

Is neurotrophic factor a second language that neuron and tooth speak?

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Neurotrophic factors are growth factors that can nourish neurons and promote neuron survival and regeneration. Dental origin mesenchymal stem cells express various neurotrophic factors during tooth development and the expression level changes during cell differentiation. Dental origin stem cells are reported to mediate neuronal tissue repair by increasing the secretion of neurotrophic factors. On the other hand, neurotrophic factors promote survival, proliferation, angiogenesis, migration and neuron-like differentiation in dental origin stem cells, which can be applied to the dental clinic. The prospective emphasizes the connection of the dental pulp stem cells and nervous system through neurotrophic factors.

Anyone who has had a toothache will have no doubt that neurons send signals from the teeth to the brain to deliver the painful message. Electronic signals and neuron transmitters are key players in the transduction of the message. But do neurons and teeth communicate in any other way? More and more evidences suggest that neurotrophic factor is the second language that the two talk to each other. Neurotrophic factors regulate sensory innervation of dental pulp and periodontal ligament (PDL) during tooth development, play multiple roles in the dental pulp proliferation, differentiation, and meanwhile can promote dental origin stem cell-mediated neuronal tissue regeneration.

Neurotrophic factor is a big family of molecules composed of cytokines, small peptides and proteins. Nerve growth factor (NGF) was the first one discovered. Later, brain derived neurotrophic factor (BDNF), glial cell line derived neurotrophic factor (GDNF) family, neurotrophins, and neuropoietic cytokines, such as ciliary neurotrophic factor and leukemia inhibitory factor are also discovered. Neurotrophic factors have been proved as important molecules to support neuron survival,

proliferation, maturation and damage repair.

Humans have two dentitions, the primary or deciduous dentition, and the permanent dentition. Development of primary teeth starts as early as embryonic week six, while the initiation of third molar (wisdom tooth) starts five – six years after birth. Dental pulp, along with dentine matrix, cementum and periodontal ligaments derived from the cranial neural crest cells, which are unique population of cells that derive from the ectoderm during early stage of embryogenesis in vertebrate. Human dental pulp stem cells (DPSCs) were first isolated from extracted third molars. DPSCs were reported to have higher proliferation rate than bone marrow derived stem cells, and have been imposed as a promising candidate for craniofacial tissue and other tissue regeneration. Soon, stem cells from human exfoliated deciduous teeth were uncovered. In comparison to the DPSCs which are isolated from permanent teeth, stem cells from human exfoliated deciduous teeth showed higher proliferation rate and higher capability of osteogenic differentiation. Many reports showed that dental pulp cells from murine and human produce neurotrophic factors. NGF, BDNF, neurotrophin 3 (NT3) and neurotrophin 4/5 (NT4/5) mRNA were expressed in a temporal-spatial pattern during tooth development. Specifically, NGF, BDNF, GDNF, NT3 and NT4/5 mRNA were seen in the inner dental epithelium and dental follicle cells in developing human teeth (Nosrat et al., 2002).

Although it is not clear how the neurotrophic factors are involved in tooth development, there are evidences showing that neurotrophic factors play critical roles in regulating dental pulp innervation. Blocking NGF signal in the dental pulp chamber by anti-NGF serum resulted in fewer neurons in the trigeminal ganglion. The neurons

were smaller compared to non-specific serum treated controls. The number of myelinated and unmyelinated axons in the trigeminal nerve innervating the treated tooth was also much less compared to controls, indicating that NGF is critical in regulating the sensory innervation of the dental pulp (Qian et al., 1994). When NGF high affinity receptor Tropomyosin receptor kinase A (TrkA) was knocked out, Tropomyosin receptor kinase A knockout mice lacked the sympathetic nerve fiber in dental pulp and substance P positive nerve fibers in the periodontal ligament (Matsuo et al., 2001). Similarly, NT4/5 knockout mice demonstrated delayed nerve maturation in the mice PDL, while recombinant NT4/5 would largely rescue the defect. GDNF expression level in the PDL of rat increased from postnatal day 3 to 8 weeks, and the signals gradually overlapped with the neurite marker in the PDL mechanoreceptors, indicating that GDNF plays a role in the maturation of mechanoreceptor Ruffini endings (Jabbar et al., 2007).

In addition, neurotrophic factors also regulate DPSCs proliferation, apoptosis, differentiation, migration and inflammatory responses. GDNF significantly stimulated proliferation and reduced tumor necrosis factor induced apoptosis in cultured dental pulp cells. NGF, BDNF as well as NT3 and NT4/5 increased expression of dentinogenic genes dentin sialophosphoprotein and type I collagen, osteogenic genes osteopontin and bone morphogenetic protein 2, and induced mineral deposition in dental pulp cells (Mizuno et al., 2007). GDNF, BDNF and NT4/5 were found in DPSCs and promoted cell migration through the activation of MAPK pathway *in vitro* (Xiao et al., 2018, 2020). The elevation of neurotrophic factors further triggers the downstream pathways to promote dental pulp regeneration.

The inflammation response of dental pulp post bacterial infection (caries) is the most common cause of tooth ache. Transient dental treatment procedures such as drilling, ultrasound sonication, mechanical forces on the teeth can also induce the pulpal inflammation. NGF positive cells accumulated at the site of injury in rat dental pulp 16–24

hours post cavity preparation and restoration. The enriched NGF at the injury site further recruited neutrophils and odontoblasts (Woodnutt et al., 2000). Similarly, *in vivo* study showed that capsaicin-induced calcitonin gene-related peptide release significantly increased in dental pulp after 13-day of NGF (1 mg/kg) subcutaneously injection in female rats, compared to NGF injected male rats, or saline injected rats of both genders (Bowles et al., 2011). The results indicated that elevated NGF expression could induce inflammatory response in the dental pulp and there was gender difference in NGF regulated dental pulp inflammation.

On the other hand, neurotrophic factors are critical in DPSCs-mediated neuronal tissue regeneration. DPSCs could be induced to differentiate into neuron-like cells as verified by the expression of neuronal markers III-tubulin and glial fibrillary acidic protein *in vitro*. The conditioned medium derived from cultured DPSCs contained higher levels of BDNF, GDNF and NT3 as compared to fibroblasts. The expression of the neurotrophic factors in DPSCs was elevated by induced neuronal differentiation (Fujii et al., 2015). When the differentiated DPSCs were injected into avian embryo, the cells continued to present neuron-like morphology. Co-culture of DPSCs with trigeminal neurons induced neurite outgrowth, while co-culture of fibroblasts with trigeminal neurons did not induce neurite outgrowth. Moreover, when transplanted to the striatum of Parkinsonian rat, differentiated DPSCs were able to improve the neurological behavior by increasing the level of dopamine in striatum, and protecting the endogenous dopaminergic neurons (Fujii et al., 2015). While anti-NGF or anti-BDNF antibodies abolished the neuroprotective effects of human DPSCs on mouse dopaminergic neurons *in vitro* (Nestic et al., 2011). More recently, nanoparticles containing curcumin and docosahexaenoic acid have been

showed to increase secretion of BDNF and promote neuroblastoma survival (Guerzoni et al., 2017). The formulation of the nanoparticles could include different combinations of drugs, which can potentially have synergistic effect in treating neurodegenerative diseases.

It is interesting that neurotrophic factors are expressed in human dental pulp cells from both the deciduous teeth and the permanent teeth. Recent evidences seem to indicate that expression of neurotrophic factors in the dental pulp fluctuates not only during tooth development but also in response to stimulation. Elevated neurotrophic factors protect dental pulp cells from further damage and promote healing in the dental pulp. While DPSCs also secrete neurotrophic factors that are critical in DPSCs-mediated neuron tissue regeneration. More research is warranted to further reveal how the neurotrophic factors connect the dental pulp with neurons.

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