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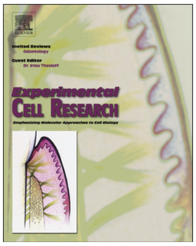

Review Article

Coordination of tooth morphogenesis and neuronal development through tissue interactions: Lessons from mouse models

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ABSTRACT

In addition to being an advantageous model to investigate general molecular mechanisms of organ formation, the tooth is a distinct target organ for peripheral nerve innervation. These nerves are required for the function and protection of the teeth and, as shown in fish, also for their regeneration. This review focuses on recent findings of the local tissue interactions and molecular signaling mechanisms that regulate the early nerve arrival and patterning of mouse mandibular molar tooth sensory innervation.

Dental sensory nerve growth and patterning is a stepwise process that is intimately linked to advancing tooth morphogenesis. In particular, nerve growth factor and semaphorin 3A serve as essential functions during and are iteratively used at different stages of tooth innervation. The tooth germ controls development of its own nerve supply, and similar to the development of the tooth organ proper, tissue interactions between dental epithelial and mesenchymal tissues control the establishment of tooth innervation. Tgf-β, Wnt, and Fgf signaling, which regulate tooth formation, are implicated to mediate these interactions. Therefore, tissue interactions mediated by conserved signal families may constitute key mechanism for the integration of tooth organogenesis and development of its peripheral nerve supply.

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Introduction

The tooth is a distinct, highly specialized organ, and its functions are dependent on a rich peripheral nerve supply. In order to find the tooth target and establish proper innervation, the dental nerve fibers grow, navigate, locate the correct target areas, survive, and, finally, differentiate. The main focus of this review is on recent studies regarding the molecular mechanisms of dental sensory axon path finding and tooth target innervation during development. In particular, attention is concentrated on how the utilization of transgenic mouse lines and developmental neurobiology has revealed novel data to suggest that the regulation of nerve growth to developing teeth is through local epithelial–mesenchymal and nerve-target tissue interactions. Since most mechanistic discoveries have, thus far, depended on work with mouse teeth, the rest of this review will focus primarily on those studies with reference to similar signaling mechanisms in other related tissues in the mouse.

Dental nerves and their function

The relationship between teeth and peripheral nerve fibers in developing and adult tooth will only be briefly introduced below with references to selected excellent review and original articles. The tooth is predominantly supplied with sensory nerve fibers that originate from the trigeminal ganglion. The major target area of the dental sensory nerves is the pulp-dentin border area. Here, the nerve fibers are located in the subodontoblastic plexus, odontoblast layer, predentin, or inner coronal dentinal tubules [1]. The number of sensory nerve endings is especially high near the pulp horn tips and there are much fewer nerve endings in peripheral pulp or dentin of the roots [2]. The dental trigeminal sensory nerve fibers protect the tooth by primarily mediating painful sensations [3,1,2]. Some of the nerves in the pulp appear to serve mechanosensitive stimuli [4]. The nerve fibers that locate to the periodontal space (another major target area of the tooth that connects roots to the alveolar bone by periodontal fibers) mediate touch and pressure sensations, as well as pain [3,1,2]. Some nerve fibers in the periodontium originate from the trigeminal mesencephalic nucleus and are involved in the sensorimotor control of mastication. Sympathetic axons extending from the superior cervical ganglion are present in association with blood vessels and serve vasoregulatory functions [3,1,2].

Tooth innervation and tooth organogenesis are coordinated

The development of the tooth takes place through complex epithelial folding morphogenesis characterized by coordinated division, growth, and differentiation of tooth- specific epithelial and neural crest-derived mesenchymal cells [5,6]. Dental trigeminal axon growth and pathfinding occur concomitantly with advancing tooth formation by a similar, strictly developmentally-regulated manner across different species [3]. Detailed immunohistochemical and molecular analyses in the mouse mandibular first molar tooth germ have revealed that the pioneer trigeminal dental axons follow specific mesenchymal pathways through intermediate targets to reach and innervate the developing tooth target [7] (Fig. 1). Although the first trigeminal nerve fibers reach the skin epithelium in the mandibular process at E10, the pioneer dental axons do not start to grow towards the first molar tooth until it is approximately at the early bud stage [8,9]. Subsequently, during crown morphogenesis, nerve fibers grow around the tooth germ and innervate the mesenchymal dental follicle target area [9].

Nerve fibers form a nerve plexus under the base of the dental papilla at the cap stage, after which there is a waiting period of about one week. The nerve fibers are allowed to enter the dental pulp postnatally, after the onset of enamel formation [10]. Of note, axons penetrate into the pulp exclusively through the presumptive sites of the mesial and distal roots of the two-rooted molar tooth, even though there is no physical barrier (i.e., the developing coronal pulp floor is not present in the middle part at the base of the pulp) [10,11]. The nerve fibers located in the dental follicle also contribute to the innervation of the future periodontal space as the roots develop and the tooth starts to erupt [3]. Thus, tooth neuronal development is a spatiotemporally controlled process that is a tightly linked to key steps of tooth histomorphogenesis.

Because the last nerve fibers emerge from the mouse trigeminal ganglion at E13, reaching the tooth germ at the late cap and (early) bell stage (E15-18) [12], the final steps of tooth innervation are dependent on the arborization and reorganization of the existing nerves. Thus, nerve fiber ingrowth to the dental pulp, patterning, and innervation of the periodontium must rely on the proper innervation and survival of the embryonic nerves within the dental follicle target field [11]. Moreover, the innervation of the replacement teeth takes place by sprouting of the axons that innervated the primary teeth [13]. Once the roots start to form, the superior cervical ganglion-derived sympathetic nerve fibers also appear in the dental pulp [10].

Local regulation of tooth innervation

The findings that tooth nerves serve as essential functions in the mature adult tooth, and that the development of the tooth nerve supply is tightly, spatiotemporally coordinated with advancing tooth histomorphogenesis led to the investigation of the mechanism that regulates this process. Experimental analysis has shown that dissected and replanted tooth germs are able to promote their own innervation and adult denervated or reimplanted teeth can also become re-innervated to some extent [14–16]. In addition, isolated dental mesenchyme exerts developmentally regulated influence on axonal growth [17]. Furthermore, the expression of neuroregulatory molecules, *Ngf* (nerve growth factor) and *Nt*-3 (neurotrophin-3), is not dependent on or regulated by nerve fibers