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EDITORIAL

Neural Stem Cells, a Step Closer to Clinic?

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INTRODUCTION

Transplantation of organs and cells from one body to another has intrigued the mind of human beings as early as the fifteenth century. Anecdotal descriptions of blood transfusions and transplantation of teeth from cadavers can be found in medical records, but their grim outcome plummeted the field of transplantation into darkness for a long time. It was not however till 1906 with the first corneal transplant performed by Austrian ophthalmologist Dr. Edward Zim that the faith and promise of organ transplants envisioned by our ancestors was renewed. Many more successful examples including skin, kidney, lung, bone marrow and intestine marked the history of organ transplants during the 20th century. The hematopoietic stem cell (HSC) transplantations pioneered by the Nobel prize winner E. Donnall Thomas in 1955 together with rapid advances in the understanding of the human major histocompatibility complex set the stage for clinical cell transplantation. The 1980s and 1990s proved to be optimistic for HSC transplants as procedures were refined and alternative sources of donor cells were found. While HSCs led the way to the clinic, cell transplantations into the brain did not start until 2005 when FDA first approved the transplantation of human fetal cells into the brains of children affected with Batten disease. The question is why it took so long for cell transplantation in brain to reach the clinic? Is this due to our limited ability to purify and study pure populations of neural progenitors from developing and adult tissues? Or to our limited understanding of signaling mechanisms that govern neural stem cell (NSC) fate determination and endogenous repair? Three papers [1–3] published in this current issue of Stem Cells bring us closer to finding answers to these questions.

Adult NSCs are present in the periventricular subependymal layer and the subgranular zone of the dentate gyrus in the brain. In the spinal cord, NSCs reside in the ependymal regions lining the central canal with the capacity to regenerate new neurons after various insults [4–7]. In their work, Wang et al. [1]. developed a genetic strategy for achieving specific labelingand purification of neural progenitor cells (NPCs) from the developing mouse cerebral cortex. This new approach utilized a progenitor cell specific promoter (*Nestin*) and a promoter of an early progenitor (*Doublecortin*) to drive the expression of two different fluorescent reporters. The onset of *Doblecortin* expression marks the fate change in progenitor cells, hence their negative selection from *Nestin* expressing cells enables effective separation of NPCs from differentiated progenitor cells which retain *Nestin* expression. The availability of a purer cell population also enables more accurate gene expression comparisons between NPCs and differentiated progenitors, thus enabling the authors of this paper to identify a unique role for the TAM receptor tyrosine kinase (RTK) in NPC maintenance. It is interesting to note that TAM receptors (Axl, Tyro-3, and Mer) also play role in glioma growth [8]. Further characterization of transcriptional, proteomic and epigenetic signature of purified NSC populations may provide insights not only into the key factors that regulate NSC proliferation but also into the onset of brain tumors [9].

Comparison of transcriptional profiles of stem cells and neural progenitors may also enable identification of factors involved in cell differentiation and regulation of the neurogenic niche. In a second manuscript, Romero-Grimaldi et al. [2]. studied the role of ADAM-17, a metalloprotease involved in neuronal cell differentiation [10]. The authors observed that ADAM-17 expression was up-regulated in NPCs after cortical injury in mice, together with two other factors that promote glial differentiation in vivo, TGF-α and EGFR [2]. Inhibition of ADAM-17 contributed to the generation of neurogenic niches in areas of brain damage and caused a significant increase of neuronal precursor around the lesion. The authors were able to demonstrate that ADAM-17 is involved in the glial/neuronal fate decision of NPCs and that this occurs by its capacity to shed the EGFR ligand TGF-α and facilitate EGFR activation. Taken together, these findings strongly suggest that ADAM-17 is a key molecule involved in the generation of a non-neurogenic niche in areas of brain injury preventing neuronal repopulation from endogenous or eventually transplanted progenitors cells. Thus, ADAM-17 emerges as a new therapeutic target for the treatment of lesions with neuronal loss, ready to betested as soon as specific inhibitors are available to selectively prevent the action of this metalloprotease.

In a third manuscript, Angela Gritti and co-workers from San Raffaele Scientific Institute in Italy investigated the therapeutic potential of an ex vivo murine or humanNSC gene therapy approach in Twitcher mice (a murine model of Globoid Cell Leukodystrophy known as GLD or Krabbe disease) [3]. They used a therapeutic vector which encodes for green fluorescent protein and for the murine galactocerebrosidase (GALC) cDNA and optimized culture conditions to transduce NSCs with high efficiency (70-90%). After transplantation, manipulated cells engrafted into the host restoring GALC

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activity to 50% of wild-type levels, demonstrating that NSC gene therapy can result in a sustained and long-lasting enzyme activity in NSCs. However, in line with previous reports, the authors found that less than 3% of injected NSCs engrafted and survived in the host central nervous system and doubling the cell numbers could not change this outcome. Moreover, the authors failed to find proof of terminal differentiation to neurons and myelinating oligodendrocytes from long-term engrafted NSCs, suggesting that transplanted NSCs function are more likely to function as effective pumps for the deficient enzyme, rather than contribute to cell replacement. Restoration of enzyme activity coupled with the privileged immunological conditions of neonatal brain, makes this approach feasible for development of allogeneic NSC-based approach in humans. Although a lot more pre-clinical studies have to be carried in animal models, this study sets a proof of principle concept that a combined NSC transplantation and gene therapy can ameliorate the pathology of GLD. This further combined with HSC transplants in the early post natal days may indeed be the method of choice for achieving sustained levels of functional enzyme in all affected tissues.

Although the three studies address the NSC transplantation and gene therapy from different angles, they all highlight how important is to understand the characteristics of donor stem cell population, the microenvironment of demised organs where they engraft and the subsequent fate and function of engrafted cells. We believe that with fast advances made in the field of stem cell biology and transplantation, we won't have to wait for centuries like our ancestors to enjoy the benefit of stem cell therapies.

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