PRIMATE EMBRYOS GROWN IN THE LAB FOR LONGER THAN EVER BEFORE

The 20-day-old monkey embryos could reopen the debate about how long the human variety should be allowed to grow in a dish.

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Two groups in China have grown embryos from cynomolgus monkeys for 20 days.

By David Cyranoski

They are the longest-lived primate embryos to thrive outside the body. The monkey embryos survived in a dish for 20 days, thanks to techniques developed by two groups working in China. The work sheds light on a crucial but little-understood phase of early development, and will probably reignite the debate about how long human embryos should be permitted to develop in the laboratory.

Researchers grow embryos to understand the earliest stages of development. In 2016, biologists in the United States grew human embryos in the lab for 13 days, but then stopped the experiments because of an internationally accepted rule not to allow growth beyond 14 days for ethical reasons. Because monkeys are a closely related species, their embryos are a window into early human development, but scientists have previously grown them for only nine days.

The two teams in China now report in *Science*[1,2] that lab-grown embryos from cynomolgus monkeys (*Macaca fascicularis*) underwent several crucial processes. In one of these, gastrulation, the basic cell types that give rise to different organs begin to emerge, at around day 14.

"The best part is that there is a system to study gastrulation *in vitro* in a model very similar to the human," says Magdalena Zernicka-Goetz, a developmental biologist at the California Institute of Technology in Pasadena. "This is very exciting."

Although the studies show that early monkey development mirrors many aspects of the first two weeks of the human process, the teams report subtle differences between the two species. This suggests that monkey embryos might not be an adequate model for studying some advanced stages of human development, says Pierre Savatier, a stem-cell biologist at the Stem-cell and Brain Research Institute in Bron, France. He predicts that the papers will reinvigorate a push to extend the 14-day policy.

The ability to grow monkey embryos for longer than ever before could also boost research in another hot and controversial field — the generation of hybrid human–monkey embryos, known as chimaeras, with the goal of investigating how human cells differentiate into organs. This research has been held back because researchers haven't been able to grow monkey embryos for long enough to see how the injected human cells behave. Savatier says he will use the culture technique to grow monkey embryos that will be injected with human stem cells. "This culture system is hugely important for chimaera experiments," he says.

Embryo bonanza

Both teams grew monkey embryos on a gel matrix that supplied higher levels of oxygen than do cells in the womb. This culture technique was developed by Zernicka-Goetz's team, which was one of two groups[3,4] in the United States that grew human embryos for 13 days, in 2016.

In one of the latest two papers, a team led by Juan Carlos Izpisua Belmonte, a developmental biologist at the Salk Institute for Biological Studies in La Jolla, California, and Ji Weizhi at the Yunnan Key Laboratory of Primate Biomedical Research in Kunming, China, reports that 46 of 200 monkey embryos survived to 20 days. The authors of

the other paper, led by Li Lei, a developmental biologist at the Institute of Zoology, Chinese Academy of Sciences, in Beijing, say they grew three embryos for that long.

The teams tracked the progress of the embryos, which were created using *in vitro* fertilization, to check whether they grew as they would have in the womb. They examined the timing and shape of structures in the embryos and the structures that support embryonic growth, the types of protein that are expressed by cells at different stages and the primordial germ cells that go on to become eggs or sperm. Then they compared these observations with what is known about development of this species from past experiments, in which embryos were removed from pregnant monkeys at different stages up to 17 days.

Both groups report that embryos in a dish develop in the same way as those in the womb. "It's ok to assume that the observations made are a representation of what happens *in vivo*," says Izpisua Belmonte.

The teams stopped their experiments on day 20, when the embryos turned dark and some cells detached — signs that the structures were collapsing. Li says it's not clear why that happened. He and Izpisua Belmonte say that culturing the cells in an extracellular matrix that better mimics the womb might help them to survive longer. Next, Ji hopes to grow embryos to the point when the primitive nervous system starts to form, around day 20.

Sutble differences

Savatier says one difference between monkey and human embryos, described in the Ji and Ispizua Belmonte paper, is that the genes that are expressed in monkey cells that form the placenta are different from those in humans. But to study these processes in later stages in human embryos, regulators would need to lift the 14-day ban.

After the US teams grew human embryos to 13 days, some scientists and ethicists pushed for a revision of the policy, and a poll conducted in the United Kingdom in 2017 reported strong public support for extending the limit beyond 14 days. Savatier and others think the latest results showing the unique features of human embryonic development will strengthen arguments to change the policy.

Researchers are optimistic that the gel matrix could be used to grow human embryos to a more advanced stage if the rules change. Ji says that another group at his institute has developed a protocol specifically for human embryos that will soon be published. "This system could be suitable for human embryos to be cultured to 20 days," he says, "but we are not planning to do it."

1. Niu, Y. *et al. Science* http://doi.org/ddn3 (2019).
2. Ma, H. *et al. Science* http://doi.org/ddn4 (2019).
3. Deglincerti, A. *et al. Nature* **533**, 251–254 (2016).
4. Shahbazi, M. N. *et al. Nature Cell Biol.* **18**, 700–708 (2016).

GENOMES TRACE ORIGINS OF ENSLAVED PEOPLE WHO DIED ON ISLAND

Former slaves left on St Helena were probably taken from west-central Africa, a genome study finds.

By Ewen Callaway

Genomes from enslaved Africans who were freed and died on a remote Atlantic island in the mid-nineteenth century are offering clues about their origins in Africa. The findings come from the largest study of genome data obtained so far from remains of enslaved people and offer insights into the transatlantic slave trade, in which an estimated 12 million Africans were kidnapped and enslaved in North and South America and the Caribbean.

Researchers analysed DNA taken from 20 people from the British island territory of St Helena, whom the British Navy had liberated and brought there. The research, posted on the bioRxiv preprint server last month, suggests that the people might have been captured in parts of west-central Africa, including present-day Angola and Gabon (M. Sandoval-Velasco *et al.* Preprint at bioRxiv http://doi.org/ddq2; 2019).

"By illustrating the history and the condition of a few, we are at the same time illustrating the condition of the many."

No island paradise

St Helena, which lies in the Atlantic Ocean nearly 2,000 kilometres west of Angola, occupies a unique chapter in the history of the transatlantic trade in people. After Britain outlawed the slave trade in 1807, its navy intercepted slave ships and sent an estimated 24,000 people to St Helena. They had been aboard ships heading largely to Brazil and Cuba between 1840 and the late 1860s.

Many of the people freed arrived in poor health and were housed in squalid conditions, and as many as 10,000 died. In 2006, construction work uncovered mass burials, and archaeologists unearthed the remains of 325 people — more than half under 18.

Unlike cemeteries in the Americas, which tend to hold multiple generations of people who had once been enslaved, nearly all of the people who died on St Helena were likely to have been born in Africa.

Shipping records — the main historical source on the African origins of people taken into captivity — tend to record only the ports from which slave ships set sail, but other records suggest that many of the people were captured farther inland.

In an attempt to better trace the Africans left on St Helena, a team led by palaeogenomicist Marcela Sandoval-Velasco and ancient-DNA researcher Hannes Schroeder, both at the University of Copenhagen, tested remains from 63 of the people for intact DNA. They sequenced partial genomes from 20.

Seventeen were male — backing up records indicating that, in its final decades, the transatlantic slave trade captured more men than women. Analysis of the genome data found that none of the people were closely related, nor did they belong to a single African population.

Comparisons with genome data from thousands of modern Africans from dozens of populations suggest that the people from St Helena are most closely related to people living today in central Gabon and northern Angola. But the researchers caution that gaps in present-day genome data from potential homelands, such as the Democratic Republic of the Congo, make it difficult to say for certain where the people buried in St Helena were taken from. "Although it's very hard to exactly pinpoint their origins, I think what we see in our results is that they are not coming from a single population," says Sandoval-Velasco.

This insight suggests that the liberated Africans on St Helena lived in a challenging multicultural setting where they might not have understood the language and customs of others left on the island. "We hope that by illustrating the history and the condition of a few, we are at the same time illustrating the condition of the many, but it shouldn't stop there," Sandoval-Velasco says.

Genome analysis shines a powerful light on people exploited in one of history's darkest chapters, says Rosa Fregel, a population geneticist at the University of La Laguna in the Canary Islands. "Usually it's just about numbers — how many people from each country. Here, we are talking about particular people and their origin," says Fregel. "Ancient DNA has the potential to tell their story."