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Editorial

CHALLENGES AND FUTURE DIRECTIONS IN PULP REGENERATION

R.J.H. Shi[1,§], H.L. Zhan[1,§], C.Y. Yuan[2,*] and K.L. Lin[1,*]

[1]Department of Oral and Cranio-Maxillofacial Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology; Research Unit of Oral and Maxillofacial Regenerative Medicine, Chinese Academy of Medical Sciences, 200011 Shanghai, China

[2]School of Stomatology, Xuzhou Medical University; Affiliated Stomatological Hospital of Xuzhou Medical University, 221004 Xuzhou, Jiangsu, China

[§]These authors contributed equally.

***Address for correspondence**: K.L. Lin, Department of Oral and Cranio-Maxillofacial Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine; College of Stomatology, Shanghai Jiao Tong University; National Center for Stomatology; National Clinical Research Center for Oral Diseases; Shanghai Key Laboratory of Stomatology; Research Unit of Oral and Maxillofacial Regenerative Medicine, Chinese Academy of Medical Sciences, 200011 Shanghai, China. Email: linkaili@sjtu.edu.cn; lklecnu@aliyun.com; C.Y. Yuan, School of Stomatology, Xuzhou Medical University; Affiliated Stomatological Hospital of Xuzhou Medical University, 221004 Xuzhou, Jiangsu, China. Email: yuanchangyong1983@foxmail.com.

Dental pulp tissue is a highly organized hierarchical structure abundant in blood vessels and nerve fibers, forming the functional pulpodentinal complex [1]. However, dental pulp trauma and infections contribute to a high prevalence of pulpitis and subsequent pulp necrosis, and 8.2 % of teeth undergone endodontic treatment globally, leading to significant clinical and quality-of-life impacts for patients [2]. The conventional treatment for pulpitis, root canal therapy (RCT), involves removing the infected pulp, disinfecting the root canal, and filling it with inorganic materials to prevent reinfection. It is reported that 55.7 % of adults over 18 have at least one root-filled tooth [3]. However, the clinical studies of primary RCT published between 2003 and 2020 report a notable failure rate of up to 20 %, with cases unable to achieve complete resolution of periapical lesions [4], resulting from residual infection and micro-leakage in the apical and periodontal tissues. Moreover, after RCT therapy, the teeth without pulp lose the ability to form secondary dentin and provide sensory responses to external stimuli, increasing the risk of fractures and undetected secondary infections. Consequently, regenerative endodontic therapy has emerged as a key area of research in oral field, aiming to precisely recreate pulp architecture and restore the full physiological functions of the pulpodentinal complex.

Pulp regeneration therapy (PRT) within the root canal requires the introduction of cells with proliferative and reparative capacities, sourcing from exogenously transplanted stem cells or recruited endogenously through cell homing [5]. The delivery of such cells relies on bioactive material systems to construct scaffolds or delivery platforms. This regenerative system not only utilizes biomaterials to provide a three-dimensional scaffold mimicking the extracellular matrix (ECM) for cell growth [6], but also delivers diverse molecules to modulate the root canal environment and stem cell behavior [7]. Although numerous technologies have shown promising results in both *in vitro* and *in vivo* studies, pulp regeneration techniques face several challenges preventing widespread clinical applications.

First, the success of PRT appears to be influenced by the stage of pulpitis. While direct clinical data on long-term PRT outcomes in cases with different pulpitis stages is limited, an animal study suggests that prior infection may adversely affect the pulp tissue regeneration process [8]. This suggests that localized infections may create a more favorable environment for regeneration, while advanced infec-

tions increase the risk of pathogen invasion into regenerative materials, potentially compromising treatment efficacy [9]. Additionally, infection-induced changes in the local microenvironment impair cell homing, further compromising outcomes [10]. For patients with periapical disease, it is essential to adjust treatment protocols to improve outcomes. This may involve using antimicrobial biomaterials to control infection prior to initiating regenerative therapies, thus lowering the risk of treatment failure. Additionally, integrating immunomodulatory strategies—such as delivering anti-inflammatory cytokines or employing biomaterials that support a balanced immune response—could help reduce chronic inflammation, creating a more favorable environment for tissue regeneration.

Second, the indications for PRT are limited, particularly in patients with systemic diseases or elderly individuals. In diabetic patients, hyperglycemia and advanced glycation end-products (AGEs) can impair cellular function, increase inflammation, and heighten susceptibility to infection [11]. Autoimmune diseases can lead to abnormal immune responses [12]. Elderly patients experience cellular senescence, metabolic issues, and inflammation [13]. Therefore, research should focus on personalized treatment strategies for patients with systemic conditions, expanding the indications for PRT.

Third, restoring the precise hierarchical structure of physiological dental pulp remains a significant challenge. Regenerating functional pulp tissue not only requires the design of complex material structures that replicate the natural architecture but also demands the re-establishment of neurovascular networks within the regenerated tissue. Achieving effective neurovascularization is essential for functional pulp regeneration, as it provides vital nutrient supply, waste removal, and sensory functions that mirror those of healthy pulp [14]. However, the structural variability of root canals complicates the adaptation of regenerative techniques to abnormal canal anatomies. Multilayer scaffold composites offer a potential solution, allowing for the balanced distribution of biomaterials, stem cells, and cytokines to promote the formation of highly organized pulp tissue [15]. Future research should prioritize the development of regenerative materials that can not only induce the hierarchical structure of pulp tissue but also be morphologically adaptable for complex root canal systems. For instance, the functionalized hydrogels might play a critical role in PRT.

Fourth, affordable manufacturing infrastructure is essential for the widespread clinical application of PRT [16]. However, a major barrier is the limited availability and high cost of Good Manufacturing Practice (GMP) facilities, which are necessary to produce safe, standardized clinical products. Establishing shared, cost-effective GMP facilities within academic or public research institutions could help facilitate more accessible clinical translation. Furthermore, effective stem cell transplantation is challenged by variability in donor cell quality and availability. Establishing a reliable dental stem cell banking system with rigorous quality control measures is therefore crucial to ensure consistent and accessible stem cells for regenerative therapies.

In conclusion, while PRT holds significant potential for future clinical applications, several challenges remain. Addressing issues such as infection control, personalized treatment strategies, the precise reconstruction of tissue architecture, and the translation of preclinical findings into clinical practice will be essential for the advancement of this field. By reflecting on these difficulties, we hope to provide insights that can guide future research and accelerate the development of effective regenerative therapies.

Availability of Data and Materials

No datasets were generated or analyzed for the work.

Author Contributions

RJHS contributed to the design of this work. RJHS and HLZ drafted the work. CYY and KLL revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriate.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. KLL is serving the Editorial Board members of this journal. We declare that KLL had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to MS.

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