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REVIEW

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Regenerative endodontics: repair or true regeneration? A narrative review

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ABSTRACT

Regenerative endodontics therapy (RET) is a pioneering approach in dentistry that aims to restore damaged dental pulp and promote tissue regeneration in non-vital teeth. It belongs to the broader field of regenerative medicine, where stem cells, scaffolds, and bioactive molecules are central components. The goal of RET is to achieve true tissue regeneration, fully restoring both the structure and function of damaged tissues, in contrast to repair, which only restores basic functionality through scar formation or tissue remodeling. Histological studies conducted in various research models, ranging from animal studies to human case studies, have provided valuable insights into the nature of tissue regeneration in RET. However, the quality of regenerated tissue can vary significantly among studies. Some research reports have described the presence of fibrous or fibrovascular tissue with limited functionality, resembling repair rather than true regeneration. This variation can be attributed to the impact of disinfection protocols on stem cell viability and differentiation potential. In conclusion, RET has the potential for both repair and true regeneration processes, with outcomes influenced by factors such as disinfection methods and the source of stem cells. Despite the remaining challenges, promising results suggest that RET could revolutionize dental pulp regeneration, especially when approaches that utilize the body's stem cells are optimized for clinical use. Further research and protocol refinement is essential to fully unlock the regenerative potential of this exciting field.

KEYWORDS

Regenerative endodontics; Repair; Regeneration; Histologic studies

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Introduction

Regenerative endodontics therapy (RET) is a relatively recent innovative concept that aims to restore damaged dental pulp, promoting tissue regeneration within the root canal system in non-vital teeth. This concept belongs to the wide umbrella of regenerative medicine that relies on the interplay of the triode: stem cells and scaffold under the influence of bioactive molecules [1]. The innovative approach of pulp regeneration is categorized into two main approaches depending on the source of the progenitor cells, namely cell-based or cell homing. Cell-based RET depends on a sophisticated implementation technique of transplanted stem cells, while cell homing encourages endogenous triggered stem cells to repopulate pulp space and undergo further proliferation and differentiation [2]. True regeneration is the ultimate goal to yield successful outcomes. It involves the process of restoring damaged tissues to their original state, both structurally and functionally. This is opposed by the concept of repair, which only restores functionality through scar formation or tissue remodeling. Studies have shown RET to be effective in promoting healing and root development in immature teeth [3], and it may also be beneficial in mature teeth with chronic periapical lesions [4]. However, the extent to which RET can achieve true regeneration of the pulp-dentin complex is still under debate. Does it truly achieve tissue regeneration or merely facilitate repair?

Translational Research

Histological studies have provided valuable insights into the nature of the newly formed tissue in regenerative endodontics. The current available body of evidence mainly draws conclusions from animal studies [5]. The available body of evidence suggests the feasibility and effectiveness of orthotopic animal models where larger animal models, such as dogs [6-9], are preferred over smaller ones like rats [10-12]. Dogs still represent a more reproducible and meaningful insight as their teeth pose high similarity to human anatomy [13,14]. In addition, the literature includes semi-orthotropic studies where safety, biological response, and effectiveness could be evaluated in which the intervention of transplanting experimental samples is carried out either subcutaneously or inferior to the renal capsule [15].

Noteworthy, the quality of the regenerated tissue can vary widely. Some studies have reported the presence of fibrous or fibrovascular tissue with limited functionality, resembling repair rather than true regeneration. The conclusion drawn by a systematic review published in 2017 confirmed the reparative nature of the newly formed tissue. Among the thirteen reviewed histological studies that could meet the inclusion criteria of the authors, less than 5% of studies could reveal true dentine formation, and the majority of the root canal dentinal walls were laid down by cementum or bone rather than dentin [16]. The argument of the fibrous nature of the newly infiltrating soft tissue, which differs from native dental pulp architecture, was particularly true for abundant research work. Such configuration was shown by Stambolsky et al., El-Tayeb et al., Ghoddusi et al., and Pagliarin et al. [9,17-19]. The deposition of cementum, as well as bone, is obvious in most of the literature [20]. Both cellular and acellular cementum were laid down on preexisting walls juxtaposed with fibrous tissue and were responsible for root thickening and elongation [21].

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In contrast, some histological evidence suggests that true regeneration is achievable in some cases. Despite the scarcity of such evidence, they still represent a great promise for the future, where true regenerative processes could be carried out with the clinically feasible approach of cell homing. Limited areas of "true regenerated tissue "were described by Palma et al., reflecting on the presence of newly formed dentin surrounded by odontoblast-like cells. However, the findings were not attributed to the surviving odontoblasts [22]. The research of Yoo et al. consolidated the pulp-like appearance where newly formed hard tissue was lined by more rounded palisading odontoblast-like cells when disinfection was carried out with a synthetic human beta defensin-3-C15 rather than the calcium hydroxide or antibiotic paste [6]. Pulp regeneration was also evident in the study conducted by El Ashiry et al. The described dentinal architecture suggested a regenerative process linked to the transplanted autologous stem cell construct. However, the configuration of well-organized dentinal tubules was lacking except for some areas, with occasional cell entrapment. This architecture was not evident in samples devoid of stem cell seeding [8].

Studies of Human Subjects

Valuable insights could be gained from Several case studies that evaluated the nature of the newly infiltrated soft tissue in human subjects. These data were gained from teeth that underwent RET and have been subsequently extracted for various reasons, such as root fractures or orthodontic reasons [20]. It was well acknowledged that regenerative procedures can lead to the formation of pulp-like tissue within the root canal space. This tissue often contains cells resembling odontoblasts and endothelial cells, and it may show signs of vascularization and innervation. In a recent study, the long-term impact of RET was assessed through histologic evaluation of lower premolars with dens evaginatus extracted four years after the regenerative procedure. The radiographic evidence of root elongation and wall thickening was correlated with cementum deposition along dentinal walls, with varying thickness and texture, in addition to the fibrous tissue ingrowth and inflammatory cell infiltrates [23]. The fibrous neo-formed soft tissue resembled the periodontal ligament with flattened or no cells lining the newly deposited hard tissue for most cases [24-27]. Such histopathological interpretation added to the accumulated body of evidence, suggesting the reparative nature of the procedure.

Conversely, histological assessment of the newly infiltrated soft tissue 3.5 weeks after the revascularization procedure revealed a pulp-similar architecture with flattened cells lining along the predentin. Despite the findings being early and non-conclusive, the regenerative potentiality of the revascularization was confirmed in immature roots with irreversible pulpitis [28]. Furthermore, the histological and topographical examination of surgically resected root fragments after sixteen years of RET revealed a configuration similar to the native tooth structure [29]. Surface topography indicated the opening of dentinal tubules of the dentin-like structure together with cellular cementum abundance. Such findings confirm the regenerative potential of the process. These variations in tissue composition and functionality suggest that RET may encompass both repair and true regeneration processes. Unfortunately, available data from the current literature is still non-conclusive and consensus despite the high interest in the biologically based procedure that is reflected in the bibliometric analysis of published articles [30]. Although histological studies deny the true regeneration of the pulp-dentin complex in the strictest sense, it does appear to promote a form of repair that functionally mimics the pulp-dentin complex, and the promoted healing supported clinical successful outcomes is acknowledged in the available literature.

Several factors can significantly influence the outcome of regenerative endodontic procedures and tilt the balance towards true dentin formation rather than a mere reparative process.

Effect of infection

Achieving successful pulp regeneration requires a more thorough level of disinfection compared to standard root canal procedures. It is imperative to emphasize that while traditional root canal treatment can lead to the resolution of periapical disease, even when some bacteria remain, the same might not hold for regenerative endodontics [31]. This aspect is of particular significance since the young, aged dentin in immature roots is shown to harbor bacterial invasion and allow for deeper bacterial penetration through dentinal tubules [32].

Unacceptable outcomes are strongly associated with the level of infection, both in translational and clinical studies [33,34]. The evidence consolidated the adverse effect of long-standing infection and bacterial contamination on the regenerative process. This is reflected through the significantly lowest gene expression of dentin sialophosphoprotein (DSPP) associated with 12 weeks of infection compared to one week, as well as immunohistochemical analysis [35]. Herein, gaining adequate disinfection is crucial in regenerative endodontics, as residual infection can impede the pulp regeneration process, leading to unfavorable outcomes. Effective disinfection ensures a conducive environment for successful tissue regeneration within the root canal system.

Effect of disinfection protocols

It is noteworthy that common disinfection protocol depends on harsh antibacterial medicaments such as calcium hydroxide or a mixture of antibiotic paste [36]. Such a mixture of antibiotics could counteract the physiologic existence and functionality of stem cells [37]. Its negative impact on stem cell viability and odontogenic differentiation is well-proven and is concentration-dependent [38]. The implemented toxicity extends even after root canal flushing, and remnants of antibiotic paste could interfere with the repopulation and attachment of progenitor cells, a critical part of the regenerative process [39,40]. The results of Ferreira et al. have proven the least release of transforming growth factor beta (TGF-β), an essential growth factor involved in dentinogenesis and triggers the differentiation of odontoblasts [40].

Presence of remnants of pulp tissue

The histological configuration of the intracanal tissue ingrowth was revealed to be close to normal pulp architecture in the experimental group where the pulp tissue was amputated partially rather than full pulpectomy. The histopathological configuration was attributed to the effect of residual pulp tissue and intact progenitor cells of epithelial

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root sheath of Hertwig or dental papilla, augmented with the inductive nature of highly growth factors loaded scaffold [41]. In the same context, pulp remnants in immature mandibular premolars were correlated to the configuration of regenerated pulp-like tissue. Histologically, the apical third of the root canal contained newly formed dentin-like and pulp-like tissue with odontoblast-like cells, transitioning to cementum-like tissue in the midportion, and cementocyte-like cells in the upper third of the root canal, surrounded by loose connective tissue [42]. Moreover, despite complete pulp amputation being intended, remnants of pulp could be left behind. This technique was further augmented through the application of photobiomodulation via low-power laser. Together, they managed to yield the histological configuration of pulp-like tissue texture revealed by Moreira et al. [12].

Effect of scaffold

Implementing platelet concentrates scaffolds like platelet-rich plasma or fibrin has gained a high interest in current literature due to the autologous nature and the speculated regenerative power due to high growth factor content. Nevertheless, a systematic assessment of published histological data revealed no advantage over conventional blood clot scaffolds. Tissue in-growth remains poorly characterized with little similarity to normal dentino-pulpal soft and hard tissue configuration [43].

Nonetheless, the newly introduced decellularized dental pulp matrix functionalized hydrogel approved great regenerative potential for pulp regeneration. This scaffold, by default, contains an abundance of bioactive molecules that actively interact with the regenerative approach [44].

Conclusions

Current literature reveals that while regenerative endodontics holds promise for achieving true regeneration, it is not consistently observed in all cases. Some studies have reported histological evidence supporting true regeneration, with the presence of dentin-like tissue and well-differentiated pulp cells. In contrast, others have reported outcomes resembling repair, with the formation of fibrous tissue and limited pulp-like characteristics.

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