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NEURAL CIRCUITS

Cortical replacements

> the tuning of new neurons by 9–15 weeks after transplantation was highly similar to that of endogenous L2/3 neurons

Cell transplantation is being explored as a treatment for various neurodegenerative disorders, but, to date, it is unclear whether cells that are introduced into the adult brain can integrate into neural circuits and genuinely replace the function of lost neurons. Falkner, Grade *et al.* now show in mice that embryonic cortical neurons transplanted into a damaged area of the adult primary visual cortex (V1) successfully integrated into existing circuits and developed visual stimulus-selective responses that eventually resembled those of adult neurons.

The authors used a laser photoactivation-based approach in young adult mice to induce apoptosis in layer 2/3 (L2/3) callosal neurons in V1. About 1 week later, they transplanted fluorescently labelled cortical cells from mouse embryos into the lesioned area. Through a cranial window, two-photon microscopy revealed that, 4 weeks after transplantation, most of the introduced cells remained at the lesion site, morphologically resembled L2/3 pyramidal cells and expressed a marker of such neurons, suggesting that the transplanted cells were indeed L2/3 pyramidal cells.

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The authors closely monitored the structural maturation of the transplanted cells by repeated two-photon imaging (up to almost a year in some cases). Many of the neurons that survived the transplantation process and initiated dendrite development shortly thereafter survived for the imaging period. Moreover, these neurons generally followed a pattern of maturation that was in line with development. Together, these findings suggest that the transplanted cells can form stable neuronal populations.

The authors next examined the connectivity of transplanted neurons. First, they conducted the transplantation experiment with embryonic cortical neurons expressing red fluorescent protein in their axons. 5 weeks after transplantation, many of the axons of the new neurons that stayed in V1 projected to L5, which is the main laminar target of V1 L2/3 pyramidal cells. Axons were also identified that projected to other well-established target areas for V1 L2/3 pyramidal cells, including other visual areas. To assess afferent connectivity, the authors injected a modified rabies virus expressing green fluorescent protein into the lesioned area some weeks after cell transplantation, which allowed retrograde monosynaptic tracing in the transplanted neurons. This approach revealed that neurons from 23 different brain regions, including V1 itself, sent inputs to the new L2/3 V1 neurons, which is in agreement with the result of other studies. Thus, the transplanted neurons seem to form connections with their appropriate upstream and downstream neural circuit components.

V1 neurons can respond to specific features of visual stimuli. Thus, to examine the function of the transplanted neurons, the authors repeated the transplantation experiment with embryonic cells expressing a genetically encoded calcium indicator and, several weeks later, recorded the calcium signals in these cells as moving gratings were shown to the eye contralateral to the lesion site. About 50% of the transplanted cells that responded to the visual stimulus exhibited strong responses to the orientation and/or direction of movement of the grating. Interestingly, repeated imaging revealed that the stimulus-induced responses of the transplanted neurons varied in the early weeks after their introduction but stabilized and became sharper by week 9 after transplantation. Strikingly, the tuning of new neurons by 9–15 weeks after transplantation was highly similar to that of endogenous L2/3 neurons, indicating functional integration of the transplanted neurons into the existing neural circuits. Together, these data show that, in mice, transplanted embryonic cells can functionally replace ablated neurons in the adult cortex.

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