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·综述·

载牙源性间充质干细胞水凝胶在牙周组织修复中的应用研究进展

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【摘要】 牙周组织的完全性功能再生(即牙槽骨、牙骨质与牙周韧带的同步重建)是口腔再生医学面临的重大挑战。牙源性间充质干细胞(DMSCs)因其多向分化潜能与免疫调节特性,是实现这一目标的理想种子细胞。水凝胶作为细胞载体,其核心优势在于能够通过精确调控的理化性质(如基质硬度、拓扑结构、降解动力学)模拟细胞外基质,构建主动调控干细胞命运的力学与生化微环境。本文综述了载DMSCs水凝胶在牙周组织修复中的应用与研究进展。文章首先分析了不同水凝胶体系的材料学特性,进而重点阐述了水凝胶通过基质硬度等力学属性调控DMSCs分化的具体分子机制:刚性水凝胶通过激活整合素-粘着斑激酶(FAK)-蛋白激酶B(Akt)哺乳动物雷帕霉素靶蛋白(mTOR)信号轴驱动成骨分化;诱导细胞骨架重构,促使Yes相关蛋白(YAP)/转录共激活因子PDZ结合基序(TAZ)去磷酸化并发生核转位,启动成骨相关基因的转录;同时稳定Wnt/β连环蛋白(Wnt/β-catenin)并激活Wnt信号通路,上调Runt相关转录因子2(Runx2)及Osterix等成骨关键转录因子的表达。此外,作为生物活性因子的程序化控释载体,水凝胶能够选择性激活Smad家族蛋白(Smad)信号亚型,促成骨因子特异性激活Smad1/5/8通路,促牙周韧带形成因子则激活Smad2/3通路,从而实现DMSCs向成骨、成牙骨质或成纤维谱系的精准定向分化。目前,该领域面临的关键科学问题包括水凝胶性能在再生过程中的动态适配、复杂口腔微环境(如微生物、机械力、炎症)的稳定控制、干细胞高效定向分化策略以及临床转化可行性。未来研究方向将集中于开发智能响应型水凝胶、结合3D生物打印技术构建个性化仿生支架,以及设计具有免疫调控功能的复合材料体系,以期最终实现牙周组织的结构与功能一体化再生。

【关键词】 牙源性间充质干细胞；　水凝胶；　基质硬度；　力学转导；　牙周组织再生；　力学微环境；　牙周炎；　组织工程；　三维支架
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Research progress on the application of dental originated mesenchymal stem cell hydrogel in periodontal tissue repair

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【Abstract】 The complete functional regeneration of periodontal tissues—specifically, the simultaneous reconstruction of alveolar bone, cementum, and periodontal ligament—represents a major challenge in oral regenerative medicine. Dental-derived mesenchymal stem cells (DMSCs) are regarded as ideal seed cells for achieving this goal due to their multi-lineage differentiation potential and immunomodulatory properties. As a cell carrier, hydrogels offer the key advantage of mimicking the extracellular matrix through precisely tunable physicochemical properties (*e.g.*, matrix stiffness, topological structure, degradation kinetics), thereby constructing a mechanical and biochemical microenvironment that actively directs stem cell fate. This review summarizes the application and research progress of DMSC-laden hydrogels in periodontal tissue repair. We first analyze the material characteristics of different hydrogel systems, and then elaborate on the specific molecular mechanisms by which hydrogels regulate DMSCs' differentiation through mechanical properties such as matrix stiffness: stiff hydrogels drive osteogenic differentiation by activating the integrin-focal adhesion kinase (FAK) - Akt/mechanistic target of rapamycin (mTOR) signaling axis; inducing cytoskeletal remodeling, and promoting dephosphorylation and nuclear translocation of Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) to initiate the transcription of osteogenesis-related genes; and stabilizing β-catenin and activating the Wnt/β-catenin signaling pathway, upregulating the expression of key osteogenic transcription factors including Runt-related transcription factor 2 (Runx2) and Osterix. Furthermore, as programmed controlled-release carriers for bioactive factors, hydrogels selectively activate Smad signaling subtypes—pro-osteogenic factors specifically activate the Smad1/5/8 pathway, whereas factors promoting periodontal ligament formation activate the Smad2/3 pathway—thereby achieving precise, directed differentiation of DMSCs toward osteogenic, cementogenic, or fibroblastic lineages. Current key scientific issues in this field include the dynamic adaptation of hydrogel properties during regeneration, stable control of the complex oral microenvironment (*e.g.*, microbes, mechanical forces, inflammation), strategies for efficient directional differentiation of stem cells, and feasibility of clinical translation. Future research directions should focus on developing smart-responsive hydrogels, constructing personalized biomimetic scaffolds combined with three-dimensional bioprinting technology, and designing composite material systems with immunomodulatory functions, aiming ultimately to achieve integrated structural and functional regeneration of periodontal tissue.

【Key words】 dental-derived mesenchymal stem cells; hydrogel; matrix stiffness; mechanotransduction; periodontal tissue regeneration; mechanical microenvironment; periodontitis; tissue engineering; three-dimensional scaffold

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牙周炎导致的牙周组织缺损(包括牙槽骨吸收、牙骨质丧失及牙周韧带断裂)是成年人牙齿丧失的主要原因[1]。传统的治疗方法难以实现牙周组织(尤其是功能性牙周膜)的原位再生,组织工程技术,特别是结合干细胞与生物材料的策略,为此带来了新希望[2-3]。DMSCs如牙周韧带干细胞(periodontal ligament stem cells, PDLSCs)和牙龈间充质干细胞(gingival mesenchymal stem cells, GMSCs)等,因其易于获取、强增殖能力、多向分化潜能(成骨、成牙骨质、成纤维)及免疫调节功能[4-5],被视作牙周再生的核心细胞来源[6]。

水凝胶因其高含水量、可调的物理化学性质及良好的生物相容性,能高度模拟天然细胞外基质的三维微环境[7],是DMSCs的理想载体[8]。近年来的研究突破在于认识到,水凝胶不仅是承载细胞的被动支架,更是通过其力学性能(如硬度、弹性模量)、拓扑结构和生化信号主动调控干细胞行为与命运的"主动指令平台"[9-10]。在牙周这一包含多种异质性组织的复杂结构中,如何利用水凝胶精确引导DMSCs向特定谱系(成骨细胞、成牙骨质细胞、成纤维细胞)分化,是实现协同再生的关键[11-12]。因此,本文旨在系统综述不同特性的水凝胶如何通过调控力学与生化微环境,影响DMSCs的生物学行为及其下游信号通路,进而推动牙周组织修复的研究进展,并深入探讨其内在机制。

1　水凝胶的构成与代表体系

水凝胶作为细胞的三维载体,其材料来源与化学构成是决定其理化与生物学性能的基础。根据聚合物来源,主要可分为天然、合成及复合水凝胶体系[13]。

1.1　天然聚合物水凝胶

天然聚合物水凝胶通常生物相容性优异,且

部分本身具有生物活性信号。明胶甲基丙烯酰（gelatin methacryloyl，GelMA）水凝胶：由明胶改性而来，保留了精氨酸-甘氨酸-天冬氨酸（arginine-glycine-aspartic acid，RGD）序列[14]，其硬度可通过光交联程度进行精确调控，是模拟不同组织力学微环境和研究细胞力学响应的常用模型[15-17]。藻酸盐是一种通过二价阳离子（如Ca^{2+}）交联的多糖[18]，其温和的凝胶条件适于包裹细胞，但因其本身缺乏细胞粘附位点，常需与RGD肽段等进行功能化修饰[19-21]。壳聚糖是自然界唯一带正电荷的天然多糖[22]，具有固有的抗菌性和促细胞粘附能力[23]，其降解速率可通过调节脱乙酰度和交联度来实现匹配组织再生进程[24-25]。

1.2　合成聚合物水凝胶

合成聚合物水凝胶，如聚乙二醇（polyethylene glycol，PEG）[26]、聚乳酸-羟基乙酸共聚物[poly（lactic-co-glycolic acid），PLGA]、聚左旋乳酸[poly（L-lactic acid），PLLA]等，其优势在于分子结构、力学性能及降解时间可实现高度可重复的精确设计与调控[27-28]。然而，其表面通常呈生物惰性，需要主动修饰（如接枝RGD肽段）才能为细胞提供有效的粘附位点，从而引导细胞行为[29]。

1.3　复合与智能水凝胶

为满足口腔复杂组织再生的多功能需求，将不同材料复合或引入智能响应组分成为重要策略。复合水凝胶旨在协同提升性能，例如GelMA-藻酸盐互穿网络可兼顾力学强度与生物活性[30]；掺入纳米羟基磷灰石（nano-hydroxyapatite，nHA）可同时增强力学模量与提供成骨矿化模板[31]。智能水凝胶则能对外部微环境变化（如特定酶、pH值或活性氧水平）产生响应，实现药物或生长因子的按需、定点释放，为牙周炎等病理条件下的智能治疗提供了平台[32-33]。

综上所述，天然聚合物水凝胶因含有天然细胞外基质成分或固有生物活性信号（如GelMA的RGD序列、壳聚糖的正电荷特性），能够有效促进DMSCs的粘附、存活及早期分化，但其局限性在于批次稳定性较差、力学强度调节范围相对有限，且部分材料（如藻酸盐）需经功能化修饰方可主动调控干细胞定向分化。合成聚合物水凝胶则凭借分子结构可编程、力学性能与降解动力学高度可控等优势，为解析基质硬度、交联密度等物理参数对DMSCs成骨/成牙骨质分化的精确调控提供了理想平台，但其生物惰性表面必须通过接枝细胞粘附配体或负载生物活性因子才能赋予其引导干细胞命运的能力。复合与智能水凝胶通过多组分协同实现了力学增强与生物功能化的一体化设计，并可借助环境响应特性在牙周炎等病理微环境中按需释放成骨/成牙骨质诱导信号，实现对DMSCs分化的时空精确干预；然而，其制备工艺复杂、多组分兼容性及体内长期稳定性仍是制约临床转化的重要瓶颈。各类水凝胶体系在载DMSCs及调控其分化方面各具优势与局限，未来研究应着力于材料性能与再生微环境的动态适配，以推动牙周组织功能再生的精准化与临床化。

2　水凝胶对DMSCs命运的多元调控策略

水凝胶不仅是物理支架，更是主动调控细胞行为的动态微环境[34]。其通过整合力学信号、生物化学因子以及结构拓扑等多维度信息，共同决定DMSCs的粘附、增殖、迁移与分化命运[35]。

2.1　基质力学性质的调控

基质的弹性模量（刚度）是引导干细胞分化的核心力学信号之一。经典研究证实，间充质干细胞在模拟骨组织硬度的基质上倾向于成骨分化[36-37]。这一规律在牙源性干细胞中得到验证：接种于较硬基质（如30~50 kPa的GelMA）上的PDLSCs，其成骨/成牙骨质相关标志物，如Runt相关转录因子2（Runt-related transcription factor 2，Runx2）[38]、骨钙素[39]（osteocalcin，OCN）、牙骨质蛋白1[40]（cementum protein 1，CEMP1）表达显著上调[41]；而较软基质则更利于其维持未分化状态或表达牙周膜成纤维细胞相关基因（如牙周韧带相关蛋白1[42]（periodontal ligament-associated protein-1，PLAP-1）、I型胶原（collagen type I，COL1））[43-45]。此外，基质的粘弹性[46]、应力松弛特性及降解过程中的动态力学变化[47]，同样深刻影响DMSCs的细胞骨架重组、核内力学信号传导及最终的分化取向。

2.2　生物化学因子的整合与递送

水凝胶是负载并可控释放各类生物活性物质的理想载体。①生长因子：例如，负载骨形态发生蛋白（bone morphogenetic protein，BMP）的水凝胶能有效诱导干细胞的成骨分化[48]。②生物活性离子：锶（Sr^{2+}）、镁（Mg^{2+}）等具有促成骨作用的离子，可被整合进水凝胶网络共载，实现持续释放以调控细胞代谢与分化[49]。③细胞外囊泡：来源于干细胞或功能细胞的细胞外囊泡[50]，可将其携带的蛋白质、核酸等活性成分通过水凝胶递送至

DMSCs，调控其旁分泌效应及再生进程[51]。

2.3　结构拓扑与粘附信号的设计

水凝胶的微观结构与粘附特性为细胞提供重要的物理和化学引导。通过调控交联方式（光交联、酶交联等）与制备工艺（如微图案化、各向异性/梯度结构构建），可以精确设计其网络孔隙、孔径、取向及力学梯度，从而物理引导细胞的定向排列、浸润与空间分布，以模拟天然组织的复杂结构[52-53]。同时，通过修饰RGD等粘附肽段并调控其在水凝胶中的密度与空间分布，可以精确干预DMSCs的粘着斑形成、细胞骨架张力和细胞内信号通路，最终调控其增殖与谱系分化命运[54]。

3　水凝胶调控DMSCs分化促进牙周再生的机制

水凝胶作为仿生的三维微环境，通过将材料本身的理化信号与所负载的生物活性信号转化为细胞内特定的分子信号，从而精准调控DMSCs的转录程序与分化命运。其核心机制集中于对细胞内关键信号通路的时空特异性激活与整合（图1）。

3.1　力学转导核心通路的激活

整合素-FAK-Akt/mTOR通路：含RGD序列的天然衍生水凝胶（如光交联GelMA）或经RGD修饰的合成水凝胶（如RGD-PEG），为DMSCs提供了明确的整合素结合位点。通过调节交联密度（如GelMA浓度、紫外曝光时间或PEG分子量），可构建硬度范围覆盖软组织至骨组织的基质。硬基质促进整合素簇集和粘着斑形成，激活FAK[55]，进而磷酸化并激活Akt和mTOR信号，驱动成骨相关基因表达和细胞周期进程[56-57]，反之，低硬度水凝胶（如低浓度GelMA或纯藻酸盐）因无法提供足够力学支撑，FAK信号微弱，细胞趋于维持静息状态。该通路的激活是驱动细胞铺展、存活及成骨基因表达的关键[58]。

YAP/TAZ通路：水凝胶的力学微环境通过调节细胞骨架张力直接控制YAP/TAZ亚细胞定位。在硬基底上（如高交联度GelMA、纳米羟基磷灰石复合水凝胶），F-肌动蛋白（F-actin）应力纤维充分发育，产生的张力抑制YAP/TAZ磷酸化，使其易位入核，与转录增强因子结构域（transcriptional enhanced associate domain，TEAD）等转录因子结合，启动促进细胞增殖、成骨分化相关基因的转录[59]；在软基质（如低浓度藻酸盐、低交联度壳聚糖）上，细胞铺展受限，YAP/TAZ滞留于胞质并被蛋白酶体降解，利于维持干细胞态或向软组织谱系分化[60]。水凝胶硬度通过调节细胞骨架张力及细胞核投影面积，与粘附配体密度协同精准调控YAP/TAZ的活性[61]。

Wnt/β-catenin通路：该通路不仅是经典的成骨发育通路，也受力学信号调节。例如，胶原-纤维联素水凝胶可能通过激活整合素信号或抑制糖原合成酶激酶-3β（glycogen synthase kinase-3β，GSK-3β）活性，稳定β-catenin[62]，使其在胞浆内积累并进入细胞核，与T细胞因子/淋巴样增强因子（T-cell factor/lymphoid enhancer factor，TCF/LEF）家族转录因子结合，激活Runx2、成骨细胞特异性转录因子Osterix等成骨关键基因的表达[63]。体内实验表明，负载PDLSCs的硬水凝胶植入骨缺损后，常伴随Wnt/β-catenin通路上调及更佳的新骨形成，印证了其在力学信号转导中的功能[64]。

3.2　生物化学信号通路的程序化激活

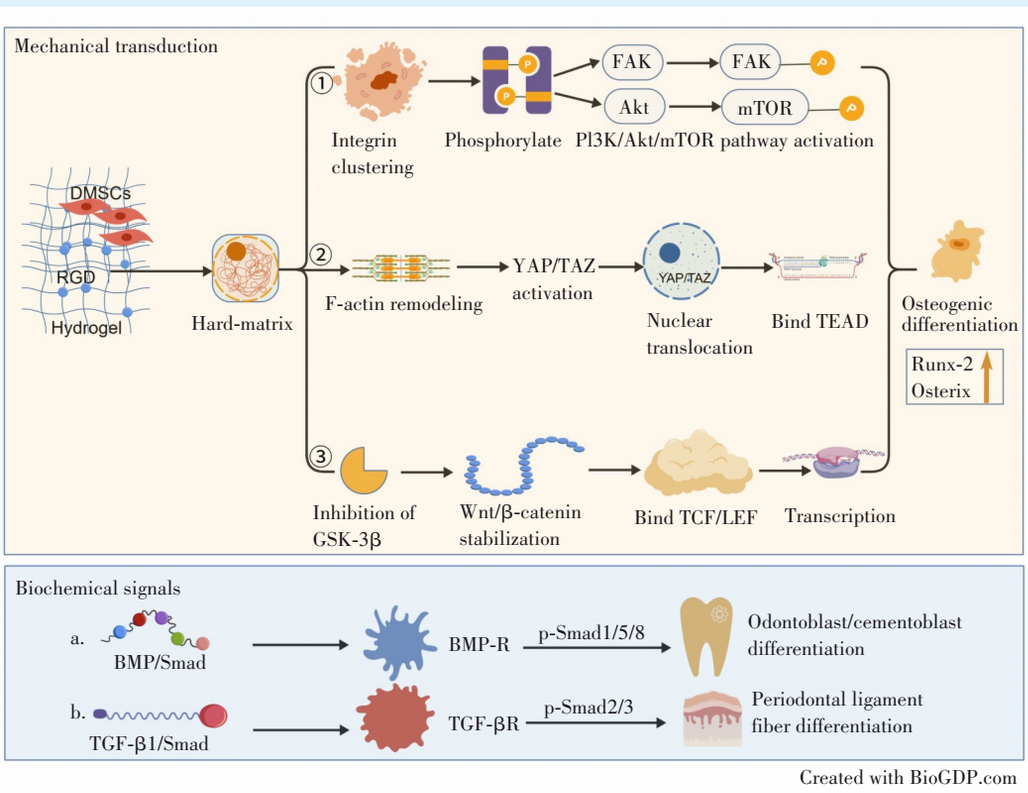
在水凝胶介导的牙周再生中，Smad家族蛋白信号通路发挥着核心枢纽作用，是不同生物化学信号引导DMSCs定向分化的共同下游执行者[65]。水凝胶通过负载并控释特定信号分子，能够选择性地激活不同的Smad亚型，从而程序化地决定细胞命运：促成骨信号主要激活Smad1/5/8通路，活化的Smad1/5/8与Smad4形成复合物入核，协同Runx2等转录因子，强力驱动成骨/成牙骨质相关基因的表达[66-67]；而促纤维化信号则主要激活Smad2/3通路，进而调控细胞外基质合成与重塑相关基因的转录，引导DMSCs向牙周韧带成纤维细胞分化[68-71]。水凝胶的智能设计（如酶响应性释放）进一步赋予了对Smad通路激活的时空精确控制能力，使其能在特定修复阶段或微环境区域中定向启动成骨或纤维生成程序，这是实现牙周软硬组织有序再生的关键分子基础[72-73]。

4　载DMSCs水凝胶在牙周组织修复中的应用进展

基于上述机制，载DMSCs水凝胶的研究已从简单的细胞输送载体，发展为能够主动调控细胞命运、引导空间有序再生的智能化生物活性平台。其核心优势在于通过材料科学与干细胞生物学的融合，精确模拟牙周复合组织的复杂微环境，从而实现对牙槽骨、牙骨质及牙周韧带一体化再生的主动引导（图2）。

4.1　牙槽骨再生

牙槽骨再生要求水凝胶不仅能支撑成骨，还需提供必要的生物力学刺激和稳定的成骨诱导微



DMSCs: dental-derived mesenchymal stem cells; RGD: arginine-glycine-aspartic acid; FAK: focal adhesion kinase; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; mTOR: mechanistic target of rapamycin; Runx2: Runt-related transcription factor 2; YAP: Yes-associated protein; TAZ: transcriptional co-activator with PDZ-binding motif; F-actin: filamentous actin; TEAD: transcriptional enhanced associate domain; GSK-3β: glycogen synthase kinase-3β; TCF/LEF: T-cell factor/lymphoid enhancer factor; BMP: bone morphogenetic protein; p-Smad: phosphorylated Smad; BMP-R: bone morphogenetic protein receptor; TGF-β1: transforming growth factor-β1; TGF-βR: transforming growth factor-β receptor

Figure 1　Schematic diagram of how hydrogels regulate the differentiation mechanism of DMSCs through mechanical transduction and biochemical signals

图1　水凝胶通过力学转导与生化信号调控DMSCs分化机制图

环境。硬质或复合增强型水凝胶已成为主流策略，它们通过整合无机纳米成分如纳米羟基磷灰石（nano-hydroxyapatite，nHA）、β-磷酸三钙或通过双网络交联提升力学性能，既能抵抗咀嚼区域的受力，又能传递促成骨机械信号[74]。例如，将PDLSCs或GMSCs负载于掺有nHA的GelMA水凝胶中，植入牙周骨缺损处，其固有的硬度和nHA释放的钙磷离子，能持续激活细胞内的机械转导通路（如YAP/TAZ）和经典的Wnt/β-catenin成骨通路，显著促进新骨形成和骨密度恢复，效果优于单纯水凝胶或细胞[75-76]。为进一步加速再生进程，将生长因子（如BMP-2）与负载干细胞的水凝胶结合，构成了“支架+细胞+因子”三联疗法。水凝胶在此扮演了BMP-2的可控缓释库，使其在局部维持有效浓度，避免了全身应用的异位骨化等副作用，并与干细胞产生协同，大幅缩短骨愈合时间[77]。最新研究还探索了在水凝胶中引入具有成骨诱导性的小分子（如地塞米松）或特定miRNA，以更安全、更经济的方式实现高效成骨[78-79]。

4.2　牙骨质再生

牙骨质再生是牙周再生的独特难点，其关键在于特异性诱导PDLSCs分化为成牙骨质细胞并分泌牙骨质特异性基质，研究通过水凝胶的精密化学修饰与物理特性设计来引导特异性分化。例如，设计表面富含磷酸酯基团或接枝维生素C（抗坏血酸）的明胶水凝胶[80]，这些化学基团不仅模拟了牙骨质形成的初始矿化界面，更能持续、局部地提供诱导信号，可成功上调PDLSCs中牙骨质附着蛋白（cementum attachment protein，CAP）、CEMP1的表达，并在动物模型中观察到新生牙骨质样组织和骨样矿化组织沉积[81]；适中硬度的水凝胶微环境最有利于成牙骨质细胞表型的维持和功能发挥，这种物理特性通过整合素介导的细胞骨架重排，激活了细胞内利于牙骨质形成的信号网络，在动物牙周缺损模型中，此类功能化水凝胶不仅能引导新生牙骨质样组织在牙根面上的沉积，还能

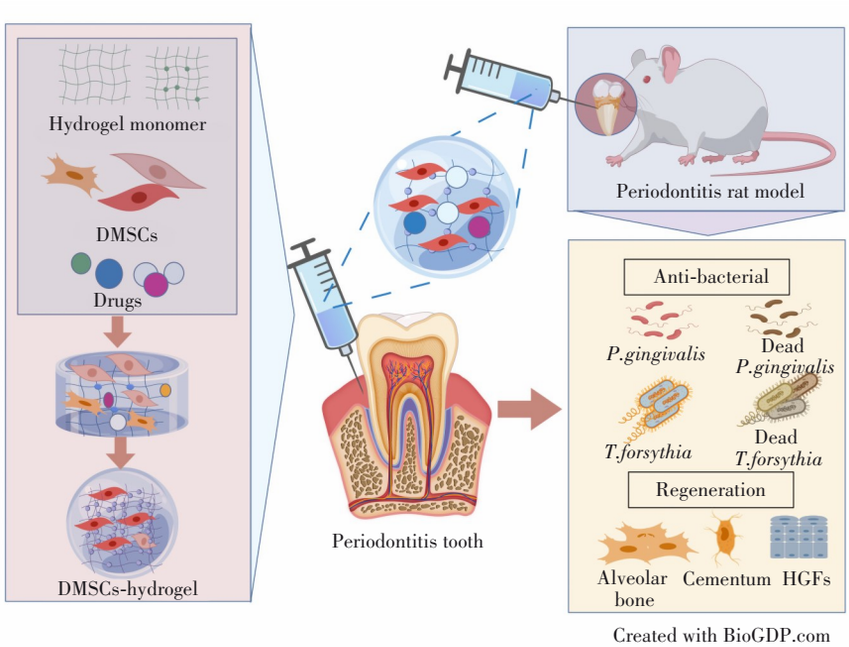
促进形成一种同时具备牙骨质和骨样组织特性的骨-牙骨质样复合矿化组织，实现了牙周韧带的锚定基础再生，这证明通过材料学手段可以突破牙骨质再生效率低下的瓶颈[82]。

4.3　牙周韧带功能重建

再生具有Sharpey's纤维结构和力学功能的牙周韧带最具挑战，策略倾向于使用各向异性或梯度水凝胶[83]。例如，利用静电纺丝或3D打印技术制备纤维定向排列的GelMA/壳聚糖复合水凝胶，其力学特性模拟天然韧带，能引导PDLSCs沿纤维方向排列生长，并高表达PLAP-1、胶原III等韧带特异性标志物[84-85]。在牙根面（硬）与牙槽骨侧（硬）之间的软性连接区，构建模量、化学成分或生长因子呈连续变化的梯度水凝胶，是模拟牙周膜-牙骨质/牙槽骨界面的前沿方向。这种梯度材料能引导细胞和细胞外基质在空间上的异质性分化与组装，促进异质性组织的整合[86]。

4.4　免疫微环境调控与协同再生

牙周炎背景下的再生，必须将破坏性的炎症微环境逆转为修复性微环境。载DMSCs的免疫调节型水凝胶在此展现出独特优势，实现了从“被动填充”到“主动免疫重塑”的跨越。例如，负载白细胞介素-1受体拮抗剂（interleukin-1 receptor antagonist，IL-1ra）可有效阻断白细胞介素1β（interleukin 1β，IL-1β）诱导的牙周膜成纤维细胞核因子-κB受体活化因子配体（receptor activator of nuclear factor-κB ligand，RANKL）表达及破骨细胞分化[87]，同时，GMSCs条件培养基可抑制脂多糖（lipopolysaccharide，LPS）诱导的含pyrin结构域NOD样受体家族3（NOD-like receptor family pyrin domain containing 3，NLRP3）炎症小体活化，将GMSCs负载于温敏壳聚糖/β-甘油磷酸钠水凝胶中，已被证明可在牙周炎大鼠模型中显著降低局部炎症因子水平，促进M2型巨噬细胞极化[88]。许多水凝胶材料本身具备免疫调节性，例如壳聚糖能抑制NLRP3炎症小体，透明质酸降解产物可促进巨噬细胞向M2型极化，当与GMSCs结合时，形成“材料源”与“细胞源”双重调节的协同效应[89]。



DMSCs: dental-derived mesenchymal stem cells; *P. Gingivalis*: *Porphyromonas gingivalis*; *T. forsythia*: *Tannerella forsythia*; HGFs: human gingival fibroblasts

Figure 2　Schematic diagram of the use of dental-derived mesenchymal stem cell hydrogel for promoting periodontal tissue repair

图2　载牙源性间充质干细胞水凝胶促进牙周组织修复示意图

5　挑战与展望

5.1　水凝胶性能的动态适配与智能响应

当前水凝胶的力学性能在植入后多为静态或单向降解，而牙周再生是一个动态过程，不同阶段需要不同的力学与生化信号支持。未来需开发性能可动态演变的“智能”水凝胶，例如初始具备一定硬度以支撑空间和启动成骨，随后梯度软化以利于韧带纤维重塑和血管神经长入。整合多重环境响应以实现药物/因子在时空上的按需释放[90]，是提升治疗效果的关键，未来的水凝胶设计将更强调“智能响应”，不仅限于pH，还可能整合酶、氧化还原等多种微环境信号[91]，将催化疗法（如纳米酶）、光热/光动力疗法[92]、药物递送等不同机制有机结合而非简单混合，能产生“1+1>2”的协同效

应,实现更精准的按需治疗。

5.2　复杂口腔微环境的应对

口腔是一个动态、潮湿、多菌的复杂环境,对水凝胶性能构成独特挑战。首先,频繁的咀嚼力、温度波动、pH变化及唾液冲刷,要求水凝胶具备优异的粘附性、自修复能力和环境稳定性[93],受盲鳗防御策略启发开发的水响应性粘附水凝胶,能在接触唾液后从流体转变为牢固粘附的凝胶,为在湿性、不规则组织表面实现稳定粘附提供了创新思路[94];其次,口腔致病菌生物膜是导致感染和修复失败的主因,多功能集成是应对关键,例如将抗菌(如4-松油醇)、抗氧化(如槲皮素)与促成骨功能整合于水凝胶,实现"抗菌-抗炎-再生"协同治疗[95];最后,组织缺损处的过度炎症反应会阻碍再生,先进的水凝胶设计不仅是被动承载细胞,更能主动调控局部免疫微环境。例如,负载阿司匹林的水凝胶可调节巨噬细胞表型,将促炎的M1型转化为促修复的M2型,从而变"不利"环境为"有利"环境[96]。

5.3　干细胞的定向分化效率

提高干细胞的定向分化效率仍是实现有效组织再生的关键[97]。尽管DMSCs具有多向分化潜能,但在实际应用中,如何精确控制其分化方向仍是一个技术难题[98]。目前,虽然已有多种方法用于调控干细胞的分化,如使用特定的生长因子、调整培养及生长条件等[99],但这些方法往往难以实现高效、精确的分化控制。因此,开发新的分化诱导策略,提高干细胞的定向分化效率,仍是未来研究的重要方向[100]。

5.4　临床应用的转化与个性化、功能化修复的未来趋势

评估将实验室研究成果转化为临床应用是另一大挑战,面对未来的临床应用,临床前应用效果的可重复性及安全性与功能的个性化定制是必然要求。严格的长期毒理学评价和免疫原性检测是临床前研究的必要环节,材料的长期留存(如用于骨再生)可能引发慢性炎症或异物反应,研究表明,具备优异生物相容性且降解产物无毒的水凝胶在植入小鼠体内24周后仍能保持结构完整且炎症反应轻微,为长期安全性提供了参考[101]。对于个性化与精准修复,基于患者缺损的影像学数据,利用CT扫描和3D生物打印技术定制个性化形状和孔隙结构的水凝胶,是实现精准修复的前沿方向,其核心挑战在于开发适合打印、同时保持细胞活性的"生物墨水"。未来水凝胶的目标不仅是填充缺损,更是恢复组织的完整功能,实现超越结构重建的功能性再生。

【Author contributions】 Li Q performed literature collection, wrote the article, and prepared the figures. Xia CP supervised the writing and revised the article. Zhang N revised the article and supervised the figure preparation. All authors read and approved the final manuscript as submitted.

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