Chimeric Monkeys: A Leap in Biomedical Science

By YAN Fusheng

A recent study published in *Cell* has achieved the first live-birth chimeric monkey with a high contribution from embryonic stem cells (ESCs). Combined with well-established gene editing techniques on these stem cells, this breakthrough could usher in a new era of utilizing such stem cells for disease research and therapeutic development.

The generation of the first live-birth chimeric monkey with high contribution of embryonic stem cells (ESCs).

In a recent study published in *Cell*, researchers have successfully created chimeric monkeys for the first time, offering new opportunities to understand embryonic development and genetic diseases. This breakthrough represents a significant leap forward in biomedical science.

The study was jointly led by Dr. LIU Zhen and Dr. SUN Qiang from the Institute of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology of the Chinese Academy of Sciences (CAS), and Dr. Miguel A. Esteban from the Guangzhou Institute of Biomedicine and Health of CAS.

Chimeras, organisms containing cells from two different species or individuals, have long been of great interest. For example, chimeras allow scientists to track the development and migration of cells from the injected embryo when these cells are genetically tagged. This helps understand what signals direct cell differentiation and migration during embryonic development. Scientists can also use chimeras to model human diseases. Adding human cells, like immune system or liver cells, to mice allows researchers to study things like human immune responses or infections like malaria in a living system, rather than a dish.

Given that chimeras are a valuable research model for studying development, cell differentiation, disease, and transplantation, creating chimeric animal models is a hot pursuit.

Chimeric mice and rats generated by complementing early embryos with homologous embryonic stem cells are well-established and have been widely utilized to produce gene-targeted models.

Considering the genetic closeness of monkey to human, chimeric monkeys represent a more valuable vessel to model human diseases and study biological processes.

However, achieving chimerism in non-human primates has not been successful because unlike mice produce litters of 6-12 pups, monkeys usually have just 1 offspring at a time after 5-6 months of pregnancy. More importantly, monkeys form a more robust immune system earlier in development compared to mice, in other words, higher possibility of immune rejection. However, scientists are interested in pursuing monkey chimeras because of their greater similarity to humans.

Until now, scientists' hard work has finally paid off.

In this new study, scientists used a novel approach to create a cynomolgus monkey chimera with a remarkably high contribution (up to 90%) from donor embryonic stem cells (ESCs), confirmed by rigorous characterization. This successful attempt, once thought near impossible in primates, is akin to a biological symphony where cells from different origins harmonize to create new life.

The process began by finding a proper culture medium to produce naive ESCs from cynomolgus monkeys, cells capable of developing into any tissue.

They found that the 4CL medium performs best among many tested media in supporting balanced genome-wide DNA demethylation and high expression of naive pluripotency genes for monkey ESCs; in other words, the 4CL medium can convert monkey primate ESCs into naive pluripotent state, a state resembling inner cell mass of early embryos. So, they picked this medium to produce naive monkey ESCs.

The timing of the injection is also critical because the mismatch of the developmental state of the donor cells with that of the embryo would lead to the elimination of donor cells. In other words, the injected donor cells should jump in at the right moment to keep the same pace with the native embryotic cells; If not, the donor cells would be easily wiped out.

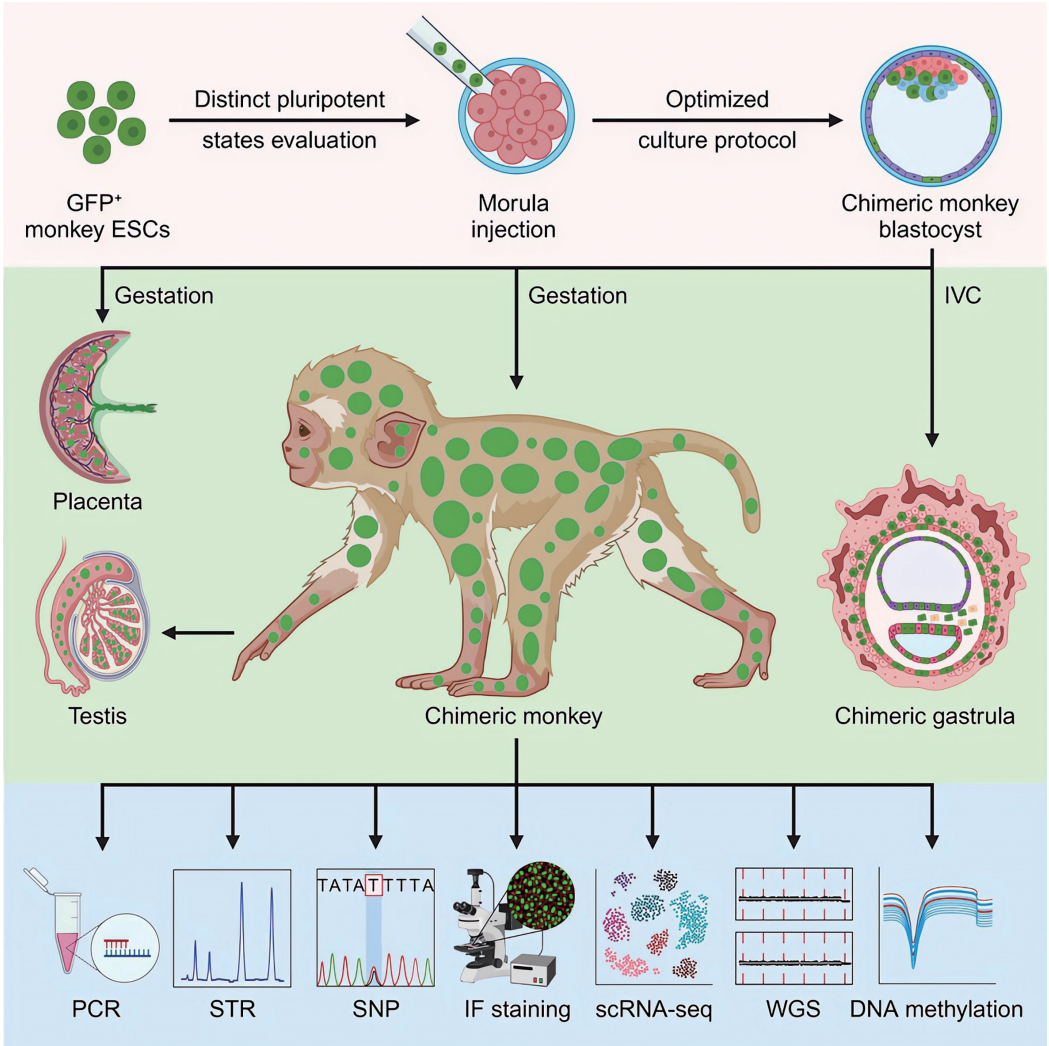
After optimizing the protocols for injecting donor cells into the early monkey embryos and *in vitro* culture of the injected embryos, the team successfully enabled donor cells to fit into the tissue niche and achieve substantial chimerism.

This success demonstrates the feasibility of high-contribution chimeras in non-human primates, previously considered extremely challenging.

Beyond creation, the study thoroughly investigated functional integration of ESC-derived cells in the chimeric monkey. Using innovative sequencing, the researchers revealed extensive ESC contribution to diverse tissues including brain, blood, and remarkably, even germ cells.

This study has profound implications for understanding naive pluripotency in primates and genetically engineering non-human primate models. The ability to generate chimeric monkeys with remarkably high ESC contribution enhances knowledge of primate ESC pluripotency and totipotency. Additionally, this lays the foundation for genetically modified primate models to study complex disorders.

Overall, chimeric models could revolutionize understanding and treatment of many medical conditions,



Charting the birth of a chimeric monkey. This schematic illustrates the creation of a chimeric monkey, from the injection of GFP-labeled monkey embryonic stem cells into an early-stage embryo, through the optimized cultivation, to the final result – a chimeric monkey. The bottom panel displays the array of genetic tests used to verify the chimeric nature of the tissues. (Credit: CAS)

bringing us closer to elusive cures.

Chimeric monkeys may offer a surrogate model to circumvent the ethical concerns that could be easily triggered when studying human embryos. However, there are also valid ethical concerns over creating chimeric monkeys, given their genetical closeness to humans. Scientists need to ensure human cells in monkey chimeras are not able to produce germline cells or human neurons that could impact cognition or behavior. Careful oversight is warranted.

The study "*Live birth of chimeric monkey with high contribution from embryonic stem cells*" was published in *Cell* on November 9, 2023. Notably, experiments followed International Society for Stem Cell Research guidelines and ethics oversight to ensure appropriate standards.

Reference

Cao, J., Li, W., Li, J., Mazid, M. A., Li, C., Jiang, Y., . . . Liu, Z. (2023). Live birth of chimeric monkey with high contribution from embryonic stem cells. *Cell, 186*(23), 4996-5014.e4924. doi:10.1016/j.cell.2023.10.005