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FROM SHARK DENTAL LAMINA TO HUMAN TEETH: GERM CELLS AS AN ALTERNATIVE TO IMPLANT-BASED DENTISTRY "NARRATIVE REVIEW"

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ABSTRACT:
Tooth loss, a pervasive global health challenge, affects billions, compromising quality of life and exacerbating socioeconomic disparities.Conventional restorative modalities—dental implants and prostheses—are hindered by prohibitive costs, limited durability, and imperfect integration with host tissues, often necessitating invasive procedures.,Drawing inspiration from the polyphyodont dentition of elasmobranchs, which regenerate teeth seamlessly via a stem cell-enriched dental lamina, this narrative review critically evaluates the potential of shark-derived molecular mechanisms to recalibrate human regenerative dentistry.Synthesizing contemporary scholarship, it elucidates conserved signaling pathways—Wnt/βcatenin, Hedgehog (Shh), and Sox2—that orchestrate shark odontogenesis and their homology with human dental stem cells, including rested lamina and dental pulp stem cells (DPSCs)., Cuttingedge bioengineering strategies, notably biomimetic scaffolds and 3D-printed enamel matrices, promise de novo tooth regeneration, surpassing implants by ensuring robust integration with bone and periodontium while mitigating complications like peri-implantitis. However, interspecies disparities, technical complexities, ethical dilemmas, and regulatory hurdles pose formidable barriers to clinical translation., This review positions shark germ cell models as a transformative paradigm, advocating for rigorous preclinical studies, interdisciplinary collaboration, and equitable access to address the global burden of oral health disparities.

KEYWORDS: Regenerative Dentistry, Bioengineering, Wnt/β-catenin, Shh signaling, Sox2

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INTRODUCTION

periodontal tissues.[1,2] Complications like peri-implantitis, affecting up to 20% of implant patients within five years, further underscore the limitations of current approaches.[11] The question arises: can dentistry transcend these constraints to offer solutions that are both biologically integrated and universally accessible?

The continuous tooth regeneration observed in polyphyodont sharks, driven by a progenitor cell-rich dental lamina, offers a compelling biological model for redefining human dental therapeutics.[3,12] Unlike mammals, whose diphyodont dentition limits replacement to a single cycle, sharks exhibit lifelong odontogenesis, replacing teeth every 3–8 weeks through a conveyor-belt mechanism.[13] This remarkable capacity, rooted in evolutionary adaptations, positions sharks as a premier system for studying vertebrate odontogenesis.[14] Historically, dental regeneration research has progressed from rodent incisor models to more complex vertebrate systems, with sharks emerging as a focal point due to their robust stem cell niches.[8,15] This review synthesizes molecular insights from shark odontogenesis, focusing on evolutionarily conserved signaling cascades—Wnt/β-catenin, Shh, and Sox2—that parallel mechanisms in human dental stem cells, including rested lamina, DPSCs, and periodontal ligament stem cells (PDLSCs).[4,5] By elucidating these shared pathways, we propose a translational framework to activate latent regenerative potential in human dental tissues, potentially rendering artificial restorations obsolete.[6,16] Such advancements could democratize access to durable, biologically integrated dental solutions, addressing disparities in oral healthcare, particularly in underserved regions where implant costs ($2,000–$5,000 per tooth) are prohibitive.[9] This analysis critically interrogates the feasibility of shark-inspired regenerative

approaches, their implications for clinical practice, and the multifaceted barriers—biological, technical, ethical, and socioeconomic—hindering their implementation.[7,11,17]

1.1 Evolution of Regenerative Dentistry

The pursuit of dental regeneration has evolved significantly since the 19th century, when early histologists identified the dental lamina's role in tooth development.[8,15] Initial studies focused on rodent incisors, which regenerate continuously via a cervical loop, but their limited applicability to human diphyodonty prompted exploration of polyphyodont models like sharks.[13,18] The advent of molecular biology in the late 20th century revealed conserved signaling pathways across vertebrates, sparking interest in shark odontogenesis as a blueprint for human applications.[14,19] Recent advances in bioengineering, including 3D-printed scaffolds and gene-editing technologies, have further accelerated this field, positioning shark-inspired models at the forefront of regenerative dentistry.[6,16] This historical context underscores the urgency of translating evolutionary insights into clinical solutions, particularly for populations disproportionately affected by tooth loss.[9,17]

2. Shark Tooth Regeneration: Mechanisms and Germ Cells

2.1 The Dental Lamina: A Regenerative Engine

In polyphyodont sharks, such as *Scyliorhinus canicula*, the dental lamina—an epithelial structure teeming with progenitor cells—orchestrates lifelong tooth regeneration, in stark contrast to the diphyodont dentition of mammals.[12,18] Unlike murine models, where incisor renewal is confined to a single tooth via a cervical loop, sharks employ a conveyor-belt mechanism to serially replace entire tooth units, a process intricately tied to evolutionary adaptations in jaw morphology and bite force.[13,14] This regenerative paradigm, characterized by rapid tooth cycling (3–8 weeks), establishes sharks as a pivotal system for studying vertebrate odontogenesis, with profound implications for human regenerative dentistry.[3,15] The dental lamina's ability to maintain a continuous supply of Sox2+ and Bmi1+ progenitor cells, even under mechanical stress, underscores its potential as a model for reprogramming human dental tissues.[4,19] Arguably, the shark's regenerative prowess challenges us to rethink the limitations of human odontogenic capacity.

2.2 Stem Cell Dynamics and Sox2 Expression

Sox2, a critical stem cell marker, sustains progenitor cell activity within the shark dental lamina, enabling perpetual odontogenesis across the animal's lifespan.[3] These Sox2+ cells exhibit superior regenerative capacity compared to human DPSCs, which are constrained by epigenetic barriers, such as histone methylation and DNA hypermethylation, that limit differentiation into ameloblasts and odontoblasts.[7,17] The conserved role of Sox2, mediated through Wnt/β-catenin signaling, in both shark and human dental stem cells highlights its translational potential for enhancing stemness and differentiation in regenerative dentistry.[4,5] For instance, Sox2 overexpression in human DPSCs has been shown to upregulate mineralization markers like RUNX2 and DMP1, suggesting a pathway to overcome age-related declines in regenerative capacity.[10] Notably, the robust proliferative niche of shark progenitors, characterized by high Bmi1 expression and low senescence, offers critical insights into surmounting human regenerative barriers, particularly in maintaining stem cell pools postnatally.[3,11] (Could human DPSCs, with targeted interventions, emulate this resilience?)

2.3 Conserved Signaling Networks

Shark odontogenesis is governed by a complex interplay of evolutionarily conserved signaling pathways, including Wnt/β-catenin, Shh, Bone Morphogenetic Protein (Bmp), and Fibroblast Growth Factor (Fgf).[12,18] Wnt3a, a key ligand, modulates cell proliferation to sustain continuous tooth replacement, a mechanism mirrored in human odontogenesis during embryonic tooth bud formation.[6,13] Shh signaling, expressed in the dental epithelium, regulates ameloblast differentiation and tooth patterning, while Bmp4 modulates odontoblast activity, ensuring the structural integrity of regenerated teeth.[14,19] The presence of nuclear chromocenters in shark tooth beds,

potentially accelerating cell division through chromatin remodeling, facilitates rapid regeneration cycles, a stark contrast to human tooth development, which ceases post-eruption.[15,20] These molecular insights illuminate strategies to address human regenerative challenges, particularly in enamel biogenesis, which remains a significant obstacle due to the apoptosis of ameloblasts after tooth eruption.[6,16] Critically, the synergy between Wnt and Shh pathways in sharks suggests a combinatorial approach to enhance human DPSC differentiation.

2.4 Evolutionary Origins of Shark Odontogenesis

The evolutionary divergence of elasmobranch dentition, dating back over 400 million years, provides a unique lens for understanding regenerative mechanisms.[8,14] Shark teeth, derived from odontogenic placodes, share developmental homology with vertebrate dentitions, as evidenced by conserved expression of Pitx2 and Pax6 in early tooth germs.[13,19] This evolutionary conservation suggests that shark odontogenesis may inform strategies to reactivate quiescent human dental lamina, particularly in pathological conditions like ameloblastoma, where Sox2+ cells exhibit uncontrolled proliferation.[3,11] The iterative replacement in sharks, driven by a stem cell niche, contrasts with the finite replacement in mammals, highlighting the potential to manipulate epigenetic and microenvironmental cues to extend human regenerative capacity.[17,21] For instance, studies of shark tooth fossils reveal adaptive variations in dental lamina structure, offering clues to optimize bioengineered scaffolds for human applications.[14,22] Such evolutionary perspectives enrich our understanding of regenerative dentistry's potential.

2.5 Pathway Interactions and Crosstalk

The efficacy of shark odontogenesis hinges on intricate crosstalk between signaling pathways, notably Wnt/β-catenin and Shh.[12,13] Wnt3a upregulates Shh expression in the dental epithelium, creating a feedback loop that sustains progenitor cell proliferation and ameloblast differentiation.[18,19] Bmp4, in turn, modulates Wnt signaling by inhibiting Dkk1, a Wnt antagonist, ensuring robust tooth cycling.[14,20] This dynamic interplay, absent in human postnatal dentition, suggests that combinatorial therapies targeting multiple pathways could enhance human regenerative outcomes.[16,21] For example, preclinical studies have shown that dual Wnt/Shh agonists increase DPSC mineralization by 30% compared to single-pathway interventions.[10,17] These findings underscore the need to emulate shark-like pathway interactions to unlock human odontogenic potential, a challenge that demands both molecular precision and bioengineering innovation

3. Human Dental Regeneration: Current Approaches and Challenges

3.1 Comparative Stem Cell Biology

Human dental regeneration research encompasses a diverse array of stem cell sources, including the rested lamina, DPSCs, periodontal ligament stem cells (PDLSCs), and stem cells from human exfoliated deciduous teeth (SHED).[7,10,17] Despite their multipotency, these cells exhibit limited regenerative capacity compared to shark germ cells, which regenerate complete tooth units throughout life.[3,12] Shark dental lamina progenitors benefit from a dynamic microenvironment that sustains Sox2+ and Bmi1+ activity, whereas human DPSCs face epigenetic constraints, such as Wnt pathway silencing and histone deacetylation, that impair differentiation into enamel-producing ameloblasts.[16,17] PDLSCs, while promising for periodontal regeneration, lack the capacity to form complete tooth structures, while SHED

[1] Regenerative Capacity: Shark vs. Human Tooth Germs

Feature	Shark Tooth Germ	Human Tooth Germ
Proliferative Niche	Sox2+/Bmi1+ progenitors in the dental lamina maintain lifelong activity (3).	Quiescent Sox2+ cells in the rested lamina; decline with age (11).
Tooth Cycling	Conveyor-belt replacement (every 3–8 weeks) via Wnt/β-catenin (6).	Single replacement (diphyodonty); no postnatal amelogenesis (16).
Enamel Regeneration	Functional ameloblasts regenerate in each cycle (6).	Ameloblasts apoptose post-eruption; no enamel repair (16).

show higher proliferative potential but limited scalability.[10,11] This disparity underscores the need to elucidate regulatory mechanisms enabling shark-like

odontogenesis, offering a blueprint for human regenerative applications.[15,19] Why do human stem cells falter where shark progenitors thrive? The answer lies in microenvironmental and epigenetic differences that regenerative dentistry must address.

3.2 Shared Molecular Pathways

Despite regenerative disparities, sharks and humans share critical signaling cascades that offer translational promise: Wnt/β-catenin: Drives proliferation in shark dental lamina and odontoblast differentiation in human DPSCs, with Wnt3a agonists like CHIR99021 enhancing mineralization in vitro by up to 40%.[6,13,18] Shh: Regulates epithelial-mesenchymal interactions in both systems, with inhibition impairing ameloblast function and tooth patterning.[4,14] Sox2: Marks pluripotency; its downregulation in human DPSCs correlates with reduced regenerative potential, a barrier potentially overcome by Sox2-targeted therapies.[5,10] These conserved pathways suggest that pharmacological interventions, such as Wnt agonists or Sox2 overexpression via viral vectors, could enhance DPSC potency, counteracting age-related declines in regenerative capacity.[17,21] Preclinical studies in murine models have demonstrated that Wnt activation induces ectopic tooth formation, providing a proof-of-concept for human applications.[13,22] Such strategies hold immense promise for translating shark-inspired insights into clinical regenerative dentistry, though their success hinges on overcoming pathway-specific barriers.

3.3 Translational Barriers

The path to clinical translation in regenerative dentistry is fraught with multifaceted challenges: Enamel Biogenesis: Bioengineered enamel lacks the hierarchical prism structure and cellular repair mechanisms of natural enamel, limiting its durability compared to dentin, which regenerates more readily.[16,20] Scalability: DPSC-derived organoids, while capable of forming tooth-like structures in vitro, lack vascularization and fail to achieve the morphological complexity of adult teeth, such as multi-rooted molars.[11,15] Cost-Efficiency: Regenerative approaches remain costlier and slower than implants, with R&D costs in the millions compared to $2,000–$5,000 per implant, posing barriers to widespread adoption.[17,23] Regulatory Hurdles: Stem cell therapies face stringent regulatory scrutiny from agencies like the FDA and EMA, requiring extensive safety and efficacy data, with clinical trials often spanning 5– Scalability: DPSC-derived organoids, while capable of forming tooth-like structures in vitro, lack vascularization and fail to achieve the morphological complexity of adult teeth, such as multi-rooted molars.[11,15] 10 years.[8,18] Patient-Specific Factors: Age, comorbidities, and genetic variability influence stem cell efficacy, necessitating personalized approaches that increase complexity and cost.[10,21] Recent advances in biomimetic scaffolds, such as 3D-printed enamel matrices with hydroxyapatite gradients, and targeted Wnt/Sox2 modulation offer viable solutions, potentially disrupting the dominance of implant-based dentistry.[6,13,22] These innovations, however, must address patient-specific challenges to ensure broad applicability.

3.4 Preclinical Models and Innovations

Preclinical models, including murine, porcine, and organoid-based systems, have provided critical insights into shark-inspired regenerative approaches.[13,22] For instance, scaffold-guided DPSC differentiation in minipigs has yielded tooth-like structures with dentin and pulp, though enamel remains elusive due to ameloblast apoptosis.[11,15] Organoid models, leveraging induced pluripotent stem cells (iPSCs), offer scalability but require vascular integration to mimic the spontaneous vascular ingrowth observed in shark tooth beds.[17,20] Emerging technologies, such as CRISPR-mediated Wnt activation and nanofiber scaffolds doped with growth factors, promise to enhance regenerative outcomes, drawing directly on shark molecular insights.[18,21] These models underscore the need for iterative testing to optimize biocompatibility, mechanical strength, and functionality before human trials.[8,23] The challenge lies in bridging the gap between preclinical promise and clinical reality, a task that demands both innovation and persistence.

3.5 Patient Accessibility and Equity

Ensuring equitable access to regenerative dental therapies is a critical yet underexplored dimension of translation.[9,17] In low-resource settings, where basic dental care is scarce, the high cost and complexity of regenerative approaches could exacerbate disparities, leaving millions without viable solutions.[10,23] Strategies to enhance accessibility include developing cost-effective scaffolds, leveraging open-source bioprinting technologies, and establishing global consortia to subsidize treatment in underserved regions.[15,22] Public-private partnerships, modeled on vaccine distribution frameworks, could further democratize access, aligning with the broader goal of addressing oral health inequities.[11,18] Shark-inspired regeneration, if realized, must not remain an elite privilege but a universal right, a principle that should guide future research and policy.

[2] Clinical Implications: Translational Challenges

Approach	Shark Insights	Human Limitations
Wnt Activation	Wnt3a overexpression induces de novo tooth formation (6).	Human DPSCs show age-related Wnt silencing (17).
Ameloblast Reactivation	Cyclic amelogenesis via Shh+ epithelium (6).	No natural ameloblast renewal; scaffolds required (16).
Vascularization	Spontaneous vascular ingrowth in pulp regeneration (14).	DPSC-derived organoids lack functional vasculature (11).

4. Applying Shark Germ Cell Research to Human Dentistry

4.1 Stem Cell Homology

The human dental lamina, though largely quiescent in adults, harbors a subset of proliferating cells expressing stem cell markers (Sox2, Bmi1, βcatenin, PH3), mirroring those in shark dental lamina.[3,11] These shared markers suggest an untapped regenerative potential, as evidenced by the proliferative activity of lamina rests in pathological conditions like ameloblastoma, where Sox2+ cells drive tumor growth.[3,15] Strategies to activate these cells, such as Wnt agonists (e.g., CHIR99021) or epigenetic modifiers like histone deacetylase inhibitors, could enable controlled tooth replacement in humans, drawing directly on shark-derived molecular insights.[13,18] For example, preclinical studies have shown that histone deacetylase inhibitors reactivate Sox2 expression in aged DPSCs, increasing mineralization by 25%.[17,21] The homology between shark and human stem cell niches underscores the feasibility of leveraging evolutionary insights to unlock human odontogenic potential, though ethical considerations must guide such interventions.[8,19]

4.2 Bioengineering Horizons

Shark dental lamina research informs a spectrum of bioengineering innovations, including 3Dprinted scaffolds that replicate the regenerative microenvironment of shark tooth beds.[6,13] These scaffolds, often composed of collagen-hydroxyapatite composites, mimic the extracellular matrix of shark dental lamina, promoting DPSC differentiation and vascularization.[15,22] By modulating Wnt/β-catenin and Shh pathways, these scaffolds enhance ameloblast and odontoblast formation, addressing critical limitations in human regenerative dentistry.[14,17] Emerging approaches, such as bioprinted vascular networks and CRISPR-edited stem cells, further amplify the translational potential of shark-inspired models, positioning them as a catalyst for transformative dental therapeutics.[8,18] These advancements hold the potential to redefine clinical practice, offering patients biologically integrated teeth that outperform traditional implants in longevity (potentially 50+ years) and functionality.[6,23] What would it mean for patients to regain teeth as resilient as those of sharks?

4.3 Ethical and Regulatory Considerations

The translation of shark-inspired regenerative therapies raises complex ethical and regulatory challenges. Stem cell-based approaches, particularly those involving iPSCs or gene editing, must address concerns about long-term safety, including tumorigenicity and immune rejection.[8,17] Regulatory frameworks, enforced by agencies like the FDA and EMA, require extensive preclinical data, with clinical trials often spanning 5–10 years and costing communication and patient education.[15,22] Ensuring

equitable access to regenerative therapies, particularly in low-resource settings, remains a critical priority, aligning with the broader goal of addressing global oral health disparities.[9,18] Ethical stewardship and robust regulatory oversight will be essential to balance innovation with patient safety and equity. Designing clinical trials for shark-inspired regenerative therapies presents unique challenges, given the novelty of the approach.[11,17] Phase I trials should prioritize safety, evaluating scaffold biocompatibility and stem cell stability in small cohorts (20–50 patients).[13,23] Phase II trials, focusing on efficacy, could assess tooth-like structure formation in patients with single-tooth loss, using metrics like dentin thickness and vascular integration.[15,21] Randomized controlled trials, comparing regenerative therapies to implants, would require multicenter designs to ensure diverse populations, addressing generalizability concerns.[18,22] Patientreported outcomes, such as pain and aesthetics, should complement objective measures, ensuring holistic evaluation.[10,19] Such trials, projected to begin by 2030, will be pivotal in establishing shark-inspired regeneration as a viable clinical alternative, provided they navigate funding and regulatory complexities.[8,23]

5. Conclusion and Future Directions

This narrative review illuminates the transformative potential of shark dental lamina-inspired mechanisms to advance human dental regeneration, offering a biologically driven alternative to implant-based dentistry. The continuous odontogenesis in sharks, orchestrated by Sox2+ progenitors and conserved signaling pathways (Wnt/βcatenin, Shh, Bmp), provides a robust framework for reprogramming human dental stem cells to achieve de novo tooth formation.[3,4,6] However, formidable challenges in enamel biogenesis, scalability, cost-efficiency, regulatory approval, and equitable access sustain the clinical dominance of dental implants, which remain the standard of care despite their limitations.[11,15,17] Emerging bioengineering strategies, including biomimetic scaffolds, 3D-printed enamel matrices, and targeted Wnt/Sox2 therapies, offer promising avenues to overcome these barriers, heralding a new era of regenerative dentistry.[6,13,22] Future research must prioritize preclinical models, such as porcine and organoid systems, to optimize scaffold vascularization, enamel durability, and stem cell potency, ensuring alignment with shark-inspired regenerative principles.[15,17] Clinical trials, particularly phase I/II studies of Wnt agonists and Sox2targeted therapies, are essential to validate safety and efficacy in human cohorts, with a focus on diverse patient populations to ensure inclusivity.[10,21]

A proposed roadmap for translation includes:

(1) developing standardized scaffold designs by 2030, leveraging advances in bioprinting; (2) initiating multicenter clinical trials by 2035 to evaluate regenerative outcomes; and (3) establishing global consortia by 2040 to ensure equitable access, modeled on global health initiatives.[8,18,23] Interdisciplinary collaboration among molecular biologists, bioengineers, clinicians, ethicists, and policymakers will be paramount to navigate the ethical, regulatory, and economic complexities of this paradigm shift.[9,19,21] This vision, rooted in the remarkable regenerative capacity of sharks, promises to redefine the future of dental therapeutics, fostering a world where regeneration supersedes restoration and oral health becomes a universal right.

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