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Star-cross’d neurons: astroglial effects on neural repair in the adult mammalian CNS

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Astroglia have long been thought to play merely a supporting role in the life of the neuron. However, these star-shaped cells have recently been the focus of intense study that has begun to emphasize remarkable and novel roles for these amazing cells. While astroglia play positive roles in the life of the neuron, they can simultaneously exert negative influences. Indeed, the inhibitory roles of astroglia upon nerve regeneration are now well documented; glial scars that typically form after injury by reactive astrocytes constitute both a mechanical and a chemical barrier that blocks nerve regeneration and axonal growth. Now, Kinouchi and colleagues [6] provide further compelling evidence for the central role of astroglia in neuronal differentiation and integration in the adult CNS.

Robust neuronal integration in a modified astroglial environment

In this elegant study, the authors used the adult mammalian retina, which contains both astroglia and Müller glia, as a model in which to characterize and assess how astroglia can influence neuronal integration. Kinouchi et al. provide crucial insight into the molecules that control this phenomenon. Specifically, and most interestingly, they show that two classically astroglial filament proteins, GFAP and vimentin, directly influence the ability of donor cells to survive, migrate and integrate upon transplantation in the adult retina in vivo.

Using transgenic mice null for GFAP, vimentin, or both, as recipients, and retinal donor cells expressing green fluorescent protein (GFP), they systematically examined migration and neurite outgrowth properties of the transplanted cells in vivo. From these studies, they conclude that a lack of the non-permissive proteins, GFAP and vimentin, contributes significantly to the success with which donor cells integrate in an otherwise inhibitory

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However, just as astroglia play positive roles in the life of the neuron, they can simultaneously exert negative influences. Indeed, the inhibitory roles of astroglia upon nerve regeneration are now well documented; glial scars that typically form after injury by reactive astrocytes constitute both a mechanical and a chemical barrier that blocks nerve regeneration and axonal growth. Now, Kinouchi and colleagues [6] provide further compelling evidence for the central role of astroglia in neuronal differentiation and integration in the adult CNS.

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environment. Contrary to results in wild-type mice (where transplanted neurons typically fail to survive and integrate in the adult retina), when postnatal-day (P0) retinal suspensions were transplanted into GFAP\(^{-/-}\)/Vim\(^{-/-}\) mice, many of the transplanted cells were able to migrate long distances away from the injection site, especially to the ganglion cell layer, resulting in an increased number of re-populated neurons. In addition, in GFAP\(^{-/-}\)/Vim\(^{-/-}\) mice, donor cells displayed a marked increase in both the number of extended neurites and the length of such neurites.

Intriguingly, the cellular integration reported by Kinouchi \textit{et al.} appeared to be somewhat cell-type- and layer-specific, with donor cells seemingly preferentially integrating into the ganglion cell layer rather than differentiating into other types of neurons, such as amacrine or bipolar cells, or into glia. Many cells were alive and appeared morphologically integrated into the recipient retina six months following transplantation, although the authors did not address whether these cells truly differentiated into retinal ganglion cells, as neither electrophysiological nor axonal projection analysis was performed. Similar results were obtained using donor cells from older mice (P14–P21), which notoriously survive and integrate more poorly following transplantation. Just as with cells from younger P0 donors, P14–P21 donor cells were also apparently able to integrate much more effectively into GFAP\(^{-/-}\)/Vim\(^{-/-}\) retinas than into wild-type retinas. It will be interesting in the future to examine the precision of differentiation of these newly integrated cells using increasingly refined marker analysis, electrophysiology, and investigation of whether at least a subset can establish the correct pattern of long-distance connections to the superior colliculus.

**Potential roles for GFAP and vimentin**

What is it about the production or presence of the intermediate-filament proteins GFAP and vimentin that limits neuronal integration? Clearly, these proteins are intimately involved in reactive gliosis and the formation of the ‘glial scar’ [7–10], but in what manner is this phenomenon occurring? To become successfully integrated into the recipient environment, a transplanted cell must be able to complete a coordinated sequence of crucial developmental steps. It must first survive, migrate to the correct final location, and then differentiate appropriately. Finally, it must be able to intercalate into the recipient environment to achieve functional integration and long-term stability. Which of these crucial steps is enhanced by the lack of GFAP and vimentin in astrogia? Are GFAP\(^{-/-}\)/Vim\(^{-/-}\) astroglia developmentally different from their wild-type counterparts [11,12]? Are these astroglia less able to form a glial scar, thus enhancing the ability of adult-born neurons to integrate and extend processes, in turn enhancing their long-term survival? Limitation of neuronal process formation by the glial scar might very well be one of the multiple normal astroglial effects that are interfered with in the absence of GFAP and vimentin. Interestingly, immediate (as well as long-term) survival of the transplanted cells appears to be enhanced in this animal model. Further experiments should consider whether GFAP and vimentin modulate interference by astrogia with molecules involved in neuronal survival. Alternatively, given the well-established role of astrogia in providing neighbouring neurons with trophic support, the lack of GFAP and vimentin might enhance the ability of astrogia to produce and/or release such growth and neurotrophic factors, although it is not at all clear by what means this process would occur at the molecular level. Another relevant issue indirectly raised by the report of Kinouchi \textit{et al.} concerns the potential compensatory or synergistic roles of different classes of astrogial filament proteins, because it appears that lack of neither GFAP nor vimentin alone is capable of enabling the robust neuronal integration that is seen when both proteins are absent. However, these double-knockout mice have modified expression of other cell adhesion molecules, such as laminin and N-cadherin [13,14]. Finally, it should also be noted that the process of cell transplantation itself might influence retinal GFAP and/or vimentin expression, and that these changes could in turn modulate the volume of the extracellular space within the retina [15,16]. A clearer understanding of the precise roles these molecules play, both in the retina and in other CNS regions, will be crucial for the development of therapeutic approaches toward directed CNS repair.

**A fine balance**

Kinouchi \textit{et al.}’s experiments provide a useful paradigm by which to probe for both inhibitory and permissive factors associated with astrogia. There is an intimate interplay between the recipient environment and the donor cells themselves, and indeed one can imagine that this complex interplay occurs at a more cell-specific level, between recipient astrogia and transplanted neurons. Just as glia exert a variety of negative influences, including glial scarring, gliosis and the presence of GFAP, vimentin and other repulsive factors [7–9,17–22], astrogia also provide support for neuronal integration and survival. These positive influences from glial cells can occur both developmentally and in adulthood; such influences can include, but are not limited to, the provision of trophic support, extracellular buffering, neurotransmitter reuptake and recycling, and cellular scaffolding for neuronal migration or for axonal or dendritic extension [23,24]. These seemingly contradictory roles of astrogia are thus of a complex and presumably complementary nature (Figure 1).

Neural transplantation involves an intricate relationship between donor cells and the recipient environment, yet the focus of the majority of transplantation studies has been on the characterization of the donor cells themselves, rather than on the environment into which these cells are introduced.
There is a clear need to understand the signals present in the recipient microenvironment that affect its ability to support neuronal differentiation, integration and/or neurogenesis from endogenous precursors, so that the local microenvironment in distinct pathological situations can be directed towards CNS repair [25]. However, there is a substantial lack of knowledge regarding the molecular mechanisms involved. The report by Kinouchi et al. provides evidence that filament proteins commonly found in astroglia can affect neuronal integration dramatically in the adult retina, and demonstrate how crucially astroglia can control neuronal fate, far beyond what is typically thought. By highlighting this pivotal role for astroglia in the adult CNS, Kinouchi et al. provide further evidence for the varied, at times seemingly contradictory, and crucial roles of astroglia. This emphasizes that work towards understanding the potentially varied and certainly vital roles of glia in CNS repair has only just begun.

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