Rat's Brain Grown in Mice

TEXT: YAN Fusheng

From science fiction to scientific reality: Imagine a world where one species' brain thrives inside another's body. It sounds like the stuff of dreams – or nightmares – but in a stunning breakthrough, scientists have turned this fantasy into fact.

In the April 25 issue of *Cell*, a research team published their work on generating functional rat forebrain tissues within living mice. This breakthrough may promise to unlock new insights into brain development, evolution, and potential therapies for neurological disorders.

The team was jointly led by Drs. YANG Hui and ZHOU Haibo from the Institute of Neuroscience (ION), Dr. GUO Fan from the Institute of Zoology (IOZ), both under the Chinese Academy of Sciences (CAS), and Dr. Jun Wu from the University of Texas Southwestern Medical Center.

This new advancement, accomplished through a technique called "interspecies blastocyst complementation (IBC)," represents a significant leap forward in the understanding of one of nature's most complex and enigmatic structures – the brain.

More specifically, the team employed a novel approach called "C-CRISPR-based blastocyst complementation" (CCBC). This method streamlined the identification of suitable candidate genes that could support the generation of rat forebrain tissues within genetically modified mouse embryos.

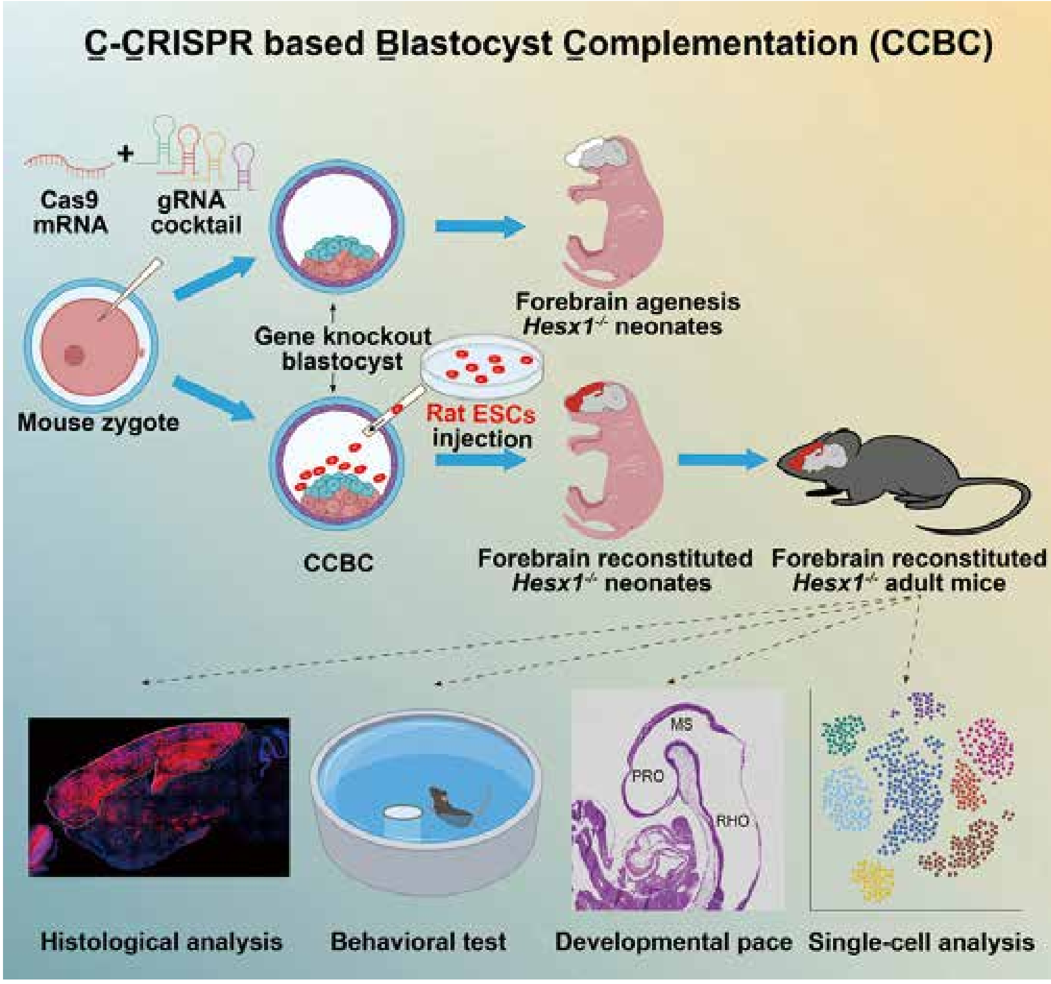
Through a meticulous screening process, the researchers discovered that knocking out the *Hesx1* gene in mouse blastocysts created a developmental niche that allowed rat embryonic stem cells (rESCs) to repopulate and reconstitute the missing forebrain region. The resulting chimeric mice, harboring rat forebrain tissues within their bodies, not only survived into adulthood but also exhibited normal brain structure, function, and cognitive abilities.

Interspecies neural blastocyst complementation allows researchers to explore the intricate interplay between external factors, like the host environment, and internal factors, such as species-specific gene expression, as the authors wrote in the article. "This dynamic interaction plays a crucial role in guiding the development of species-specific neuronal circuits and functions."

The study revealed fascinating insights into the interspecies dynamics at play during brain development. Remarkably, the rat forebrain tissues developed at the same pace as their mouse counterparts, synchronizing with the host species' developmental timing. However, the single-cell transcriptomic analysis revealed that the rat-derived neurons maintained their species-specific gene expression patterns, suggesting an intriguing interplay between cell-autonomous and non-cell-autonomous mechanisms governing brain development.

"We anticipate that the CCBC platform can be broadly applied to a wide range of organs, paving the way for utilizing large animals as hosts in blastocyst complementation experiments involving human cells," explained the researchers.

As a matter of fact, this new



Graphic: CAS

Chimeric mice with rat forebrain tissues, generated by injecting functional rat embryonic stem cells into genetically modified mouse embryos, survived to adulthood with normal brain structure, function, and cognitive abilities.

progress holds significant potential for addressing global organ shortages and advancing regenerative medicine. By utilizing large animal hosts, such as pigs or non-human primates, interspecies blastocyst complementation could pave the way for generating human organs for transplantation, offering new hope for patients awaiting life-saving organ donations.

Moreover, the ability to generate interspecies brain tissues opens exciting avenues for studying neurological disorders and developing novel therapeutic strategies. By introducing human stem cells into animal models with reconstituted human brain regions, researchers could gain unprecedented insights into the pathogenesis of conditions like Alzheimer's, Parkinson's, and other neurodegenerative diseases, ultimately accelerating the development of effective treatments.

However, as with any groundbreaking discovery, ethical considerations must be carefully navigated. The potential for generating human brain tissues in animals may raise complex questions regarding consciousness, cognition, and the moral boundaries of such endeavors. Robust ethical frameworks and rigorous oversight will be essential to ensure responsible and ethical implementation of this technology.

Despite these challenges, the successful generation of rat forebrain tissues in mice represents a significant milestone in our quest to unravel the mysteries of the brain and harness the potential of regenerative medicine. As this groundbreaking research continues to unfold, it may promise to reshape our understanding of brain development, evolution, and the treatment of neurological disorders.

Reference

Huang, J., He, B., Yang, X., Long, X., Wei, Y., Li, L., . . . Wu, J. (2024). Generation of rat forebrain tissues in mice. *Cell*, 187(9), 2129-2142.e2117. doi:10.1016/j.cell.2024.03.017