stem cell
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COMMENTARY

Mesenchymal stem cells of dental origin as promising tools for neuroregeneration

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See related research by Ellis *et al.*, http://stemcellres.com/content/5/1/30

Abstract

The adult central nervous system has only a very
limited ability to newly generate lost neurons and
glial cells. Therefore, its self-renewal efficiency after
degenerative damage or acute injuries is very limited.
Mesenchymal stem cells of various tissue origins,
including dental tissues, are among the most promising
tools in stem cell therapeutic approaches. In a previous
issue of *Stem Cell Research & Therapy*, Ellis and
colleagues demonstrated the neuronal differentiation
potential of murine dental pulp stem cells. Our
commentary discusses the significance of the study,
the parallel efforts of other laboratories, the present
limitations of neuronal transdifferentiation using cells
obtained by various available methods, and the
possible breakthrough by combining the various
cellular resources with pharmacological and tissue
engineering methods.

Neurodegenerative diseases such as Alzheimer's disease
and Parkinson's disease and traumatic disorders such as
stroke or spinal cord injury are deteriorating disorders
of the central nervous system. What is common in these
disorders is that it is very hard, or impossible, to treat
them by conventional medical therapies since the ner-
vous system has only a very limited ability to newly gen-
erate neurons and glial cells because of the limited
number of necessary precursor cells. Therefore, novel
technologies such as the application of stem cells hold
great promise for their cure in the near future. The
present article is a commentary on original research by
Ellis and colleagues [1], which appeared in a previous
issue of *Stem Cell Research & Therapy* and which is of

great interest in this perspective. The authors demon-
strated the neuronal differentiation of dental pulp stem
cells (DPSCs) from murine incisors *in vitro* and provided
evidence that these cells are organized in neuronal-like
networks. This is indeed just a small step toward clinical
application. Yet, combined with the data of others in
similar directions, it creates great hopes and high expec-
tations that mesenchymal stem cells (MSCs) of tooth
origin may serve as cellular resources to renew damaged
neuronal structures.

At present, the most promising candidates among
adult stem cells for regenerative therapy are MSCs, a
class of multipotent cells originally identified in bone
marrow. Since the discovery of MSCs in bone marrow,
similar populations from other tissues have been charac-
terized. Recent studies, including our work, have also re-
vealed their presence in the human dental pulp and the
periodontal ligament [2-4]. A very special and attractive
feature of dental stem cells is that they are actually an-
cestors of neuronal precursors. During mammalian
tooth development, the oral epithelium invaginates into
the underlying neural crest-derived mesenchyme. The
ectomesenchymal cells are derived from the dorsal-most
aspect of the neural tube and contribute to local tissues,
including the dental pulp [5]. From this aspect, it has
been of great interest to identify a progenitor pool in
dental tissues and investigate its regenerative potential
for nervous system defects.

An increasing number of studies on human dental
pulp and periodontal ligament-derived neural progeni-
tors or neurons *in vitro* have described neuron-specific
marker expression and demonstrated their functional ac-
tivity [2,4,6]. These studies revealed that multi-step
pharmacological transdifferentiation protocols are more
efficient than simple differentiation procedures [2,4].
These studies unequivocally showed neuronal morpho-
logical differentiation and the appearance and increased
expression of neuronal markers at both mRNA and pro-
tein levels. Additionally, they provided evidence for the

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presence of at least some functional elements that are necessary for neuronal behavior, such as specific calcium, sodium, and potassium channels. However, the functional activity of these channels showed great variability depending on the experimental settings, indicating that both the differentiation procedures and the detection methods need to be further optimized in order to receive highly reproducible transdifferentiation results with a high yield of fully differentiated neuronal cells. *In vivo*, the available information is even more sporadic. The neuroregenerative capability of MSCs of human dental pulp origin has been shown in a brain injury [7,8] and in a spinal cord injury [9] model in animals.

Although human DPSCs have strong immunoregulatory properties [10], xenotransplantation is often problematic because of immune rejection. Therefore, it is of great interest to develop rodent models for autologous or allogenic neural stem cell transplantation. Two groups, including us, reported that rat incisor DPSCs do have neurogenic potential through the successful formation of cells with neuron-like multipolar morphology that expressed neuronal markers *in vitro* [11,12], but our investigation also revealed that the efficiency of rat DPSC neurodifferentiation is much less efficient than that of human DPSCs [12]. Additionally, although the transdifferentiated rat cells showed neuronal morphology, they did not functionally exhibit the neuron-specific sodium and potassium channels (our unpublished data). This observation is actually in accordance with the observation of Ellis and colleagues [1]. They used the same protocol that we developed for human DPSCs [4] and found that neuronally differentiated murine DPSCs are immature, expressing only L-type calcium, but not neuron-specific sodium or potassium, channels. The differences in the neuronal phenotypes of human versus rodent DPSCs are certainly due in part to species differences, but the available data also suggest that the efficacy of currently available neurodifferentiation protocols has to be improved to obtain cell populations that are suitable for therapeutic purposes. Ideally, the protocols used by Ellis and colleagues [1] to transdifferentiate murine DPSCs to neuronal progenitors should be further enhanced by using the present knowledge obtained in induced pluripotent stem cell and direct reprogramming research. Despite many challenges and drawbacks, cellular therapies, including the application of MSCs of dental origin, are very promising and have great potential for curing human neuronal disorders in the future.

Abbreviations

DPSC: Sental pulp stem cell; MSC: Mesenchymal stem cell.

Competing interests

The authors declare that they have no competing interests.

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References

1. Ellis KM, O'Carroll DC, Lewis MD, Rychkov GY, Koblar SA: Neurogenic potential of dental pulp stem cells isolated from murine incisors. *Stem Cell Res Ther* 2014, **5**:30.
2. Kadar K, Kiraly M, Porcsalmy B, Molnar B, Racz GZ, Blazsek J, Kallo K, Szabo EL, Gera I, Gerber G, Varga G: Differentiation potential of stem cells from human dental origin - promise for tissue engineering. *J Physiol Pharmacol* 2009, **60**:167–175.
3. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S: Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc Natl Acad Sci U S A* 2000, **97**:13625–13630.
4. Király M, Porcsalmy B, Pataki A, Kádár K, Jelitai M, Molnár B, Hermann P, Gera I, Grimm WD, Ganss B, Zsembery A, Varga G: Simultaneous PKC and cAMP activation induces differentiation of human dental pulp stem cells into functionally active neurons. *Neurochem Int* 2009, **55**:323–332.
5. Tucker A, Sharpe P: The cutting-edge of mammalian development; how the embryo makes teeth. *Nat Rev Genet* 2004, **5**:499–508.
6. Arthur A, Rychkov G, Shi S, Koblar SA, Gronthos S: Adult human dental pulp stem cells differentiate toward functionally active neurons under appropriate environmental cues. *Stem Cells* 2008, **26**:1787–1795.
7. Kiraly M, Kadar K, Horvathy DB, Nardai P, Racz GZ, Lacza Z, Varga G, Gerber G: Integration of neuronally predifferentiated human dental pulp stem cells into rat brain in vivo. *Neurochem Int* 2011, **59**:371–381.
8. Inoue T, Sugiyama M, Hattori H, Wakita H, Wakabayashi T, Ueda M: Stem cells from human exfoliated deciduous tooth-derived conditioned medium enhance recovery of focal cerebral ischemia in rats. *Tissue Eng Part A* 2013, **19**:24–29.
9. Sakai K, Yamamoto A, Matsubara K, Nakamura S, Naruse M, Yamagata M, Sakamoto K, Tauchi R, Wakao N, Imagama S, Hibi H, Kadomatsu K, Ishiguro N, Ueda M: Human dental pulp-derived stem cells promote locomotor recovery after complete transection of the rat spinal cord by multiple neuro-regenerative mechanisms. *J Clin Invest* 2012, **122**:80–90.
10. Li Z, Jiang CM, An S, Cheng Q, Huang YF, Wang YT, Gou YC, Xiao L, Yu WJ, Wang J: Immunomodulatory properties of dental tissue-derived mesenchymal stem cells. *Oral Dis* 2014, **20**:25–34.
11. Sasaki R, Aoki S, Yamato M, Uchiyama H, Wada K, Okano T, Ogiuchi H: Neurosphere generation from dental pulp of adult rat incisor. *Eur J Neurosci* 2008, **27**:538–548.
12. Varga G, Bori E, Kallo K, Nagy K, Tarjan I, Racz GZ: Novel possible pharmaceutical research tools: stem cells, gene delivery and their combination. *Curr Pharm Des* 2013, **19**:133–141.