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A new chimeric model to study human brain development and disease

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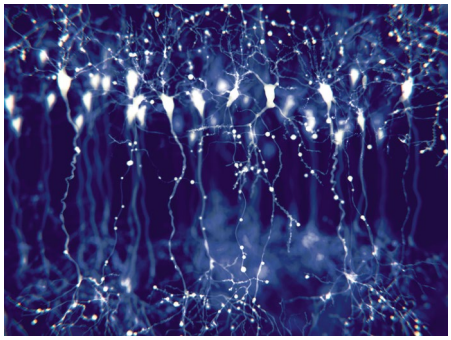
Despite their importance to understand many aspects of human brain development, animal models cannot reveal developmental features that are unique to humans. Human pluripotent stem cell (hPSC)-derived neurons hold the promise of better relevance for human brain research but human brain organoids don't accurately recapitulate all aspects of neuronal development. By bridging the gap between hPSC technology and animal models, a chimera model based on the xenotransplantation of human cells into the mouse brain provides new insights into human neuronal development and opens novel avenues for the investigation of human neuronal function and disease.

In previous studies, the transplantation of human PSCs-derived into mouse brain was achieved by using cell-compact transplants comprising a large number of cells, which might have limited the access of the transplanted cells to the host tissue and affected their circuit integration. In this study, investigators from KU Leuven in Belgium injected human embryonic stem cell-derived cortical pyramidal neurons into the mouse cortex in presence of EGTA—a Ca^{2+} ion chelator that dissociates adherens junctions—to facilitate cell integration into the brain. Brain examination 24 h after transplantation revealed that GFP^+ human cells had integrated as single cells within the mouse cortex and were migrating along radial glia processes. At later stages, from 2 weeks to 1 month post-transplantation, human neurons were found within the cortical gray matter from deep to superficial cortical layers, confirming their successful integration in the mouse cortex.

Analysis of brain slices at different time points showed that transplanted human neurons developed morphologically and functionally following a similar timeline to the one reported in the human developing brain. Human cortical neurons are known to display an unusually prolonged development compared with other species. This human-specific feature is referred to as neoteny—the retention of juvenile traits in a more mature organism—and could contribute to the differences in cognitive abilities and developmental disorders observed between humans and other mammalian species. Ex vivo whole-cell patch clamp recordings and analysis of cell morphology revealed a progressive maturation of human neurons, including changes in functional properties, dendritic length and complexity, as well as dendritic spine density and morphology. In vivo imaging of GFP-labeled transplanted cells at 2-week intervals for up to 12 weeks using a two-photon microscope through an implanted glass window positioned over the mouse cortex revealed that human cortical neurons displayed juvenile-like dendritic spine dynamics, despite their integration in the cortex of an adult mouse. Altogether these results indicate that transplanted human neurons integrate into the mouse cortex and show protracted maturation over months. By contrast, mouse neurons transplanted in the mouse cortex were shown to mature in only a few weeks, a similar maturation rate to that of endogenous mouse cortical neurons. "We show that the transplanted neurons mature following a prolonged human-like timeline, indicating that human neuronal neoteny has a strong intrinsic component," say the investigators in the introduction of their study.



Pyramidal neurons in the cerebral cortex. Credit: JUAN GAERTNER/SCIENCE PHOTO LIBRARY

Next, to assess the functional synaptic integration of the transplanted neurons in vivo, the investigators performed cellular Ca^{2+} imaging of the cells, which revealed that >25% of the xenotransplanted cells could respond to visual stimulation. In addition, xenotransplanted neurons showed diversely tuned responses to specific properties of visual stimuli (such as stimulus orientation and direction) resembling those of mouse neurons in control and transplanted animals. These findings show that human neurons could receive inputs from host neurons and had successfully integrated and inherited functions of the host cortical neurons, including tuned responses to sensory stimuli.

"This model robustly recapitulates key milestones of human neuronal development not reported so far using xenotransplantation or in vitro models," explain the investigators in the discussion. In particular, the study reports that transplanted human cortical neurons have a prolonged timeline of morphological development, which is in line with human cortical neoteny. "Our model thus constitutes a promising experimental system to elucidate the mechanisms controlling the timeline of neuronal maturation, in particular genes potentially involved in human neuronal neoteny," they add.

Their model also provides a unique opportunity to model human neuronal plasticity in health and disease, given that many human psychiatric and neurological conditions have developmental origins but cannot be studied adequately in animal models. By showing that the transplanted cells can integrate mature cortical tissues and gain information-processing functioning, the study also suggests that the transplantation of juvenile neurons might be an interesting cell-based therapeutic strategy to restore damaged brain tissue.

Alexandra Le Bras

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