Olfactory glia and CNS repair: a step in the road from proof of principle to clinical application

Considerable advances have been made in the last decade in devising and evaluating cell transplantation strategies for enhancing axon regeneration for patients with spinal cord trauma, and in achieving remyelination in chronic demyelinating diseases such as multiple sclerosis. Thus, a number of studies have established that transplantation of glial cells can have beneficial consequences in experimental models of spinal cord trauma and demyelination. In particular, in rats, it has been shown that implantation of Schwann cells or olfactory glial cells results in significant regeneration of axons across spinal cord transection sites and that this is associated with an improvement of locomotor function (Cheng et al., 1997; Xu et al., 1999; Ramón-Cueto et al., 2000). A potential therapeutic superiority of olfactory glia over Schwann cells was demonstrated by experiments in which the number of regenerating axons crossing a transection site was dramatically increased when olfactory glia were placed at the interface between a Schwann-cell-filled guidance tube and the damaged spinal cord (Ramón-Cueto et al., 1998). The reports of such experiments stimulate considerable media interest and, not unexpectedly, raise patient hopes for a cure to their disability. There are therefore a major challenge for neuroscientists and clinicians to build on the proof of the principle established by these experimental studies with a view to adapting the approach for clinical use.

In any situation where cell therapy is being considered, a number of practical issues have to be addressed before any clinical trial can be contemplated. One of the most fundamental of these issues is whether the required cells can be obtained from the patient themselves, since this would avoid the necessity for immunosuppression. With Schwann cells this issue has largely been resolved. It is possible to expand human Schwann cells from small amounts of starting material, using a combination of heregulin and forskolin, and to drive cell multiplication to a point where sufficient cells could be available for use in a patient. The article by Barnett and colleagues in this issue of Brain demonstrates that the same can now be achieved for olfactory glia (Barnett et al., 2000). This paper represents the first report of the in vitro cultivation and expansion of human olfactory glial cells. An animal model of persistent demyelination is then used to establish that in vitro expansion has not led to loss of function or uncontrolled cell proliferation. This study thus represents a significant advance for those considering olfactory glia as a potential cell type to use in clinical trials aimed at enhancing regeneration of axons following spinal cord trauma.

This paper also highlights another important point for those trying to make the transition from a proof of principle established using rodents to the use of the approach in man, because it demonstrates once again that the cultivation and expansion of human cells is not as straightforward as expansion of their rodent counterparts. Thus, while rodent olfactory glia can be selected through their expression of antigens recognized by the O4 monoclonal antibody, human cells do not express this antigen. Instead, use had to be made of another marker for this cell type, the low affinity NGF receptor. However, in contrast to rodent cells this receptor is downregulated during culture, making identification, and thus further selection of olfactory glia difficult, should this be required prior to therapeutic use. Such observations indicate that new reagents and techniques have to be developed by those who need to work with human cells. This imposes considerable difficulties for the researcher, since obtaining regular supplies of human cells required to test and evaluate culture methods and reagents is less straightforward than is the case with rodent tissue, making progress slow. A further constraint to making the rodent–human transition is that the development work required is often perceived as unattractive scientifically because progress is slow. Moreover, the work is also often perceived as lacking the novelty so essential if work is to be published in high-ranking journals, a prerequisite for survival in these competitive days. Therefore, it is important that journals such as Brain take a special interest in the studies that are required to take proof of principle established in experimental rodent models through to their clinical application.

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References


