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GUEST EDITORIAL

Is there a role for chromaffin progenitor cells in neurodegenerative diseases?

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Transplantation of cells from the sympathoadrenal lineage has been suggested in the treatment of neurodegenerative diseases and pain. Currently, this approach is not practical due to a shortage of organ donors, lack of tissue homogeneity and expandable cells, and disappointing survival rates of grafted cells. This article suggests that the isolation, propagation and differentiation of chromaffin progenitors from the adult adrenal medulla may be a novel strategy with a powerful therapeutic potential worth considering for autologous transplantation and cell-based therapy.

Chromaffin cells of the adrenal medulla are neuroendocrine cells of the sympathoadrenal lineage of neural crest derivatives and therefore are closely related to sympathetic neurons. They are one of the most intensively studied neural crest derivatives. They contain and secrete a wide range of bioactive substances such as catecholamines, but also neuropeptides, growth hormones, including nerve growth factor and endorphins such as met-enkephalin. In contrast to the closely related sympathetic neurons, cells of the adrenal medulla are able to proliferate throughout life.[1] Owing to the close relation of adrenomedullary chromaffin cells to sympathetic neurons, early postnatal adrenal chromaffin cells can be 'transdifferentiated' into neuron-like cells with characteristic neurite outgrowth. The existence of multipotent cells within the adrenal anlagen and the adult adrenal medulla is furthermore indicated by the fact that embryonic and adult adrenal cells from different species, including human,[2] co-express catecholaminergic and neural properties.

Due to this close relation to neurons, their plasticity, and the restorative neurotrophic growth hormones secreted from chromaffin cells, autologous intrabrain transplantation of adrenomedullary chromaffin cells has raised early hopes of curing neurodegenerative diseases such as Parkinson's disease. Indeed, improvement of clinical symptoms after adrenal medulla transplantation in a substantial number of Parkinson's patients has been described worldwide; about 390 patients received autologous adrenal autotransplants from 1988 to 2001. The beneficial effects, however, were transient and long-term survival and functional efficacy of these grafts were poor, and the clinical improvements disappeared after 1–2 years.[3]

Transplantation of fetal dopaminergic neural progenitors from the midbrain of aborted embryos and fetuses is another promising strategy. Several clinical open-label trials with these transplants have proven successful in the treatment of Parkinson's patients where dopamine release was restored in the striatum and to significantly reverse some of the symptoms of the disorder. This initial success, however, was not supported by the results from two controlled NIH trials.[4] Presently, there are no major ongoing trials using transplantation of fetal neural tissue.

In recent years, progress in stem cell research has ignited the hope of curing neurodegenerative diseases by transplanting cells differentiated from neuronal or embryonic stem cells. Neural stem cells can be isolated from either the developing or the adult brain and methods for their propagation and differentiation into neurons, astrocytes and oligodendrocytes are established. However, the generation of functional dopaminergic neurons from these multipotent neural progenitors is difficult and has not yet been achieved.[5]

Protocols have recently been developed to differentiate human embryonic stem cells (hESCs) into electrophysiologically active neurons with, for example, functional characteristics of dopaminergic neurons.[6] However, the potential therapy of neurodegenerative diseases with hESCs is not without problems, especially in that the tumorigenic properties of hESCs so far restrict their usefulness in clinical cell transplantation.

The need for neural precursors in transplantation procedures brings a new momentum to a chromaffin cell-based strategy. The isolation of fetal chromaffin cells from aborted fetuses is one possibility that is now under investigation and the use of these cells is suggested in pain therapy for spinal cord injury or terminal cancer.[2] Owing to their bipotentiality (neural and endocrine), these cells should also bear the potential for neural differentiation and potentially brain repair. Human fetal adrenal tissue, however, is limited or, for ethical reasons, unavailable. In the search for potential sources for cell-based treatment of Parkinson's disease, chromaffin cell aggregates of the Zuckerkandl's organ, an extra-adrenal paraganglion with properties similar to the adrenal medulla, are being tested for their suitability.[7] These transplants induced gradual improvement of functional deficits in Parkinsonian rats. This functional regeneration was attributed less to the replacement of functional neurons as to the chronic trophic action of neurotrophic factors secreted by the grafted cells.

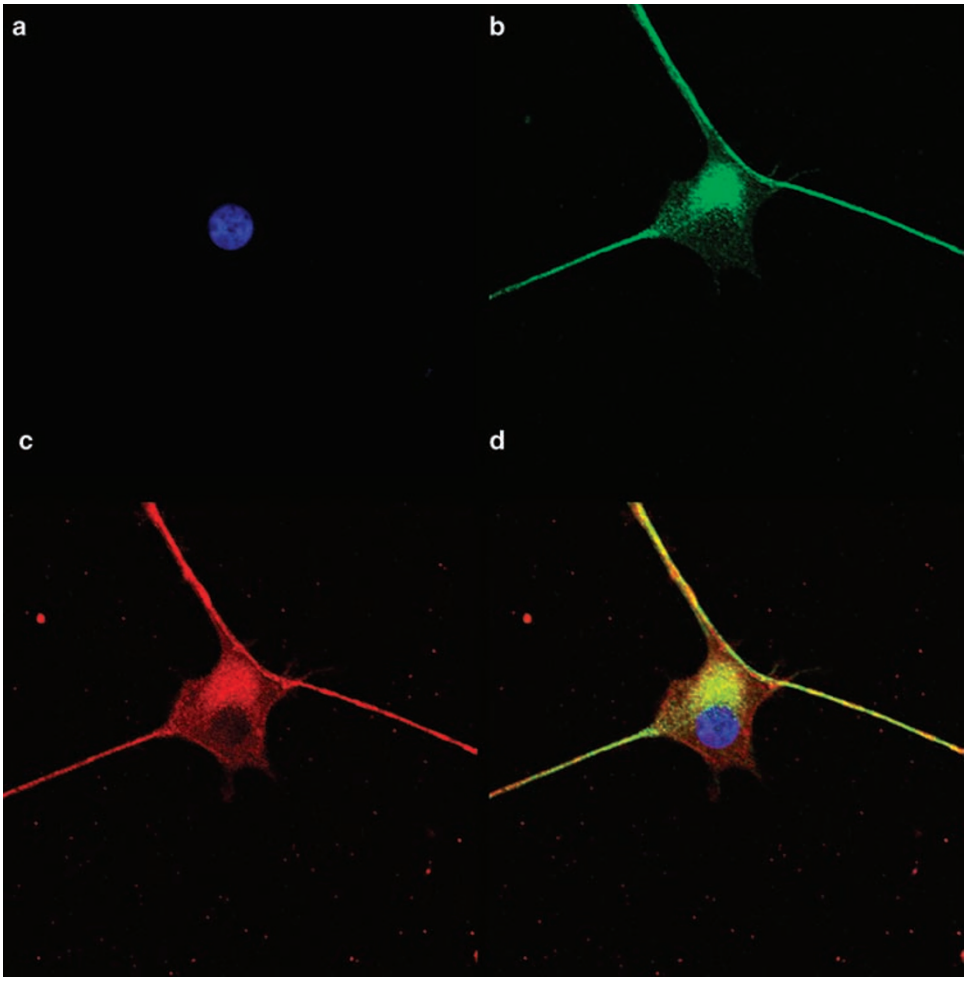

Figure 1 Neuron-like cell differentiated from a chromaffin progenitor cell. Immunostained for neural marker β-III tubulin (**b**) and catecholamine synthesis (**c**) nuclei are stained with 46-diamidino-2-phenyl indole (DAPI) (**a**); (**d**) merged pictures.

In addition to their application in neurodegenerative diseases, grafts of differentiated adrenal chromaffin cells were clinically tested in the cell therapy for pain treatment after spinal cord injury since these cells secrete factors for the alleviation of pain, such as met-enkephalin. Also for this application, the lack of homogeneous, expandable cells from the adrenal lead to the development of alternative strategies. Immortalized chromaffin cells are a possibility now suggested as source for antinociceptive agents.[8]

Clinical transplantation of fully differentiated adrenomedullary chromaffin cells was disappointing, especially due to the low survival rate of the grafted cells. In addition, in the adult adrenal, the proportion of dopaminergic cells is low (1% of the cells); the vast majority of cells produces epinephrine and to a lesser extend norepinephrine. This, together with the observation that overexpression of the epinephrine-synthesizing enzyme phenylethanolamine *N*-methyltransferase leads to increased aggression levels and disturbances in energy balance in these animals[9] furthermore indicates caution in transplanting fully differentiated adrenomedullary chromaffin cells.

The use of adrenal cells, however, would have the tremendous advantage that autologous transplantation of cells from one of the patient's adrenals could be used, thus avoiding immune suppression. Furthermore, human adrenals could be easily sourced from kidney transplantations in which they are removed together with the kidneys. Taking into consideration the plasticity and restorative properties of chromaffin cells, these cells bear a great potential in the treatment of neurodegenerative diseases and in pain treatment. Therefore, to overcome the problems associated with the transplantation of adult chromaffin cells, the isolation, propagation and differentiation of progenitors from the adult adrenal medulla is a strategy worth considering.

A major advance in stem cell research was achieved with the discovery that an undifferentiated multipotent population of neural cells can be grown in suspension as neurospheres. A strategy for isolating chromaffin progenitor cells from the adrenal medulla has now been established. Similar to neurospheres, these cells, when prevented from adherence, grow in spheres, referred to as chromospheres. 'Stemness' of

cells in the chromospheres is indicated by the expression of progenitor markers such as nestin, Sox1, Sox9 and musashi 1, their ability to self-renew *in vitro* and to form clonal spheres. These chromosphere cells are capable to be differentiated into the chromaffin and neural lineage (KF Chung *et al.*, submitted for publication) (Figure 1). The capacity to differentiate into neuron-like cells suggests that isolated chromaffin progenitors may have therapeutical potential in the treatment of neurodegenerative diseases. Defined protocols for the propagation of the progenitor cells and their commitment *in vitro* towards an endocrine or neural phenotype need to be established for subsequent use in cell transplantation. This strategy will provide a more defined and homogeneous cell population instead of the previously used chromaffin tissue. Furthermore, transplantation of progenitor cells instead of differentiated cells should significantly improve the survival of the grafted cells.

In addition to their direct effect of replacing neurons, chromaffin grafts, through the cocktail of neurotrophic factors they produce, may enhance survival of co-transplanted neural grafts.[10] In this context, glial cell line-derived neurotrophic factor (GDNF) has potent *in vivo* effects in protecting and restoring neural tissue,[4] and chromaffin cells are known to express and release a whole cocktail of growth factors including GDNF. Therefore, adjuvant chromaffin cell therapy may help to improve the outcome of cell-based therapies. Similarly, it has been shown recently that one mechanism for the therapeutic action of grafted neural progenitors in reversing a wide variety of neurobehavioral defects is due to enhancing the production of endogenous cells in addition to the replacement of cells.[11] Furthermore, the bipotentiality of chromaffin progenitors, neural and neuroendocrine, could make these cells an alternative source for the treatment of pain with opiod-producing neuroendocrine cells. The differentiation of chromaffin cells requires a gradient of matrix, growth factors and neuropeptides[12] that needs to be defined for their differentiation into the neural and neuroendocrine lineage.

Eventually, the isolation and propagation of chromaffin progenitor cells and their commitment to the endocrine or neural lineage may become a promising therapeutic option for the treatment of neurodegenerative diseases, neurobehavioral defects or pain.

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