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Editorial
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Are ASCs Really Able to Differentiate into Nerve Cells?

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Editorial

Adult tissues feature populations of stem cells intended for tissue homeostasis. In some cases, however, repair mechanisms are not adequately efficient to recover functionality after injuries or degenerative diseases. In the Central Nervous System, Neural Stem Cell (NSC) niches are mainly confined in the sub-ventricular zone of the lateral ventricle wall and the dentate gyrus sub-granular zone of the hippocampus. For this reason, these populations are not able to repair severe or extensive neuronal damage [1]. Therefore, cell based strategies have been developed for therapeutic applications in cases of neurodegenerative diseases.

Since NSCs are not easily available, other sources of stem cells have been investigated. Human adult Mesenchymal Stem Cells (MSCs) can differentiate not only into mesodermal lineage cells, but also towards other cell types. From *in vitro* studies, a successful neural-like differentiation has been reported for a variety of MSCs, including those derived from the bone marrow, umbilical cord or dental pulp. In this context, Adipose-derived Stem Cells (ASCs) feature several advantages [2]. They are easily harvested from the subcutaneous tissue with minimal discomfort for subjects; they are characterized by high proliferation rate and differentiation ability; their use is not affected by ethical issues, as occurs for embryonic stem cells. Moreover, because of their low immunogenicity, they are suitable not only for autologous transplantation, but also for heterologous administration.

If the osteogenic, chondrogenic and adipogenic differentiation of ASCs has been already well established, their ability to differentiate toward nerve cells is still under investigation [3]. Different protocols have been adopted to induce ASC differentiation into neural-like cells. In 2002, Safford et al. [4] were able to induce ASCs towards a neural phenotype, by using a culture medium containing valproic acid, butylated hydroxyanisole, insulin, and hydrocortisone. Thereafter, several other chemical agents have been used, such as isobutylmethylxanthine, dimethyl sulfoxide, and retinoic acid. In addition, positive effects have been described by using growth factors (EGF, bFGF, BDNF). Recently, amore physiological strategy was successfully adopted by using conditioned media derived from nerve cell cultures [5]. Altogether, results show that a neural differentiation may be induced, as testified by the expression of typical neuronal and glial markers (NeuN, NSE, SYN1, MAP2 and GFAP), and by morphological modifications: cytoplasmic retraction of the cell body, presence of thin and elongated neurite-like processes [1]. In addition, a functional parallelism between adult neurogenesis of NSCs and neural differentiation of ASCs has been described by Cardozo et al. [6] about the expression pattern of proneural and neural factors (Pax6, Mash1, Ngn2, NeuroD1, Tbr2 and Tbr1). It remains to be demonstrated whether these phenotypical, morphological and molecular changes are indeed associated with functional features, in particular, with their electrophysiological properties. In this field, few data are available. In 2003, Ashjian et al. [7] reported that ASCs, phenotypically differentiated into early neural progenitors, were not capable of depolarization and repolarization in patch-clamp tests. A few years later, four types of ion currents were reported by Bai et al. [8] innaïve ASCs. By whole-cell patch-clamp recording, these authors found that the majority of ASCs showed a delayed rectifier-like K^+ current; only a few of them displayed a Ca^{2+}-activated K^+ current and a transient outward K^+ current; only a very small percentage of cells (8%) were characterized by a Tetrodotoxin(TTX)-sensitive transient inward sodium current. After neural induction, ASCs showed typical neural markers and some neuronal electrophysiological features [9]. In particular, they showed a negative resting membrane potential, voltage-dependent TTX-sensitive sodium currents, and outward potassium currents. Interestingly, action potentials were recently recorded by Guo et al. [10].

Positive results obtained *in vitro* encouraged experiments in animal models of stroke and neurodegenerative diseases, such as Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Huntington's Disease and Parkinson's Disease. In these animals, improved motor performance and cognitive functions were repeatedly reported. Indeed, most authors agree that the neuroprotective/neurotrophic effects observed following ASC administration were mainly induced by their paracrine

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activity. In fact, many beneficial effects were also obtained after administration of ASC conditioned media.

In conclusion, although the mechanisms involved are largely unknown, ASC-based therapeutic approaches have been proven useful in recovering neurological functions, by promoting neuronal regeneration and improving neuronal survival. However, results obtained so far often show an initial level of ASC neural differentiation, characterized by an early stage of neural progenitor cells rather than mature neurons or glial cells. More work has to be done to produce fully functional elements able to repair a damaged brain network.

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