Human Neurons in Rat Neural Circuits

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The concern regarding whether animal-based research models can produce results applicable to humans has long been well-integrated within the field of neuroscience. A recent study has shown that human cortical organoids (hCO) developed from human induced pluripotent cells (hiPS) and transplanted into the primary somatosensory cortex (S1) of rats in early development can undergo maturation and integration into the rat's existing neural circuits (Revah et al., 2022). The implications of such findings are extensive, although the primary goal of the researchers was to utilize the model as a means of studying human neurodegenerative and neuropsychiatric disorders.

The researchers stereotactically transplanted 3D hCO into the S1 of early postnatal rats (Figure 1). Consecutive MRI scans across a period of three months showed a ninefold increase in hCO volume, confirming successful growth of the implanted organoid. Previous attempts in utilizing transplanted brain organoids to study neural activity were short lasting, as the cells were unable to receive adequate nutrition from blood vessels and enough stimulation to grow (Reardon 2022). However, Revah et al. (2022) reported a high survival rate of the transplanted rats even 12 months after the transplantation. Using specific staining techniques, the researchers confirmed the presence of vascularization and microglia throughout the transplanted hCO (t-hCO). Furthermore, comparing the genetic sequences of t-hCO to hCO, the researchers discovered that both organoids exhibit similar classes of cells with the exception of a lack of oligodendrocytes and the presence of GABAergic neurons in hCO. Such conditions provide a favorable cellular and molecular environment for the successful growth and development of t-hCO within the rat brain.

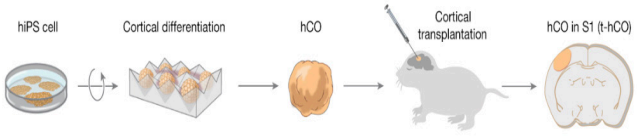

Figure 1. Experimental Design. hiPS cells used to generate hCO, which was transplanted into the S1 of postnatal rats (Revah et al., 2022).

Further comparisons between t-hCO and hCO revealed that the transplanted organoids have larger cell bodies, more dendrites of greater lengths, and higher dendritic spine density compared to hCO (Figure 2). Electrophysiological differences were also evident as the t-hCO was shown to be more active overall, with increased levels of synaptogenesis, astrogenesis, and myelination compared to hCO. Additionally, human cortical pyramidal neurons from the postnatal human cortex were found to be more similar to t-hCO than hCO.

To assess the applicability of the t-hCO model in studying advanced neurologic diseases, Revah et al. (2022) generated hCO from patients with Timothy Syndrome (TS). This neurodevelopmental disorder is caused by a gain-of-function mutation in a gene that is involved in activity-dependent neuronal gene transcription. Upon implanting the TS-hCO into the rat brain, the researchers found altered dendritic morphology in TS neurons, leading to an increase in synaptic spine density and frequency of spontaneous EPSPs in TS compared to the control. This difference, however, was not present in non-transplanted TS hCO, illustrating the ability of the model to successfully mimic human disease phenotypes.

The researchers used whole-cell recordings to confirm that t-hCO had become anatomically and functionally integrated within the pre-existing circuits of the rat brain. Brief displacements in the whiskers of the rats (a sensory stimulus) caused an increase in activity in a subset of t-hCO cells in response to the stimulation. Therefore, t-hCO is capable of responding to environmental stimuli. Using an operant conditioning paradigm, the rats were trained to associate licking during optogenetically induced blue light stimulation with a water reward. t-hCO rats displayed increased licking during blue light stimulation compared to controls, implicating t-hCO in driving reward-seeking behavior.

Ultimately, the findings of Revah et al. (2022) serve as a foundation for potential future research methods involving transplantation of human-grown cells into animal models. For now, researcher Paola Arlotta claims the procedure is still too expensive and complex to become the new standard (Reardon, 2022). The next steps for the research team includes exploring how integration into the rat brain occurs at the level of the individual neuron, rather than the organoid.

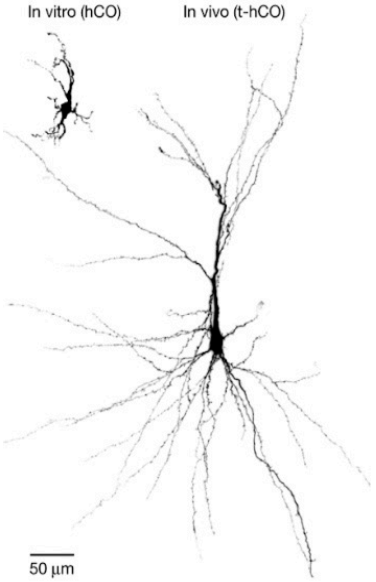

Figure 2. A comparison of hCO and t-hCO neurons after 8 months of differentiation. Neurons transplanted into the rat brain (right) display more growth than those cultivated in a dish (left). (Reardon, 2022)

References

Reardon, S. (2022). Human brain cells implanted in rats prompt excitement – and concern. *Nature*. 610, 427-428

Revah, O., Gore, F., Kelley, K.W., et al. (2022). Maturation and circuit integration of transplanted human cortical organoids. *Nature*. 610, 319–326.