells taken from a 6-year-old sheep into 277 unfertilized eggs. The experiment produced 29 embryos that were inserted into 13 ewes. One ewe became pregnant and gave birth to a healthy lamb (Dolly).

Conclusion

Scientists first take a unfertilized egg cell from a female and remove it from the nucleus containing DNA. From the body of the animal which be cloned, take the appropriate cell, such as a skin cell, whose core contains all genetic information about its owner. This cell (or just its core) scientists then entering into the egg cell from which they removed the core. This process achieves the unification of the cell and the ovarian cytoplasm. Once the new nucleus is obtained, the egg cell begins to split as if it was fertilized, thus the clone of the animal from which the body was taken is started.

The embryo can then be implanted into the uterus surrogate of the mother, where, in rare instances, when everything goes along plan, continue to develop until the time comes for the whelp to come to the world. There is another possibility, that is to keep the embryo in the uterus just as long as embryoblasts fail to isolate embryonic stem cells that can be kept in culture. Scientists believe that this fundamental principle of cloning should be effective in the case of humans. In fact, the attempt to clone a man was done with the intention of getting embryonic stem cells. Cloning for this purpose is called therapeutic cloning.

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