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Review Article

Ability of stem and progenitor cells in the dental pulp to form hard tissue

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Summary Dental pulp has an important ability to form mineralized hard tissue in response to a variety of external stimuli. The formation of mineralized tissue within the pulp cavity has been widely examined in both clinical and animal studies. Despite these studies focusing on the phenomena of reparative dentin and dentin bridge formation, the mechanisms of their induction remain unknown. Recently, several morphological studies revealed that the source of cells for hard tissue formation is the dental pulp itself, even after pulp injury. This finding indicates that the dental pulp tissue contains undifferentiated cells participating in dentin and pulp regeneration. Additionally, stem and progenitor cells isolated from the dental pulp were found to differentiate into odontoblasts as well as osteoblasts. This review presents current evidences for the multipotent ability of dental pulp cells and their usefulness in tissue engineering applications as a cell resource.

Contents

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1. Introduction

Dental pulp is a loose connective tissue surrounded by dentin. Because hard tissue formation by odontoblasts and pulp cells is an important protective response to external stimuli, every effort must be made to maintain their vitality and function. Four distinct zones are histologically distinguishable in the dental pulp. The outermost layer of the pulp is termed the odontoblast layer, which is composed of odontoblasts forming dentin under normal physiological conditions. Beneath this layer, a cell-free zone (zone of Weil) is observed specifically in the coronal pulp, and it connects with a cell-rich zone characterized by high cell density. These cell-free and cell-rich zones are collectively referred to as the subodontoblastic layer [1]. Besides the surface cell layers, the central region of the pulp is populated by the major vessels and nerves as well as by dental pulp cells and extracellular matrix. The dental pulp tissue contains several types of cells such as odontoblasts, fibroblasts, macrophages, dendritic cells, as well as undifferentiated mesenchymal cells that regulate the homeostatic function of the dentin—pulp complex [2].

Recent progress in identifying stem and progenitor cells from adult tissues suggests their potential application for clinical use in some fields [3,4]. Mesenchymal stem cells have been recognized in many organs and tissues such as skeletal muscle and central nervous system [5,6], as well as classically in hematopoietic lineage, skin, and gut [7—9]. In addition, the existence of stem cells within the dental pulp has been reported in the case of human permanent [10] and deciduous [11] teeth. These dental pulp stem cells show self-renewal ability and multilineage potential [12,13]. The pulp tissue also contains a wide variety of undifferentiated cells that can differentiate into odontoblast-like cells. Many morphological studies have suggested that the dental pulp is capable of forming hard tissues including dentin and bone [14,15]. The mechanisms of pulp calcification have also been analyzed by use of *in vivo* experimental techniques such as tooth [16] and pulp [17] transplantation.

This review focuses on pulp function regarding the formation of hard tissue. Additionally, we introduce recent findings on a cell population having hard tissue-forming ability, and thereafter discuss the potential of pulp stem cells for regenerative therapy.

2. Pulp calcification

The formation of mineralized tissue within the pulp cavity has been widely examined in both clinical and experimental animal studies. Many reports have described reparative dentin and dentin bridge formation following injuries such as dental caries [18,19], cavity preparation [20—25], and direct pulp capping [26—30]. Of interest, bone-like tissues are found after tooth replantation [31—33], traumatic injury [34], and laser irradiation [35—37], in addition to dentin formation. During the reparative process in the injured pulp, primary odontoblasts lost as a result of extensive damage are replaced by newly differentiated hard tissue-forming cells secreting a dentin- or bone-like matrix [38]. This process consists of the sequential steps of proliferation, migration, and differentiation of stem and progenitor cells, along with reinnervation and revascularization [39].

The cell origin of the hard tissue-forming cells after pulp injury is still controversial. Several possibilities can be proposed to explain the origin of cells involved in pulp regeneration. One is that bone marrow-derived mesenchymal cells participate in osteoblast-like cell differentiation. Such undifferentiated cells might be supplied to the injured pulp *via* the bloodstream and then differentiate into hard tissue-forming cells [40,41]. A second possibility is that stem and/or progenitor cells in the dental pulp itself differentiate into odontoblast- or osteoblast-like cells and form hard tissue. This possibility is supported by earlier reports indicating that undifferentiated mesenchymal cells exist within the dental pulp [10,11]. The majority of these stem cells are found at the periphery of blood vessels in the central region of the pulp [42,43]. The cells in the subodontoblastic cell-rich layer have also been shown to have high mineralization ability and form a bone-like matrix *in vivo* [44]. Moreover, the periodontal ligament (PDL) is thought to be a source of hard tissue-forming cells. PDL cells possess high alkaline phosphatase activity [45] and produce bone matrix proteins [46] and mineralized nodules [47] under osteoinductive culture conditions. Indeed, they extensively migrate after transplantation [48,49]. In this context, several morphological studies demonstrate that hard tissue formation in dental pulp cells is mainly caused by the pulp cells themselves, and merely formed by mesenchymal cells that entered from outside (Table 1).

Several reports have described hard-tissue formation in the pulp cavity of rat molar after tooth transplantation into subcutaneous tissue [14,50,51]. Because pulp calcification can be investigated without inflammation due to infection, this study model is very useful and reproducible. After transplantation, the coronal pulp cavity becomes necrotic at the early period, and then three distinct types of mineralized hard tissue are formed in the pulp. Cell-rich hard tissue is formed at the root apex and is immunonegative for dentin sialoprotein (DSP), which is a marker of the dentin matrix [52,53]. This tissue resembles bone from both histological and immunohistochemical perspectives. Additionally,