Translational Regenerative Dentistry

Translational Regenerative Dentistry:

A Learning Companion for Dental Students

By

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CHAPTER ONE

INTRODUCTION TO REGENERATIVE DENTISTRY

Regenerative dentistry represents a transformative approach in oral healthcare, aiming to restore the structure and function of dental tissues through the integration of stem cell biology, biomaterials science, and tissue engineering. The field has evolved from ancient practices focused on alleviating dental discomfort and performing extractions, as evidenced by archaeological findings such as tooth fillings made from beeswax and resin, to a sophisticated discipline that leverages biological principles to promote tissue regeneration (Saberian et al. 2024). The progression toward modern regenerative strategies was catalyzed by foundational insights into dental anatomy and the development of specialized instruments, laying the groundwork for contemporary interventions. Central to regenerative dentistry is harnessing the body's intrinsic healing potential. This is achieved by employing stem cells, particularly induced pluripotent stem cells (iPSCs) and dental pulp stem cells (DPSCs), in combination with engineered scaffolds that provide a supportive microenvironment for cellular proliferation and differentiation (Ahmed et al. 2024; Demarco et al. 2011). iPSCs have garnered significant attention for their versatility in differentiating into various cell types relevant to dental tissue repair, including those required for pulp regeneration and craniofacial reconstruction. However, their clinical translation necessitates rigorous safety assessments and careful navigation of ethical considerations (Ahmed et al. 2024). Scaffold design is a cornerstone of successful regenerative therapies. Scaffolds serve as three-dimensional templates that guide tissue formation by supporting cell attachment, migration, and organization. The biocompatibility of these scaffolds is paramount; materials must integrate seamlessly with host tissues while minimizing adverse immune responses. Scaffold composition directly influences their biological performance, with recent advances enabling precise control over geometry and porosity through 3D printing technologies. These innovations enable customization tailored to patient-specific anatomical requirements, thereby enhancing both mechanical strength and biological compatibility. Composite scaffolds that combine polymers with bioactive ceramics, such as hydroxyapatite (HA), further optimize the balance between structural integrity and cellular support (Saberian et al. 2024). HA-based materials have emerged as preferred choices for hard tissue repair due to their chemical similarity to natural bone mineral. Their porous architecture facilitates osseointegration and supports cellular colonization, making them suitable not only for bone augmentation but also as platforms for tooth replacement. The adaptability of HA scaffolds is further enhanced by incorporating trace ions or blending with natural polymers, such as gelatin and chitosan, which improve biocompatibility and mimic the extracellular matrix environment, thereby promoting cell differentiation (George Ittycheria et al. 2024). The application of scaffold-based methodologies extends beyond hard tissues to encompass soft-tissue regeneration in endodontics. In this context, scaffolds are essential for restoring vitality to damaged dental pulp and periapical tissues by providing a framework that supports angiogenesis, neurogenesis, and odontogenic differentiation. (Saberian et al. 2024). Establishing functional vascular networks within engineered pulps remains a critical challenge; optimizing conditions for rapid vascularization is essential for clinical success (Demarco et al. 2011). Translational challenges persist in bridging laboratory advances with routine clinical practice. These include sourcing reliable stem cell populations, ensuring reproducible scaffold fabrication, achieving consistent biocompatibility across diverse patient populations, and addressing regulatory hurdles associated with novel biomaterials (Ahmed et al. 2024). Furthermore, interdisciplinary collaboration among clinicians, material scientists, biologists, and regulatory bodies is necessary to navigate these complexities effectively. Recent research underscores the importance of integrating surface modifications on implant biomaterials with advanced assessment techniques to enhance procedural outcomes in scaffold-mediated dental implantology. Such integration not only improves immediate clinical results but also supports long-term durability by promoting stable interactions between implants and surrounding tissues. Regenerative dentistry stands at the intersection of multiple scientific domains. By synthesizing advances in stem cell technology, scaffold engineering, and translational research methodologies, it offers promising avenues for restoring lost or damaged dental tissues. Ongoing efforts focus on refining scaffold properties, expanding our understanding of stem cell behavior in vivo, and overcoming translational barriers to realize the full therapeutic potential of regenerative approaches in everyday dental practice.

CHAPTER TWO

FOUNDATIONAL CONCEPTS IN ORAL TISSUE REGENERATION

Historical Development of Regenerative Dentistry

The historical development of regenerative dentistry is characterized by a shift from traditional restorative methods to biologically inspired strategies that utilize the body's innate repair mechanisms. Early dental treatments focused primarily on mechanical restoration or replacement of lost tissues, such as prosthetic devices and dental implants. However, these methods often failed to fully replicate the complexity and function of natural oral tissues, prompting the search for more effective solutions (Tatullo 2018). A key milestone in this evolution was the recognition of the body's natural regenerative potential, which became clearer as tissue engineering and regenerative medicine advanced. Researchers began investigating how scaffolds, growth factors, and stem cells could be used to stimulate regeneration in dental tissues, particularly in structures such as the dental pulp and periodontal tissues. Initial experiments in dental regeneration used basic methods but laid the foundation for later innovations. The first successful efforts to regenerate dental pulp marked a turning point, proving that biological restoration was possible beyond mechanical repair (Saberian et al. 2024). As understanding deepened, the integration of cell biology, biomaterials science, and nanotechnology further propelled the field. The use of stem cells, particularly those derived from dental pulp, and biodegradable scaffolds enables more precise control of tissue regeneration (Orsini et al. 2016). These advances enabled not only partial repair but also the functional restoration of complex dental structures. For instance, protocols for stem cell isolation and scaffold-based tissue engineering have shown promise in regenerating both hard and soft oral tissues (Orsini et al. 2016; Yasui et al. 2017). The development of biomaterials explicitly designed for oral use has played a key role in this progress. Scaffolds now provide structures that closely mimic native tissue environments while incorporating bioactive components to influence cellular behavior. This has improved outcomes in procedures such as bone augmentation for dental implants and periodontal regeneration. The flexibility and versatility of these biomaterials continue to inspire innovation within modern dentistry (Saberian et al. 2024). Regenerative endodontics has emerged as a specialized area focused on restoring damaged or diseased dental pulp to its original function through biological methods rather than synthetic materials. Techniques like stem cell banking, biological pulp implants, and advanced scaffold delivery systems are being developed for clinical application (Torvi and Munniswamy 2014). These methods mark a shift from traditional treatments toward therapies aimed at genuine tissue regeneration. Alongside these technological developments, educational efforts have started to emphasize regenerative concepts within dental training. Teaching future researchers and clinicians about stem cell biology and tissue engineering is considered vital to ongoing progress in this field (Tatullo 2018). The collaboration across disciplines has established regenerative dentistry as a vibrant field ready to redefine standards of care. Despite these successes, challenges remain. Issues related to scaffold design, the sourcing of appropriate stem cells, ensuring biocompatibility, and achieving consistent clinical outcomes remain under investigation (Saberian et al. 2024; Orsini et al. 2016). Nonetheless, the journey from early experiments to cutting-edge approaches highlights a significant transformation in oral health restoration, shifting from tissue replacement to genuine biological regeneration.

Principles of Tissue Engineering

Tissue engineering in regenerative dentistry primarily relies on the triad of cells, scaffolds, and signaling molecules, each serving a distinct yet interconnected role in guiding tissue regeneration. The integration of these components is crucial for effective restoration of dental tissues, including pulp, periodontal ligament, bone, and enamel. A key principle of tissue engineering is choosing and sourcing suitable cell populations capable of contributing to tissue repair and regeneration. Mesenchymal stem cells (MSCs), obtained from sources such as bone marrow, adipose tissue, and dental pulp, are particularly valued for their multipotency and immunomodulatory properties. These cells can differentiate into various lineages relevant to oral tissues, like osteoblasts for bone formation, cementoblasts for cementum regeneration, and fibroblasts for connective tissue repair. The use of iPSCs has further expanded the range of available cell types by enabling the creation of patient-specific cells that can be directed toward desired phenotypes. In periodontal regeneration, combining multiple cell types—including periodontal ligament cells, osteoblasts, cementoblasts, and gingival fibroblasts—is essential for reconstructing the complex structure and function of periodontal tissues (Ahmed et al. 2024). Equally important is designing and fabricating scaffolds that provide a three-dimensional framework that supports cell attachment, proliferation, differentiation, and extracellular matrix production. Scaffold materials must be biocompatible to prevent adverse immune reactions and possess mechanical properties similar to those of native tissues. Advances in scaffold technology have led to nanofibrous polymer scaffolds with high surface area and interconnected porosity. These features enhance cell-scaffold interactions by facilitating nutrient delivery and waste removal and by providing physical cues that influence cellular behavior. Nanofibrous scaffolds outperform microfibrous or other shapes by promoting positive cell-extracellular matrix interactions, maintaining cell phenotype, supporting stem cell differentiation, and activating key signaling pathways vital for tissue development, which can lead to necrosis within implanted constructs despite optimal scaffold design or cell seeding strategies (Zhang et al. 2017). Addressing these challenges necessitates ongoing improvements through preclinical studies that evaluate not only biological effectiveness but also safety profiles. Ethical considerations underpin all phases of translational research in regenerative dentistry. Following established ethical frameworks ensures patient safety during clinical translation and upholds research integrity throughout experimental design and data analysis. Regulatory compliance guides material selection, manufacturing processes, and clinical protocols. A sophisticated integration of stem cell science, advanced biomaterials, scaffold architecture, molecular signaling, and strict ethical oversight defines the principles of tissue engineering for oral regeneration. This multidisciplinary approach continues to evolve with emerging technologies, offering promising avenues for restoring form and function in damaged dental tissues.

Biological Basis for Dental Tissue Repair

Dental tissue repair is primarily guided by the interaction of cellular mechanisms, extracellular matrices, and signaling pathways that coordinate the restoration of structure and function in oral tissues. The oral cavity includes various tissues such as enamel, dentin, pulp, periodontal ligament, cementum, and alveolar bone, each with unique biological properties and regenerative abilities (Amrollahi et al. 2016). The biological foundation for dental tissue repair depends on understanding the distinct characteristics of these tissues and the cellular agents involved in their regeneration. Central to dental tissue repair are stem cells located within dental tissues. In addition to DPSCs, periodontal ligament stem cells (PDLSCs) and MSCs are known to differentiate into cell types relevant to dental tissue regeneration. DPSCs, located in the dental pulp, exhibit remarkable plasticity and can differentiate into odontoblast-like cells that form dentin. PDLSCs are crucial for regenerating the periodontal ligament and supporting structures because they can differentiate into fibroblasts, cementoblasts, and osteoblasts (Saberian et al. 2024). MSCs from bone marrow or other sources also contribute to bone and periodontal regeneration by differentiating into osteogenic lineages (Shopova et al. 2023). The process begins when injury or disease triggers signals that activate resident stem cells or attract progenitor cells from nearby tissues. These cells respond to biochemical cues such as growth factors and cytokines released during inflammation or healing. Platelet-rich plasma (PRP), for example, contains a mixture of growth factors that stimulate cell growth and matrix production; however, the exact molecular mechanisms of PRP-driven regeneration are not fully understood (Banu and Khan 2023). Cellular responses are further influenced by interactions with biomaterial scaffolds designed to mimic the native extracellular matrix. Scaffolds provide structural support and guide cellular organization while presenting biochemical signals that regulate adhesion, movement, growth, and specialization. Proper scaffold integration is essential for successful tissue repair because it promotes seamless attachment with host tissues and encourages vigorous cellular activity necessary for regeneration. Scaffold design must consider biocompatibility, mechanical strength, degradation rate, and surface chemistry to optimize cellular responses (Saberian et al. 2024; George Ittycheria et al. 2024). In enamel regeneration, epithelial cell populations, such as epithelial rests of Malassez (ERM), have the potential to differentiate into ameloblast-like cells under appropriate conditions. When ERM cells are co-cultured with dental pulp cells or seeded onto scaffolds and transplanted in vivo, they can recapitulate the stages of amelogenesis, leading to enamel-dentin complex formation. Immortalized ameloblast-lineage cells retain key enamel matrix proteins like tuftelin and amelogenin and can induce mineralization both in lab settings and in living organisms (Dalir Abdolahinia et al. 2023). The foundation for repair extends beyond stem cell differentiation. Intercellular communication among different cell types within dental pulp or periodontal tissues is mediated by complex signaling networks involving ligand-receptor interactions that control gene expression patterns crucial for tissue homeostasis and regeneration (Ren et al. 2022). These molecular signals ensure coordinated responses during healing. Biomaterials also serve as vehicles for drug delivery, not just as scaffolds. For example, nano-hydroxyapatite has been used for its ability to remineralize enamel and as a carrier for therapeutic agents for periodontal diseases (George Ittycheria et al. 2024). Incorporating antimicrobial agents into scaffold materials helps address infection risks during regeneration procedures (Bottino and Thomas 2015). Despite these advances, challenges remain in translating research into clinical practice. Variability in nanomaterial behavior across different biological environments complicates predictions of biocompatibility and immune reactions. Nanomaterials may interact unpredictably with cellular components, including DNA and proteins, depending on their surface properties or coatings (George Ittycheria et al. 2024). This highlights the need for a thorough evaluation of biomaterial safety alongside effectiveness. Recent research emphasizes the significance of the body's own responses in bone regeneration. Pharmacological manipulation of endogenous MSCs offers a promising approach that leverages natural repair processes rather than relying solely on exogenous cell transplants (Shopova et al. 2023). These insights show that effective dental tissue repair depends on a detailed understanding of stem cell biology, scaffold design, intercellular signaling, and biomaterial-tissue interactions. Ongoing research is developing these core ideas to improve clinical outcomes in regenerative dentistry (Saberian et al. 2024).

Interdisciplinary Perspectives

Interdisciplinary perspectives are essential to advancing translational regenerative dentistry, as restoring complex oral tissues requires integrating multiple scientific and clinical disciplines. The integration of stem cell biology, biomaterials science, tissue engineering, and clinical dentistry lays the groundwork for new therapeutic strategies to regenerate dental pulp, periodontal tissues, enamel, and salivary glands. Each area offers unique expertise vital for overcoming the many challenges of oral tissue regeneration. Dentists provide essential clinical insight into the anatomical, functional, and pathological aspects of dental tissues. Their understanding of patient-specific needs and practical treatment challenges informs the development of regenerative protocols that are both clinically relevant and feasible. Biologists bring in-depth knowledge of stem cell behavior, differentiation pathways, and developmental processes that underlie tissue regeneration. For example, studies have shown that MSCs taken from dental pulp express markers such as CD29, CD44, CD90, CD166, and CD105. These cells can self-renew and differentiate into multiple lineages, thereby producing odontoblast-like cells, neurons, chondrocytes, and adipocytes in vitro (Yasui et al. 2017). These discoveries underscore the importance of cellular characterization in developing effective regenerative therapies. Bioengineers are vital to the design of scaffolds and biomaterials that mimic the native extracellular matrix. Developing scaffolds requires careful consideration of biocompatibility to support cell growth, while minimizing toxicity and immune responses (Saberian et al. 2024; Ahmed et al. 2024). The testing process includes a thorough evaluation of cytotoxicity, immunogenicity, and allergic reactions before clinical use. This helps ensure scaffolds support cell attachment and growth and integrate well with the host tissue. Materials scientists further improve this process by developing biocompatible and biodegradable materials suited to specific dental applications, such as implants and tissue scaffolds (Saberian et al. 2024; Ahmed et al. 2024). Their work allows the production of biomaterials with ideal mechanical properties and biological integration capabilities. The interaction between these fields is evident in scaffold design for dental tissue engineering. Assessing scaffold safety is a vital step in regenerative medicine research. Scientists use various methods to evaluate whether scaffolds are suitable for biological processes. This multidisciplinary review supports the use of scaffolds to translate laboratory findings into clinical practice (Saberian et al. 2024; Ahmed et al. 2024). Selecting appropriate biomaterials is crucial for ensuring the long-term stability and function of dental implants. An in-depth analysis of material properties supports decision-making for their application in medical implants (Saberian et al. 2024). Stem cell sourcing is one area in which collaboration across disciplines is essential. Isolating and characterizing stem cell populations requires advanced techniques such as fluorescence-activated cell sorting (FACS), which relies on dye efflux or surface marker expression (Yasui et al. 2017). Safety concerns also need to be addressed, particularly for pluripotent stem cells such as iPSCs. While iPSCs hold great promise for regenerating various dental tissues, including periodontal tissues and dental pulp, their use underscores the importance of safety assessments to reduce risks such as tumor formation or genetic instability (Sakai 2016). Preclinical studies, including laboratory tests and animal models, are necessary before initiating human trials. Regulatory agencies oversee this process by setting guidelines to ensure safety and ethical standards for regenerative products. Collaboration among clinicians, scientists, engineers, regulators, and ethicists is crucial to navigate these rules while developing safe therapies (Ahmed et al. 2024). The evolving field of regenerative dentistry also benefits from ongoing communication between researchers studying fundamental mechanisms—such as epithelial-mesenchymal interactions in tooth development—and those focused on practical applications. For example, understanding how neural crest-derived mesenchyme guides epithelial differentiation into ameloblasts facilitates the replication of these processes with engineered tissues or organoids (Xiao and Nasu 2014; Sui et al. 2020). Personalized approaches are becoming more influential in regenerative dentistry. By combining patient-specific data with advances in stem cell and biomaterial sciences, personalized dentistry aims to provide precise, individualized treatments (Saberian et al. 2024). This shift depends on interdisciplinary teamwork to turn research findings into tailored clinical solutions. Interdisciplinary perspectives drive progress in oral tissue regeneration by combining expertise from clinical practice, basic research, engineering, materials science, regulatory affairs, and ethics. Such collaboration is essential to addressing challenges in scaffold design, stem cell sourcing, biocompatibility testing, and safety validation, ultimately enabling the successful restoration of complex dental tissues.

CHAPTER THREE

ORAL STEM CELLS AND THEIR NICHES

Types of Dental Stem Cells

Dental Pulp Stem Cells

Dental pulp stem cells are a unique group of postnatal MSCs found within the dental pulp tissue. These cells have attracted considerable attention for their ability to self-renew and differentiate into multiple cell types, making them essential for dental tissue regeneration. DPSCs express markers associated with bone, cartilage, blood vessels, and neural tissues, underscoring their broad differentiation potential and their suitability for regenerative dentistry applications. Their capacity to form a dentin/pulp-like complex has been shown in several studies, highlighting their importance in repairing damaged or diseased dental pulp (Shopova et al. 2023). Recent stem cell research has further detailed the regenerative abilities of DPSCs. Notably, they can differentiate into odontoblast-like cells, which are crucial for dentin formation. This trait is particularly relevant to strategies aimed at regenerating the dentin-pulp complex, a key component of successful dental pulp regeneration. Using DPSCs to create dentin-like tissues offers an innovative approach that leverages their natural plasticity and responsiveness to environmental cues (Saberian et al. 2024). These advancements present promising opportunities for restoring the structural and functional integrity of teeth affected by trauma or disease. The diversity within dental stem cell populations is also significant. For example, comparative studies between stem cells from human exfoliated deciduous teeth (SHEDs) and DPSCs have identified both similarities and differences in their regenerative potentials. While both cell types exhibit self-renewal and multipotency, DPSCs are especially well-understood for their ability to form mineralized tissue. They not only express osteogenic markers but also produce mineralized nodules under suitable conditions (Shopova et al. 2023). This osteogenic potential extends the applications of DPSCs beyond dentistry, suggesting potential roles in craniofacial bone regeneration. In addition to their differentiation capacity, the interactions of DPSCs with biomaterials and other cell types are a key research focus. For instance, co-culture experiments using DPSCs and human umbilical vein endothelial cells on gelatin methacryloyl hydrogels have demonstrated that DPSCs can acquire pericyte-like traits when exposed to endothelial signals. Specifically, these co-cultures increase α-smooth muscle actin expression, indicating a shift toward a perivascular phenotype that could enhance vascularization in engineered tissues (Parthiban et al. 2020). These findings highlight the importance of microenvironmental factors in guiding DPSC behavior and improving tissue engineering outcomes. The potential of DPSCs for clinical use is further supported by evidence showing that they can replicate key features of native dental pulp tissue when transplanted in vivo. Human DPSCs from postnatal sources have been shown to generate structures resembling the dentin-pulp complex, providing proof-of-concept for their role in regenerative therapies (Shopova et al. 2023). Despite these promising results, several challenges must be addressed before these approaches can be widely used in clinical practice, including obtaining sufficient high-quality stem cells, ensuring compatibility with scaffold materials, and achieving robust integration with host tissues through continued research and technological advances.

Additionally, ethical issues related to stem cell sourcing are less problematic with DPSCs than with embryonic stem cells, since they can be harvested from extracted teeth, which are often considered medical waste. This reduces donor risk and ethical concerns (Saberian et al. 2024; Shopova et al. 2023), making them a practical option for autologous or allogeneic transplantation. Dental pulp stem cells occupy a central place in oral stem cell biology owing to their remarkable regenerative potential and translational promise. Their ability to differentiate into odontogenic and other mesenchymal lineages makes them key players in efforts to repair damaged or missing dental tissues using advanced tissue engineering methods (Parthiban et al. 2020). As research advances in optimizing protocols for DPSC isolation, expansion, and directed differentiation, these cells are expected to play an increasingly important role in regenerative dentistry.

Periodontal Ligament Stem Cells

Periodontal ligament stem cells are a unique group of postnatal mesenchymal stem cells located within the periodontal ligament (PDL). This is especially important for the PDL, a specialized connective tissue that connects the tooth root to the alveolar bone. The PDL not only holds the tooth in its socket but also provides nutrients to the alveolus and cementum, protects teeth, and maintains homeostasis through the activity of PDLSCs (Xiao and Nasu 2014). These stem cells are characterized by their ability to self-renew and by their expression of mesenchymal markers, including CD146/MUC18, CD105, CD166, and STRO-1, which distinguish them from other dental or bone marrow-derived mesenchymal stem cells. The diversity of cell populations within the PDL allows them to differentiate into cells that form cementum and bone, which is crucial for periodontal regeneration (Demarco et al. 2011). PDLSCs have demonstrated the capacity to form structures resembling cementum and PDL in vivo, making them a lead candidate for regenerative therapies aimed at periodontal tissues (Xiao and Nasu 2014). Their multipotent nature is further supported by their expression of tendon-specific markers, indicating broader differentiation potential within craniofacial tissues (Demarco et al. 2011). In preclinical studies, transplanting PDLSC sheets into periodontal defects has led to notable improvements in tissue healing, including new bone formation, regeneration of functional periodontal ligament fibers, and cementum deposition. For instance, Akizuki et al. applied PDLSC sheets to dehiscence defects in canine models and observed strong regeneration of periodontal structures (Akizuki et al. 2005). Ding et al. reported that allogeneic PDLSC sheets could promote periodontal tissue regeneration and reduce inflammation in miniature pig models of periodontitis (Ding et al. 2010). The immunomodulatory capabilities of PDLSCs were also highlighted by their ability to suppress T-cell and B-cell activation, thereby moderating inflammatory responses associated with periodontitis. Further research has aimed to enhance the regenerative potential of PDLSCs, for example by using vitamin C to induce telomerase activity, resulting in improved outcomes in swine models of periodontal defects compared with untreated controls. This indicates that modulating cellular pathways can enhance the therapeutic effects of PDLSCs. Other oral MSC sources, like human gingiva-derived mesenchymal stem cells (GMSCs), have also been studied for periodontal regeneration. In canine models with class III furcation defects, transplanted GMSCs significantly improved regeneration of damaged periodontal tissues, including alveolar bone. Nevertheless, PDLSCs remain the preferred choice due to their natural location within the PDL and their proven capacity to restore functional tissue (Xiao and Nasu 2014). Clinical translation of PDLSC-based therapies is progressing, with several clinical trials investigating MSCs derived from both the periodontal ligament and bone marrow for periodontal regeneration. Although results vary regarding increases in bone volume and attachment levels, these studies demonstrate the feasibility and safety of using autologous or allogeneic stem cell sources to treat periodontitis-related defects (Tran et al. 2019). Ongoing trials are also assessing adipose-derived MSCs as alternative sources. The integration of PDLSCs into scaffold-based regenerative methods is an active area of research. Scaffold design must support cell adhesion, migration, and differentiation while mimicking the native extracellular matrix structure of the PDL (Lombaert et al. 2017). Advances in biomaterial science have enabled fabrication techniques that combine scaffold composition with bioactive agents to enhance biocompatibility and enable personalized regenerative solutions (Saberian et al. 2024). Functionally graded membranes created through sequential electrospinning have been proposed to engineer new periodontium by improving tissue regeneration and preventing unwanted gingival tissue downgrowth (Bottino and Thomas 2015). Despite promising preclinical data and early clinical experiences, challenges remain regarding standardizing cell sourcing protocols, assessing long-term safety, scaling for widespread clinical use, and navigating regulatory issues related to stem cell manipulation (Lombaert et al. 2017). Nonetheless, ongoing research continues to deepen our understanding of PDLSC biology and its potential for restoring damaged periodontal tissues through innovative regenerative strategies.

Dental Follicle Stem Cells

Dental follicle stem cells (DFSCs) are a unique group of mesenchymal progenitors found within the dental follicle, a connective tissue sac that surrounds the developing tooth germ before eruption. The dental follicle is often discarded as medical waste during the removal of an impacted tooth, yet it contains a reservoir of stem cells with notable regenerative potential. These cells can differentiate into various cell types essential for periodontal tissue formation, including osteoblasts, cementoblasts, and PDL fibroblasts (Shopova et al. 2023; Amrollahi et al. 2016). The differentiation capacity of DFSCs has been confirmed through comparative studies with other dental stem cell sources. Notably, DFSCs and apical papilla stem cells (SCAPs) exhibit higher proliferative capacities than bone marrow-derived stem cells, indicating an inherent advantage for applications requiring extensive cell expansion (Shopova et al. 2023). This increased proliferative capacity is especially relevant in translational regenerative dentistry, where large numbers of functional cells are needed for effective tissue engineering. In addition to their multipotency, DFSCs have demonstrated osteogenic potential both in vitro and in vivo. Studies have shown that when cultured under appropriate conditions, DFSCs can produce mineralized tissues resembling alveolar bone and cementum. This makes them promising candidates for regenerating periodontal structures damaged by disease or trauma. Additionally, precursor cells from the dental follicle have been successfully induced to differentiate into mature tissues resembling the periodontium, underscoring their utility in reconstructing complex dental structures (Amrollahi et al. 2016). The clinical relevance of DFSCs goes beyond their differentiation ability. Their easy access from routinely extracted third molars provides an ethically simple and minimally invasive source compared to other stem cell niches. This practical benefit supports both autologous and allogeneic therapies while reducing donor site complications (Shopova et al. 2023; Amrollahi et al. 2016). Moreover, the developmental origin of the dental follicle provides its stem cells with molecular cues that favor integration into the periodontal environment. Single-cell transcriptomic studies further reveal diversity within dental follicle-derived populations, identifying distinct subpopulations with expression profiles associated with extracellular matrix production, growth factor signaling, and immune modulation (Krivanek et al. 2020). These insights assist in scaffold design and biomaterial choices by identifying molecular targets that can improve engraftment or guide lineage development. Despite these promising traits, several challenges remain in translating this research. Scaffold biocompatibility and mechanical stability need optimization to support DFSC survival and function after transplantation (Nör 2006; Albuquerque et al. 2014). The physical features of carriers should match those needed for restorative procedures, ensuring a well-sealed interface that prevents microleakage and contamination during tissue regeneration (Nör 2006). Regulatory issues concerning the clinical use of biological inducers or engineered constructs with DFSCs require thorough preclinical testing before broad implementation. Recent advances in scaffold technology, such as nanocomposite fibrous matrices, provide controlled delivery systems for bioactive agents that can influence DFSC behavior at the injury site (Albuquerque et al. 2014). These innovations aim to mimic aspects of the native stem cell niche, offering structural support and biochemical signals essential for successful tissue regeneration. Current research highlights the versatility and potential of dental follicle stem cells in regenerative dentistry. Their high proliferation rate, multipotential differentiation, ease of harvest, and compatibility with emerging biomaterials make them key players in efforts to restore periodontal tissues using biologically based engineering strategies (Shopova et al. 2023; Amrollahi et al. 2016).

Gingival and Epithelial Stem Cells

Gingival and epithelial stem cells are two distinct but interconnected cell populations in the oral cavity, each playing a unique role in tissue health and regeneration. Epithelial stem cells are characterized by their versatility, slow division rate, and strong long-term self-renewal abilities. These cells form a single stem-cell pool that can generate all epithelial lineages through asymmetric divisions, thereby supporting both physiological renewal and wound healing in stratified tissues such as the skin and in specialized simple epithelia such as the gut. Notably, transplantation and lineage-tracing experiments have shown that epithelial stem cells can generate diverse epithelial cell types and differentiate into neuroendocrine Merkel cells. This plasticity highlights their importance in maintaining tissue integrity and responding to injury. In the oral environment, both MSCs) and epithelial stem cells have been successfully isolated from tissues such as the gingiva, teeth, and periodontal ligament. Preclinical studies using immunodeficient animal models and in vitro differentiation tests have confirmed the strong regenerative potential of these oral-derived stem cells across multiple tissues and organs (Xiao and Nasu 2014). The gingiva is a rich source of several stem cell types, including GMSCs, gingival tissue-derived stem cells, and gingival multipotent progenitor cells, all of which exhibit multipotency in laboratory assays. These findings emphasize the versatility of gingival tissues as sources for regenerative medicine. The importance of these gingival stem cells goes beyond their mere existence. GMSCs exhibit properties that make them well-suited for tissue engineering to repair oral soft tissues. Their accessibility, high growth rate, and immune-modulating effects make them promising for regenerative therapies. Additionally, isolating various progenitor populations from soft oral tissues like the oral mucosa broadens the range of cell sources available for clinical treatments targeting oral defects (Nicolescu 2016). Epithelial stem cells from human oral tissues have shown great potential for organ and tissue regeneration, especially when transplanted into immunodeficient animals or used in preclinical differentiation protocols (Xiao and Nasu 2014). Their role in normal renewal is particularly relevant to wound healing after oral cavity surgery or injury. From a biomaterials perspective, advances in scaffold design have facilitated the use of these stem cells for gingival regeneration. Hydrogels are emerging as promising scaffolds because they are biocompatible and support cell attachment, movement, and growth. In vitro studies indicate that incorporating natural polymers, such as collagen, chitosan, or hyaluronic acid, into hydrogels can enhance their performance by mimicking the body’s natural extracellular matrix. Functionalization with peptides, such as arginine-glycine-aspartic acid, or with growth factors further enhances cell attachment and migration, which are crucial for successful tissue regeneration. Chitosan-based hydrogels are especially useful for controlled drug delivery and growth factor release, supporting blood vessel formation during tissue repair. Collagen-based scaffolds are also promising for mimicking the extracellular matrices of tissues such as bone and teeth. These scaffolds offer structural support while facilitating cell interactions needed for effective regeneration. Adding bioactive glass containing zinc or magnesium ions into polymer matrices has been suggested to boost antibacterial properties, biological activity, and mechanical strength of scaffolds used in bone and soft tissue engineering. However, despite these advances, challenges remain. Scaffold biocompatibility must be carefully evaluated to ensure integration without eliciting immune reactions. Additionally, obtaining enough high-quality gingival or epithelial stem cells requires standardized methods to isolate and preserve their healing abilities while minimizing damage at the donor site.

Gingival and epithelial stem cells are central to dental regenerative medicine because they are accessible, multipotent, and compatible with advanced biomaterial scaffolds. Ongoing research aims to improve methods for using these cells in clinical applications to restore function and appearance to damaged oral tissues (Shopova et al. 2023; Xiao and Nasu 2014; Nicolescu 2016).

Stem Cells from Exfoliated Deciduous Teeth

Stem cells from exfoliated deciduous teeth, commonly referred to as SHEDs, have emerged as a promising source of MSCs for regenerative dentistry. These cells are isolated from naturally shed primary teeth, which are usually discarded, making them an accessible and ethically preferred resource for stem cell collection (Parthiban et al. 2020; Angelova Volponi et al. 2018). The ease of gathering them is a key benefit, as it avoids the invasive procedures needed to obtain other stem cell types. Additionally, the large number of exfoliated deciduous teeth in children ensures a reliable supply for research and treatment use (Shopova et al. 2023; Parthiban et al. 2020). SHEDs show notable plasticity and multipotency, which are crucial for their use in tissue engineering and regenerative therapies. They can differentiate into multiple cell types important for dental tissue regeneration, including odontoblasts, osteoblasts, adipocytes, and neural-like cells, , and outperform other dental stem cell sources in this area because of their superior ability to mimic natural tissue structure (Angelova Volponi et al. 2018).

Additionally, transplantation studies have demonstrated that SHED-derived cells can form mature bone tissue with complete vascularization, further highlighting their versatility in craniofacial regenerative applications. The availability of SHED from discarded teeth not only makes sourcing easier but also reduces the risks associated with autologous transplantation. Since these cells can be collected from the patient's own exfoliated teeth or those of close relatives, immunological compatibility is improved, thereby minimizing the risk of rejection or adverse immune responses (Shopova et al. 2023). This is especially relevant for pediatric patients who may benefit from early treatment using autologous or allogeneic SHED-based therapies. Compared to other dental stem cell types, such as DPSCs and SCAPs, SHED offer distinct advantages. While DPSCs and SCAPs are also readily obtainable from extracted teeth and have demonstrated regenerative potential (Parthiban et al. 2020), SHED stand out for their higher proliferation rates and broader differentiation capabilities (Angelova Volponi et al. 2018). These qualities make them particularly suitable for large-scale tissue engineering where both cell quantity and quality are critical. Despite these benefits, several obstacles must be overcome before they can be widely used in clinics. Standardizing isolation procedures, refining culture methods to retain multipotency, and thoroughly evaluating safety are crucial steps toward clinical use. Additionally, understanding the molecular mechanisms behind SHED differentiation will help in precisely controlling lineage fate during tissue regeneration. In conclusion, stem cells from exfoliated deciduous teeth are a valuable addition to the range of oral MSCs available for regenerative dentistry. Their easy access, high growth potential, multipotency, and proven ability to produce functional dental tissues make them promising candidates for future therapies to repair damaged or diseased oral structures. (Shopova et al. 2023; Parthiban et al. 2020; Angelova Volponi et al. 2018).

CHAPTER FOUR

BIOMATERIALS AND SCAFFOLD TECHNOLOGIES

Fundamentals of Biomaterials

Classification and Properties of Biomaterials

Biomaterials are vital to tissue engineering strategies in regenerative dentistry, acting as the structural and functional foundation for scaffolds that support cell attachment, proliferation, and differentiation. Their classification primarily depends on origin and composition, which directly influence their properties and suitability for specific dental applications. The main categories include natural biomaterials, synthetic biomaterials, and hybrid systems that combine features of both. Natural biomaterials such as collagen, hyaluronic acid, and fibrin are widely used owing to their inherent biocompatibility and their ability to mimic the extracellular matrix (ECM) of native tissues. For example, collagen creates a favorable environment for cellular activities essential to periodontal regeneration. These materials are biodegradable and support cell adhesion and migration, which are critical for tissue integration and remodeling. However, natural biomaterials can vary in mechanical strength and degradation rates, potentially limiting their use in applications requiring higher load-bearing capacity (Ahmed et al. 2024). Synthetic biomaterials offer greater control over physical properties like porosity, degradation rate, and mechanical strength. Polymers such as polylactic acid (PLA) and polyglycolic acid (PGA) exemplify this category; they can be engineered with customizable features tailored to specific dental tissue needs. Their versatility in design and manufacturing makes them essential in scaffold-based approaches for dental tissue regeneration. Synthetic materials also reduce the risk of immunogenic reactions associated with animal-derived products but may lack certain bioactive cues present in natural ECM components. Synthetic biomaterials are selected based on their ability to interact with host tissues without provoking adverse reactions. Hybrid biomaterials represent an innovative approach by combining natural polymers with synthetic ones. This strategy aims to balance biocompatibility with mechanical strength. For example, scaffolds composed of collagen (natural) and PLA or PGA (synthetic) can create a microenvironment that promotes cell growth while maintaining structural integrity during tissue formation. These hybrid systems can be engineered to closely resemble the hierarchical architecture of native dental tissues, supporting both functional integration and long-term stability (Saberian et al. 2024). The intrinsic properties of biomaterials—such as biocompatibility, biodegradability, mechanical strength, porosity, surface chemistry, and bioactivity—are crucial determinants of their performance in regenerative applications. Biocompatibility ensures that the material does not elicit an immune response or cause toxicity upon implantation. Biodegradability allows for gradual replacement by new tissue without harmful residues. Mechanical strength must be sufficient to withstand physiological forces in the oral cavity and maintain scaffold integrity during tissue regeneration. Porosity is vital for nutrient diffusion and vascularization within engineered structures. Surface chemistry plays a key role in modulating cell behavior by influencing protein adsorption and cell attachment. Biomimetic modifications, such as the addition of signaling molecules or the creation of hierarchical structures, can further enhance cellular responses by mimicking aspects of the native ECM environment (Ahmed et al. 2024). These strategies have been shown to promote cell alignment, organization, and functional integration with surrounding tissues.

Classifying biomaterials as natural, synthetic, or hybrid reflects a range of properties that can be strategically utilized in specific regenerative dentistry applications. The careful selection or design of these materials is guided by considerations of biocompatibility, degradability, mechanical performance, structural mimicry of native tissues, and their ability to support cellular functions necessary for successful tissue regeneration (Saberian et al. 2024; Ahmed et al. 2024).

Biocompatibility and Immunogenicity

Biocompatibility and immunogenicity are key considerations in the development and translation of biomaterials for regenerative dentistry. The interaction between biomaterials and host tissues influences not only the success of tissue integration but also the long-term stability and function of engineered constructs. Biocompatibility refers to a material's ability to perform its intended function without causing undesirable local or systemic effects in the recipient, while immunogenicity involves the potential of a material to trigger an immune response. HA is well known for its bioactive properties, which support new bone growth, enhance tissue integration, and accelerate healing. Applying HA as a coating on metallic implants transforms inert surfaces into environments that closely resemble natural hard tissues. This enhances bone-to-implant contact, encourages mineralized tissue ingrowth, and boosts biological fixation. Nano-hydroxyapatite (nano-HA) coatings on titanium and stainless-steel implants have been shown to improve bone bonding and osseointegration, which are vital for reducing healing times and extending implant lifespan. The biocompatibility of HA is further demonstrated by its ability to enhance surface wettability, promoting clot adhesion during periodontal regeneration. However, HA is brittle and unsuitable as a bulk implant material under load-bearing conditions, making it primarily used as a coating rather than a structural component. The method used for applying apatite coatings significantly affects biocompatibility and immunogenicity. Techniques like sol–gel coating, plasma spraying, and biomimetic deposition are often used to produce uniform coatings with optimal thickness and crystallinity. These approaches aim to maximize surface bioactivity while minimizing adverse immune reactions (George Ittycheria et al. 2024). The choice of technique can influence protein adsorption, cell attachment, and subsequent tissue responses. In dental pulp regeneration, hydrogels made with dental curing lights have been shown to be compatible with pulp-like tissue engineering and blood vessel formation within root canals. These hydrogels support stem cell survival and differentiation without the need for exogenous growth factors such as TGF-β, indicating natural biocompatibility that supports the body’s own regenerative processes. Furthermore, stem cell-laden hydrogels facilitate microvascular network formation, a process essential for nutrient delivery and waste removal, without provoking significant inflammatory responses (Parthiban et al. 2020). The immunogenicity of biomaterials depends on their composition, surface features, and degradation byproducts. For example, synthetic polymers or poorly characterized natural materials may release harmful byproducts that elicit inflammation or foreign-body reactions. Conversely, biomimetic approaches that mimic native extracellular matrix components tend to lower immunogenicity by providing familiar biochemical signals to host cells. Recent advances in enamel regeneration use self-assembling peptides or elastin-like polypeptides to guide mineralization in demineralized areas. These methods primarily act on the surface but show promise for achieving robust structural integration with minimal immune response because they resemble natural enamel proteins (Angelova Volponi et al. 2018). The cellular response to scaffold materials also affects biocompatibility. For instance, DPSCs grown on suitable substrates show increased expression of mineralizing markers while maintaining low pro-inflammatory gene levels (Parthiban et al. 2020). This indicates that scaffold composition can steer stem cell fate while reducing immune reactions. Comparing dental pulp cells and bone cells reveals shared features in their interactions with the extracellular matrix and in their signaling pathways. These similarities suggest that knowledge from bone tissue engineering on biocompatibility can inform dental applications. Signaling pathways, such as the Mitogen-Activated Protein Kinase Pathway, which are important in odontoblast differentiation, underscore the need to design scaffolds that do not disrupt crucial cellular signaling during tissue regeneration. Successful regenerative dental strategies depend on the use of biomaterials that are both highly biocompatible and minimally immunogenic. This requires careful attention to material composition, surface features, manufacturing techniques, and their interactions with resident stem cells and the immune system. Ongoing research aims to improve these factors to enhance clinical results and reduce risks of immune reactions (George Ittycheria et al. 2024; Parthiban et al. 2020; Angelova Volponi et al. 2018; Simon et al. 2011).

Degradation and Resorption Profiles

Degradation and resorption profiles are crucial for the design and application of biomaterials in regenerative dentistry. The timing of scaffold breakdown must be carefully coordinated with tissue regeneration to ensure that the biomaterial provides support during key healing phases without lingering long enough to hinder tissue integration or cause chronic inflammation. Biodegradable scaffolds, such as those made from PLA and PGA, have gained attention due to their controlled degradation properties. These materials are designed to degrade gradually, providing structural support when needed most and allowing new tissue to assume functional load-bearing roles as the scaffold resorbs. Scaffold degradation is not just passive dissolution but is carefully crafted to align with natural healing processes. According to the literature, these scaffolds act as supportive frameworks that are gradually replaced by native bone or dental tissues. Their slow degradation ensures that the scaffold does not outlive its usefulness, reducing the risk of foreign body reactions or fibrous encapsulation. This strategy exploits the biocompatibility of advanced biomaterials, which are engineered to interact positively with host cells and the extracellular matrix, promoting optimal bone growth and regeneration. Composite scaffolds illustrate further innovation by combining multiple material phases to control degradation rates and mechanical properties. These composites can be designed so that one component degrades rapidly to create porosity for cell infiltration, while another persists longer to maintain structural stability during early tissue formation. Injectable scaffolds offer another advancement, enabling minimally invasive delivery and in situ gelation that adapts to the defect shape while undergoing controlled resorption. The clinical application of these technologies depends on balancing scaffold longevity with the appropriate timing of resorption. Rapid degradation could result in insufficient support for new tissues, risking collapse or incomplete regeneration. Conversely, overly persistent scaffolds may impede remodeling or trigger adverse immune responses. Natural and synthetic scaffolds are the two main types of materials used in regenerative dentistry, each with unique advantages and limitations that affect their suitability for specific clinical uses. Natural scaffolds, typically made from biological polymers like collagen, chitosan, or elastin, are valued for their inherent biocompatibility and ability to mimic the ECM. This mimicry promotes cell adhesion, migration, and differentiation, all of which are essential for effective tissue regeneration. However, natural materials can face challenges such as batch-to-batch variability, limited mechanical strength, and unpredictable degradation rates. These issues can limit their use in situations requiring precise control of scaffold properties or mechanical load-bearing capacity (Demarco et al. 2011; Amrollahi et al. 2016). Some synthetic materials may release acidic degradation products that influence local pH and cellular behavior. Therefore, scaffold selection must account for the specific needs of the target dental tissue. For pulp regeneration or periodontal repair, where blood supply and integration with native tissues are critical, natural or composite scaffolds may offer advantages due to their ECM-like structure and bioactivity (Saberian et al. 2024; Demarco et al. 2011). On the other hand, applications requiring robust mechanical support or specific degradation timelines might benefit from purely synthetic options (Albuquerque et al. 2014). Recent progress also involves incorporating growth factors or stem cells into natural and synthetic scaffolds to enhance regeneration. Incorporating growth factors into scaffold matrices has accelerated periodontal and bone healing in preclinical studies (Amrollahi et al. 2016). Seeding scaffolds with stem cells adds a cellular component capable of turning into various dental tissues, especially in conducive microenvironments (Demarco et al. 2011; Torvi and Munniswamy 2014). Ongoing research aims to improve scaffold design by combining the strengths of both natural and synthetic materials while addressing their limitations. Developing composite systems that integrate natural bioactivity with synthetic tunability moves us closer to optimized scaffolds for regenerative dentistry (Saberian et al. 2024; Amrollahi et al. 2016).

3D Printing and Additive Manufacturing

3D printing, also known as additive manufacturing, has become a key technology for designing and producing scaffolds in regenerative dentistry. This method enables the precise fabrication of scaffolds with features such as porosity, architecture, and mechanical strength, which are vital for regenerating complex dental tissues. The ability to customize scaffold properties at high resolution ensures that structures can be engineered to meet strict criteria for biocompatibility and safety, both of which are essential for successful clinical application. Using 3D printing in scaffold fabrication offers unmatched accuracy in mimicking the detailed microenvironment of dental tissues. By utilizing computer-aided design and layer-by-layer deposition, researchers can craft scaffolds that closely resemble the native extracellular matrix. This biomimicry is critical for encouraging effective cell adhesion, growth, and differentiation, ultimately boosting tissue regeneration results. These advances have transformed scaffold production by enabling the creation of patient-specific designs that address individual anatomical and functional needs (Saberian et al. 2024). Additionally, 3D printing allows for the integration of bioactive molecules, growth factors, or drugs directly during scaffold fabrication. This feature supports targeted delivery of therapeutic agents to specific dental tissues, enhancing regenerative processes while reducing systemic exposure. The versatility of additive manufacturing applies to many dental areas, including pulp regeneration, periodontal repair, and bone augmentation. Constructing scaffolds with controlled architecture not only ensures structural stability but also promotes functional recovery of damaged or missing tissues. Recent innovations focus on improving scaffold biocompatibility by choosing materials that support cell survival and minimize immune responses. Proper selection and processing of biomaterials guarantee that printed scaffolds create a supportive environment for tissue growth without causing toxicity or inflammation. Moreover, advances in multi-material printing enable the fabrication of composite scaffolds with regions of varying properties, further enhancing their suitability for complex dental applications. The impact of 3D printing on regenerative dentistry is clear, as it can streamline clinical processes and reduce variability in scaffold quality. Automated manufacturing enhances reproducibility and scalability, facilitating the translation of laboratory results into standardized clinical products. As additive manufacturing continues to develop, it is expected to play an increasingly important role in overcoming challenges related to scaffold design and production.

3D printing marks a major advancement in scaffold engineering for regenerative dentistry by enabling precise customization, better biocompatibility, and the incorporation of bioactive signals. These technological advances are expected to improve long-term tissue regeneration and expand treatment options for clinicians and patients alike (Saberian et al. 2024).

Bioactive and Smart Materials

Bioactive and smart materials have become central to scaffold design and fabrication in regenerative dentistry, providing dynamic platforms that interact with biological tissues to promote healing and regeneration. The integration of bioactivity into scaffolds is achieved by incorporating molecules such as growth factors, anti-inflammatory agents, or signaling peptides, which can modulate cellular responses and enhance tissue repair. Functionalized scaffolds, especially those created through advanced techniques like direct-writing electrospinning, demonstrate this approach by allowing precise spatial control over the distribution of bioactive compounds within the scaffold matrix. This enables targeted delivery of therapeutic agents directly to the periodontal microenvironment, promoting tissue regeneration while also reducing inflammatory responses (Saberian et al. 2024). Such scaffolds not only act as passive frameworks for cell attachment but also actively guide cellular behavior through controlled release profiles. The ability of these materials to deliver multiple bioactive agents in a timed manner further increases their therapeutic potential. For example, multilayered membranes have been designed to release antibiotics, anti-inflammatory drugs, and osteogenic stimulants like simvastatin in sequence. By adjusting the erosion rates of different polymer layers, a staged release can be achieved—first eliminating infection, then reducing inflammation, and finally promoting bone growth. Importantly, studies show that the bioactivity of these released agents remains intact throughout the process (Bottino and Thomas 2015). This approach addresses several clinical challenges in periodontics by decreasing bacterial colonization and supporting regeneration. Hydroxyapatite-based materials are another class of bioactive scaffolds widely used in dental applications because of their chemical similarity to natural bone mineral. These calcium phosphate polymers can be derived