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Review

Cells of the sympathoadrenal lineage: Biological properties as donor tissue for cell-replacement therapies for Parkinson's disease

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Abstract

Sympathoadrenal (SA) cell lineage encompasses neural crest derivatives such as sympathetic neurons, small intensely fluorescent (SIF) cells of sympathetic ganglia and adrenal medulla, and chromaffin cells of adrenal medulla and extra-adrenal paraganglia. SA autografts have been used for transplantation in Parkinson's disease (PD) for three reasons: (i) as autologous donor tissue avoids graft rejection and the need for immunosuppressant therapy, (ii) SA cells express dopaminotrophic factors such as GNDF and TGFβs, and (iii) although most of SA cells release noradrenaline, some of them are able to produce and release dopamine. Adrenal chromaffin cells were the first SA transplanted cells in both animal models of PD and PD patients. However, these autografts have met limited success because long-term cell survival is very poor, and this approach is no longer pursued clinically. Sympathetic neurons from the superior cervical ganglion have been also grafted in PD animal models and PD patients. Poor survival into brain parenchyma of grafted tissue is a serious disadvantage for its clinical application. However, cultured sympathetic cell grafts present a better survival rate, and they reduce the need for levodopa medication in PD patients by facilitating the conversion of exogenous levodopa. SA extra-adrenal chromaffin cells are located on paraganglia (i.e., the Zuckerkandl's organ), and have been used for grafting in a rodent model of PD. Preliminary results indicate that long-term survival of these cells is better than for other SA cells, exerting a more prolonged restorative neurotrophic action on denervated host striatum. The ability of SA extra-adrenal cells to respond to hypoxia, differently to SA sympathetic neurons or adrenal medulla cells, could explain their good survival rate after brain transplantation.

Theme: Development and regeneration
Topic: Transplantation

Keywords: Sympathoadrenal; Chromaffin; Paraganglia; Neurodegeneration; Neurotrophic; Cathecolamine; Grafting; Parkinson's disease; Dopamine

Contents

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1. The sympathoadrenal cell lineage

Sympathoadrenal (SA) cell lineage encompasses sympathetic neurons, small intensely fluorescent (SIF) cells of sympathetic ganglia and adrenal medulla, and chromaffin cells of adrenal medulla and paraganglia. SA cells derive from a common progenitor of the neural crest (for a review, see Refs. [101,106]). The neural crest is a cell population that detaches and migrates after the closure of the embryonic neural tube, colonizing throughout the whole embryo (Fig. 1). Cells of the premigratory neural crest are multipotent and generate a wide variety of cell types (Table 1) [17,18,79]. SA progenitors derive from a population of neural crest cells that detach from the top of the neural tube and migrate throughout the embryo (Fig. 1). As neural crest cells migrate, they become developmentally restricted. SA progenitors are one of these developmentally restricted progenitor cells, which give rise two main cell sublineages: sympathetic neurons and chromaffin cells [2]. SA progenitors express tyrosine–hydroxylase (TH), the rate-limiting enzyme in catecholamine biosynthesis, and the transcription factor Phox2 during the aggregation of neural crest cells to form the sympathetic ganglion primordia [34,107]. SA differentiation into cathecolaminergic cells, which express SA1 to SA5 markers, is induced by bone morphogenetic proteins (BMP4, BMP7) produced by cells of the adjacent dorsal aorta [78]. After initial aggregation, a population of SA cells remains in the ganglion primordia and differentiate into SIF and sympathetic neurons which loose SA1 expression and now express the sympathetic marker B2. Other SA cells migrate and invade the adrenal primordium or the extra-adrenal paraganglion primordia, evolving into two chromaffin cells types: (i) adrenal cells of the adrenal gland medulla and (ii) extra-adrenal cells forming the chromaffin fascicles of the paraganglia. All SA chromaffin cells express SA1-5 markers [54] and are ‘adrenergics’, which means that they synthesize either adrenaline (80% of adrenal chromaffin cells) or noradrenaline (20% of adrenal chromaffin cells, all extra-adrenal cells and sympathetic neurons, and 20% of SIF cells) [98].

The ultimate fate of progenitor in SA lineage is modulated by environmental factors [31]. Thus, TH+ cells in the sympathetic ganglion and the adrenal gland acquire distinct phenotypes under the influence of the trophic factors FGF and CNTF produced in the ganglion environment. Mature sympathetic neurons develop from SA cells that express NGFR and respond to the NGF produced by sympathetic ganglion primordia [85]. Chromaffin cells represent a default pathway of SA cells development by the absence of environmental NGF [104–106]. Thus, SA chromaffin cells transdifferentiate ‘in vitro’ into sympathetic neuron-like cells by NGF and other neurotrophic factors (i.e., FGF or CNTF) induction [24,27,104,105,108], demonstrating that the absence of these factors – secondary to the lack of sympathetic ganglion environment – triggers the SA chromaffin cells differentiation. Moreover, SA cells differentiate into adrenal chromaffin cells under the influence of glucocorticoids, which in turn block SA neuronal transdifferentiation [107]. However, chromaffin cells develop normally in glucocorticoid receptor deficient knockout mouse [39], although the induction of phenylethanolamine-*N*-methyltransferase (PNMT), the adrenaline synthesizing enzyme, is disrupted [39]. Therefore, during normal development, glucorticoid hormones suppress SA neuronal

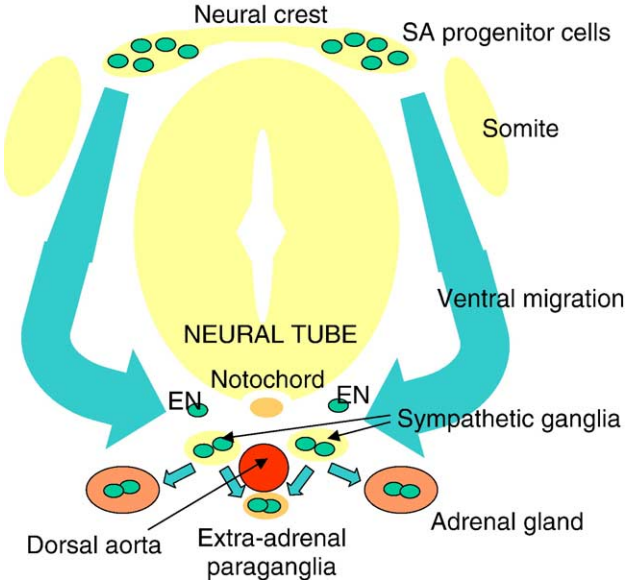

Fig. 1. Migratory routes of sympathoadrenal (SA) cell lineage progenitors. SA progenitors give rise to two cell sublineages, sympathetic, and chromaffin cells, as well as serotonergic enteric neurons. After ventral migration, neural crest cells aggregate to form the sympathetic ganglion primordia near the notochord. After this initial aggregation, SA cells remaining in the ganglion primordia differentiate into sympathetic neurons and SIF cells of the sympathetic ganglia. Other SA cells migrate ventrally, colonize the mesodermal adrenal primordium or the extra-adrenal paraganglion primordial, where they proliferate and differentiate into either adrenal gland or extra-adrenal paraganglia chromaffin cells. EN, enteric neurons (serotonergic).