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Dentin–Pulp Regeneration: A Requirement-Driven Comparison of Scaffold-Based, Scaffold-Free, and Hybrid Strategies

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Abstract. The failure of the dentin-pulp complex in many situations can lead to problems in tissue function, and therefore there is a need for regenerative strategies that can restore the structural and biological integrity of the tissue. In this review, the different approaches to dentin-pulp regeneration, including single-material natural scaffolds, single-material synthetic scaffolds, scaffold-free strategies, and hybrid/composite scaffolds, are evaluated. These approaches are then compared based on seven criteria for successful regeneration: biocompatibility, cellular activity, structural stability, controlled degradation, vascularization, tissue organization, and reproducibility/feasibility in a clinical setting. At present, the evidence points to the fact that no individual strategy is consistently better. Natural scaffolds, for example, support biological interactions but have variable characteristics and insufficient mechanical properties. Synthetic scaffolds offer greater control, predictability, and reproducibility, but lack some of the inherent bioactivity of natural scaffolds. Scaffold-free strategies maintain cell-to-cell interactions and ECM formation but are less stable and reproducible. These hybrid/composite scaffolds provide a potentially beneficial scaffold structure in which they can combine biological and physical characteristics. The added complexity of a hybrid/composite approach, however, adds even more challenges. Overall, the successful dentin-pulp regeneration may be more dependent on defining the optimal strategy to satisfy the needs of the dentin-pulp complex than on identifying the best and optimal material.

Keywords: dentin-pulp regeneration, tissue engineering, scaffold-free regeneration, hybrid scaffolds, biomaterial scaffolds

1. Introduction

Trauma, infection, or even restoration can lead to damage of the dentin-pulp area. Conventional treatments for disease and preservation or replacement of damaged structures are generally successful, but not always successful in complete restoration of original biological tissue. For example, results in respect of pain relief, maintenance of pulp vitality, and formation of reparative dentin may indicate healing, but without complete restoration of the original complex. True regeneration, on the contrary, depends on the restoration of cellular activity, vascularization,

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innervation, the extracellular matrix (ECM) environment, and dentin production to full capacity [1]. So, there has been a surge of interest in strategies that can yield effective results and the differences between them.

Biomaterial scaffolds are one strategy that has been highlighted for building an environment conducive to regenerative processes. Scaffolds offer a three-dimensional environment for cells to attach, grow, and mature, and can also serve as platforms for delivering bioactive materials. But different demands affect the decision-making process in the choice of the scaffolding application approach to be selected. Generally, natural scaffolds offer more biocompatibility and biological interactions, but they are too variable and have too poor intrinsic mechanical support in some cases. In other instances, synthetic biomaterials overcome the issue of control and reproducibility, but sadly, do not possess the biological attributes of native natural environments [2].

In contrast, scaffold-free regeneration enables the cells to arrange themselves so that they can form their own ECM without any outside influence [3]. Cell sheets, spheroids, and tissue strands eliminate foreign material and therefore maintain the interactions between natural cells. But such methods have their drawbacks, mainly in terms of their structure and scalability [4]. Therefore, the advantages and disadvantages exist for both scaffold-based and scaffold-free regeneration methods, and no one method can be used entirely in place of the other.

Due to their respective compromises, no subsection of biomaterials can be regarded as better than another. The hybrid/composite scaffolds illustrate this balance well, as they allow compromises to be made between the biological and physical characteristics, but also require compromises in processing, scalability, and predictability aspects [5]. Thus, rather than trying to define one strategy as being the optimal one, the question that really should be asked is which framework is most effective in addressing the need for a specific target tissue.

Requirements for successful dentin-pulp regeneration are first reviewed, then approaches like single-material scaffolds, scaffold-free regeneration, and hybrid/composite scaffolds and their ability to meet the requirements are evaluated. Although all regenerative strategies do not create the same effect or yield, the hybrid/composite scaffolds offer the most promising starting framework for dentin-pulp regeneration because of their flexibility to the biological and physical environment. However, scaffold-free principles that complement the scaffold-based principles may be helpful too and can be used where appropriate for successful dentin-pulp regeneration.

2. Necessary conditions to achieve dentin-pulp regeneration

Successful dentin-pulp regeneration requires the establishment of a biological environment closely resembling the original dentin-pulp complex. In this context, multiple biological events take place, such as recruitment of stem and progenitor cells, proliferation and differentiation of cells, deposition of extracellular matrix (ECM), and more. Important among these other processes are the processes of angiogenesis and neurogenesis [1]. Angiogenesis is especially important because tissue cells that have been formed depend on a proper vascular system for nourishment during their development. Similarly, neurogenesis plays an important role in sensory and neural activities of healthy pulp tissue. Other aspects, however, are involved, such as age, and the condition of the pulp tissue directly affects the success of dentin-pulp regeneration [1].

In addition to the biological factors for successful regeneration, there are many criteria that must be met for success with a scaffold-based solution. First, an effective scaffold, if necessary, should be biocompatible and biodegradable, allowing it to provide support for tissue growth while avoiding any negative consequences of biological responses. Second, the overall structure of the scaffold needs to be malleable in shape, size, and porosity (pore volume) to allow nutrients, growth factors,

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and waste products to move throughout the scaffold, thereby supporting cell communication and other biological functions. Finally, a scaffold should facilitate important cell processes like cell attachment, proliferation, and differentiation. However, the overall requirements make the design of scaffolds particularly challenging, as there is no single scaffold design that could satisfy all the requirements for successful dentin-pulp regeneration [2]. Consequently, the following seven requirements can be assessed for single-material scaffolds, scaffold-free approaches, and hybrid/composite scaffolds: biocompatibility, cellular activity, structural stability, controlled degradation, vascularization, tissue organization, and reproducibility/feasibility in the clinical setting. These criteria determine which one is the most suitable for the dentin-pulp regeneration requirements.

3. Single material scaffolds

Natural scaffolds provide more than only their natural materials. They possess a unique property to interact with the biological environment conducive to dentin-pulp regeneration. Natural and naturally derived polymers include signals and growth factors, which encourage cells to adhere, proliferate, and differentiate, as well as being able to form hydrogels that hold a high percentage of water. Fortunately, these scaffolds are easily accessible and made from natural resources, making them relatively inexpensive. Collagen, alginate, cellulose, and other polysaccharides are appreciated for their outstanding biocompatibility and low toxicity. However, the greatest advantages of these scaffolds are also their greatest disadvantages: they are derived from biological sources and often have poor mechanical properties and are subject to batch-to-batch variability, making their behavior extremely hard to standardize. Therefore, although natural scaffolds are favorable in terms of cellular activity environments, their compatibility alone is not sufficient to provide all the requirements for the ultimate success in dentin-pulp regeneration [2].

This is well illustrated in a review on collagen scaffolding for dentin-pulp regeneration, in which the trade-off between such scaffolds (which are naturally occurring and single-material) and synthetic, composite scaffolds is highlighted. Collagen offers a very high degree of biocompatibility and a hydrophilic environment but has the drawbacks of weak mechanical properties and rapid enzymatic degradation, meaning that there is a lack of physical stability in the structure before new tissue can fully develop. To overcome these limitations, crosslinking and combinations of natural and synthetic materials have been explored to compensate for insufficient mechanical strength and better control degradation. This further demonstrates that additional improvements are still needed to meet the requirements of tissue regeneration [6].

But there is one thing that synthetic polymeric scaffolds have that natural scaffolds don't: predictability. The synthetic scaffold materials polylactic acid, polyglycolic acid, and polylactic-co-glycolic acid are manufactured under controlled and monitored conditions, so that their behaviors are predictable and can be reproduced in different applications. In addition, they are claimed to be more advantageous for certain applications than natural materials due to their tunability and longer shelf life. The downside, however, is that these synthetic polymers aren't necessarily as naturally biological as natural scaffolds, which have biological cues that encourage healthy behaviors in an effortless manner. In addition, synthetic scaffolds have hydrophobic structures which further reduce biological activity. Thus, synthetic scaffolds definitely solve the problem of natural biomaterials but also introduce another series of limitations [2].

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4. Scaffold-free regeneration

Scaffold-free regeneration can be considered an option that eliminates the fabrication and implantation of scaffolds. Biomaterial degradation and other biological immune responses to scaffolds are no longer a risk factor because of cell-to-cell and cell to ECM interaction which allow the cells to self-organize. Scaffold-free regeneration encompasses three main strategies: cell sheets, cell spheroids, and tissue strands, each with its own advantages and disadvantages. First, cell sheets are formed by treating cell cultures with acid or temperature-responsive materials and can be used and detached from a polymer without negatively impacting cell-to-cell and cell-to-ECM interactions. The cellular aggregation that forms also promotes ECM deposition, cell proliferation, and differentiation. Then, the spheroids also further improve cell communication and exhibit tremendous potential in terms of vascularization and neurogenesis, which also applies to tissue strands [4]. The ability to vascularize has also been realized in experiments. Dental pulp stem cells extracted from human third molars (aged in late teens to early twenties) were self-assembled as spheroids with or without human umbilical vein endothelial cells. Endothelial cells, alone, were unable to survive for more than 12 hours or form microtissue spheroids; however, when co-cultured with dental pulp stem cells, spheroids were formed, and endothelial cells were organized into vascular-like networks [7]. Generally, outside of this experiment, tissue strands enable cells to be aligned and arranged in a linear fashion within the strands, which become mini tissues. These properties of the scaffold-free approaches render scaffold-free regeneration especially appealing because tissue organization is mainly promoted by a process of cellular self-assembly and endogenous ECM formation [4].

Eliminating the need for an external scaffold also exacerbates risks for structural complications during the formation of new tissue. Cell sheets have no inherent 3D structure from the beginning, compromising mechanical stability. In thicker constructs, this can decrease nutrient transport, which can lead to cell death due to lack of vascularization and hypoxia. While this issue is less of a problem in spheroids, which are three-dimensional aggregates of cells, it is still a tremendous hurdle – especially when it comes to creating aggregates with the right proportion of cells, as in the actual scaffolds in nature, which is not easily replicated between constructs. In a similar fashion, tissue strands enable the cells to be grouped into larger structures while still maintaining the risk of mechanical instability. Accordingly, scaffold-free approaches face great difficulties in controlling the tissue architecture and stability, while they do not have to deal with scaffold-related issues. Control of three-dimensional structure, stability, vascularization, and reproducibility are therefore integral components of the success of dentin-pulp regeneration [4].

5. Hybrid/composite scaffolds

The limitations of single biomaterials can be overcome by simply combining materials with properties that complement each other, as in the case of hybrid/composite scaffolds [8]. For example, hybrid hydrogels can be composed of natural and synthetic compatible polymeric chains, each of which can be beneficial with respect to the other. Therefore, this method shows one way to overcome the limitations of a single material in providing the biological and physical properties suitable for dental tissues [9]. Polymers with little mechanical stiffness can be mixed with materials that are comparatively much stronger. Similarly, polymers, which are not particularly bioactive, can be loaded with ceramics which are extremely bioactive [10]. Collagen-based composites, a widely used and studied scaffolding strategy, are a good example. Collagen naturally has extremely favorable biological properties such as bioactivity and biocompatibility. Sadly, it has little

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mechanical stability and tissue-formation strength [8]. So, additional materials that allow for more mechanical integrity derived from calcium phosphate, for example, can be incorporated to bring about further advancement. Hybrid scaffolding can be used to combine the advantages of several materials into a single structure [10].

This process is further illustrated by hydrogel-based systems. Hydrogels are three-dimensional and possess a hydrophilic polymer network, which shares many traits with the natural ECM in terms of its high-water content, flexibility, and elasticity. In this instance, hybrid/composite hydrogels incorporate natural proteins and peptides into regulated synthetic networks, which often enhance cell-cell interactions, organization, and adhesion. It is noteworthy that one of the perpetual advantages of this scaffolding is that it can be modified by crosslinking. Some examples are alginate/laponite hydrogels and natural polymers like fibrinogen modified with polyethylene glycol [9]. In one experimental application, hybrid RGD-alginate/laponite hydrogel microspheres were used to simultaneously deliver human dental pulp stem cells and vascular endothelial growth factor. The properties were modified by varying the laponite content, and stem cell viability was not compromised and was found to be more than 85%. In a mouse model, with implantations, the construct promoted vascularized pulp-like tissue to form along with microvessels [11]. In such systems, the benefits of hybrid/composite designs can be integrated and tailored in one scaffold to modify and combine physical and biological properties [10].

But there are drawbacks to hybrid/composite scaffolds. The construction of hybrid/composite scaffolds is a complex process, and the engineering of such scaffolds poses several challenges in different fields. Moreover, the reproduction of the dental tissue structure in various situations must be related to the proper choice of biomaterial(s) and the proper integration of materials. Mixing biomaterials is not always the answer to an optimum scaffold: more of a particular biomaterial to overcome the shortcomings of another scaffold part does not necessarily equal an optimal solution. Multiple interactions have to be considered, designed, and put together before desired properties would even start to appear. Moreover, in biomedical applications, the hybrid/composite scaffolds have been shown to have the potential for dentin-pulp regeneration and tissue engineering, but the use of these scaffolds is not sufficiently explored, and there are many unknown factors that hinder their use. Thus, hybrid scaffolds offer a potential way to balance the limitations of natural and synthetic scaffolds, but their multifaceted, complex design and optimization are the main challenge in their use [10].

6. Discussion

6.1. Comparative analysis

The most striking feature in the various ways dentin-pulp regeneration strategies are different is where they score on the seven criteria used to evaluate dentin-pulp regeneration strategies. Natural and naturally derived scaffolds, on the other hand, have the best biocompatibility, abundance, availability, and cost. Their mechanical performance, however, was poor, and the natural and naturally derived scaffolds have a relatively weak structural stability that is complicated by the difficulty in reproducing them batch to batch [2]. Synthetic polymers, on the other hand, are the exact opposite: they are reproducible, predictable, and tunable, with the ability to allow researchers to include elements like growth factors and other bioactive materials to reduce concerns about bioactivity. However, synthetic materials are not as conducive to the natural biological environment in which dentin-pulp is able to regenerate [2]. Hybrid/composite scaffolds are an amalgamation of the strengths and advantages of both cases, as they contain biological elements of natural materials

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and mechanical elements of engineered materials. But of course, their potential to balance bioactivity, mechanical stability, and other aspects is limited by their lack of research and complexity [10].

A completely different approach, scaffold-free regenerative strategies, allows cells to create their own microenvironment, eliminating the need for an artificially engineered scaffold. In these types of systems, a microenvironment allows for advantageous interactions between cells such as cellular communication and adherence. These benefits directly contradict the idea that scaffolds are the way to go with respect to dentin-pulp regeneration. In fact, scaffold-free and scaffold-based methods are more often than not referred to as complementary rather than competitive [3]. But while these integrated strategies might be able to put together an even more complete approach, it does present a scenario with even greater complexity in translational integration and shouldn't automatically be assumed as preferable. These compromises suggest that identifying a universally superior regenerative strategy may not be the most useful objective. The literature reports the different biological, mechanical, and translational limitations associated with the different strategies for dentin-pulp regeneration [5]. Therefore, the most suitable solution is the one that meets the criteria for tissue regeneration on a wider dentin-pulp scale and not the one that is 'the best' class.

Since the requirements can conflict in some way, for instance, if structural stability improvements are at the cost of cellular response capabilities, adaptability is especially valuable. For dentin-pulp regeneration in particular, this system would mark hybrid scaffolds as the most promising starting point. The evaluation of the regenerative strategies is done in a general manner based on seven criteria: biocompatibility, cellular activity, structural stability, controlled degradation, vascularization, tissue organization, and reproducibility/clinical feasibility. Hybrids are not constrained by a set of properties but have unique versatility and tunability [2]. Thus, the merit of hybrid/composite approaches is not that they are better than the other approaches all the time, but that they can adapt to the requirements in various environments and scenarios. Thus, in cases where those needs are not met by hybrid/composite designs, alternative methods like scaffold-free designs may offer different merits [3]. Also, scaffold-free principles should not be assumed to be automatically combined with scaffold-based principles, due to additional complexity issues, but should be used when appropriate. So, the current evidence could be considered to support a hybrid scaffold, not as the best scaffold design, but as a very good starting design for the dentin-pulp strategy.

6.2. Remaining barriers and clinical transition.

In the field of dentin-pulp regeneration, while there have been progressions in regeneration strategies, there are still some obstacles. Scaffold-based strategies are still limited because they lack both sufficient vascularization and complete reconstruction of native tissue, and the long-term integration remains unclear [5]. Furthermore, immature and underdeveloped tissues are frequently seen in regenerated tissues, and the structure of the natural dentin-pulp tissues is not present [1]. Achieving full vascular and neural restoration is crucial, as restoration of tissue transcends just the formation of the tissue itself, requiring biological function and other characteristics of healthy pulp to be present as well [1]. These limitations have led researchers to consider integrated approaches. But, as discussed previously, the potential advantages of integration do not necessarily justify its application in a more widespread manner, especially when considering the greater design and translation complexity it brings forth [5].

Other challenges, however, lie between experimental progress and the reality of regeneration from a clinical point of view. Importantly, small sample sizes, heterogeneous treatment protocols,

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short follow-up durations, and lack of standardized evaluations limit the clinical evaluation to a great degree [1]. This uncertainty is also present in human histological evidence. A systematic review of tissue formation following regenerative procedures showed that the evidence available suggested that either simple tissue repair or repair and regeneration occurred, but not predictably in the form of the dentin-pulp complex per se. The review involved twelve eligible studies, though, and the evidence was deemed relatively low quality, and therefore further highlights the need for more and stronger clinical evidence to be able to accurately and reliably establish any true regeneration standard [12].

The other consideration is that evaluation, unfortunately, is based primarily on indirect information, including radiographic changes, relief of pain, and testing the pulp vitality. These results may be unclear and aren't always a good sign of successful and complete restoration of the dentin-pulp complex. Further, comparative clinical studies between the regenerative approaches are also scarce, resulting in limited evidence regarding long-term outcomes (e.g., vascular and neural restoration). An evaluation procedure that is standardized is therefore important in evaluating the success of any individual strategy; their clinical effectiveness can be compared in the future by distinguishing between true regeneration and simply tissue repair [1].

7. Conclusion

The ideal dentin-pulp regeneration demands several requirements, which are the restoration of the biological and physical functions of the dentin-pulp complex in a complete and true manner. Natural scaffolds are desirable due to their high biological interactions, but their mechanical strength and variability are problematic, whilst synthetic scaffolds are advantageous because they are mechanically strong and have low variability but lack inherent biological interactions. Scaffold-free approaches vary, as they do not include a scaffold structure and the cells create their own microenvironment, which has the advantage of not being bound by the limitations of any artificial biomaterial. The types of microenvironments, however, are hard to control and lack mechanical stability, scalability, and reproducibility. Overall, the focus on finding a single 'best' strategy can distract from the question that really needs to be asked – what strategy is best suited to meet the needs of a particular regenerative context. Hybrid/composite scaffolds provide a very interesting entry point within this framework, as these scaffolds can combine materials to achieve biological and physical goals simultaneously. But this does not make hybrid scaffolds better, as the downside to this flexibility is complexity. Finally, dentin-pulp regeneration should not use all the available strategies but should start by considering the overall needs of the target tissue and include strategies as they are warranted.

This system holds great promise, although there are many hurdles that need to be overcome to be able to achieve predictable clinical outcomes. At present, studies are limited by a lack of uniformity in research protocols, a lack of distinction between true regeneration and repair of the tissues, and a lack of long-term clinical studies. Future research, therefore, will need to aim to overcome some of these challenges by developing more standard metrics for functional regeneration, and will need to compare strategies of regeneration under more controlled, consistent, and good conditions. Overall, successful dentin-pulp regeneration does not necessarily require a one-size-fits-all material, but rather a flexible framework that can be customized based on specific needs and requirements, considering the unique characteristics of each tissue and environment.

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