

[DOI] 10.12016/j.issn.2096-1456.202550175

· 综述 ·

4D 打印技术在骨组织工程中的研究进展

王培煜, 石雅茹, 孙一帆, 徐晓薇

吉林大学口腔医院牙周科, 吉林 长春(130021)

【摘要】 骨缺损的修复依赖于动态的成骨微环境。传统3D打印构建的静态支架因结构固定、活性因子释放不可控及血管再生较难等问题无法模拟骨缺损修复过程中微环境变化规律,如何突破这种静态支架的局限性,实现对成骨微环境的智能、动态调控,是当前骨组织工程领域的关键科学问题。4D打印技术将骨修复材料的动态响应能力与智能设计理念相结合,通过响应内、外源性刺激,调控支架微观与宏观结构,并通过功能化设计,发挥药物递送、抗菌等功能,提供更优良的成骨微环境,为骨组织工程提供了新的方法。但是,该技术目前存在动态响应材料设计困难、打印技术精度不足、多刺激响应体系与骨组织代谢节律不匹配及复合支架功能化不足等问题。未来的研究应聚焦于开发具有优异动态响应能力及生物活性的智能响应材料、创造新型打印技术和设计个性化、精准化的骨修复方案等。本文旨在从材料种类、响应机制及应用三个方面综述骨组织工程4D打印的研究现状,为未来功能性骨修复材料的开发与临床转化提供理论依据。

【关键词】 4D打印; 骨缺损修复; 动态响应能力; 智能设计; 支架材料; 成骨微环境; 功能化设计; 个性化设计

【中图分类号】 R78 **【文献标志码】** A **【文章编号】** 2096-1456(2026)01-0075-11

【引用著录格式】 王培煜,石雅茹,孙一帆,等. 4D打印技术在骨组织工程中的研究进展[J]. 口腔疾病防治, 2026, 34(1): 75-85. doi:10.12016/j.issn.2096-1456.202550175.

Research progress on 4D printing technology for bone tissue engineering WANG Peiyu, SHI Yaru, SUN Yifan, XU Xiaowei. Department of Periodontics, Hospital of Stomatology, Jilin University, Changchun 130021, China
Corresponding author: XU Xiaowei, Email: xiaoweixu@jlu.edu.cn

【Abstract】 The repair of bone defects is heavily influenced by the dynamic osteogenic microenvironment. Static scaffolds constructed by traditional 3D printing technology cannot simulate the dynamic nature of the microenvironment during bone defect repair due to the fixed structure, uncontrollable release of active factors, and difficult regeneration of blood vessels, among other factors. Breaking through the limitations of these static scaffolds and realizing the intelligent and dynamic regulation of the osteogenic microenvironment is a key scientific issue in the field of bone tissue engineering. 4D printing technology combines the dynamic responsiveness of bone restoration materials with the concept of intelligent design to regulate the micro and macro structure of scaffolds. This technology provides a new method for bone tissue engineering by responding to endogenous and exogenous stimuli and creating a better osteogenic microenvironment through functionalized design, including drug delivery and antibacterial function. However, this technology currently suffers from challenges related to dynamic response material design, insufficient precision of printing technology, and mismatches between multi-stimulus response systems, metabolic rhythms of bone tissue, and functionalized composite scaffolds. Future research should focus on the development of smart response materials with excellent dynamic responses and bioactivity, the creation of new printing technologies, and the design of personalized and precise bone repair solutions. The aim of this paper is to review the current research status of 4D printing for bone tissue engineering in terms of material types, response mechanisms, and applications to provide a theoretical basis for the development



微信公众号

【收稿日期】 2025-04-24; **【修回日期】** 2025-07-07

【基金项目】 国家自然科学基金面上项目(82470957); 吉林大学研究生创新基金资助项目(2024CX254)

【作者简介】 王培煜,住院医师,硕士,Email: wangpeiyu0309@163.com

【通信作者】 徐晓薇,主任医师,博士,Email: xiaoweixu@jlu.edu.cn

and clinical application of functional bone repair materials in the future.

【Key words】 4D printing; bone defect repair; dynamic responsiveness; intelligent design; scaffold materials; osteogenic microenvironment; functional design; personalized design

J Prev Treat Stomatol Dis, 2026, 34(1): 75-85.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from National Natural Science Foundation of China (No. 82470957) and Graduate Innovation Fund of Jilin University (No. 2024CX254).

过去几十年间,3D打印技术被广泛应用于骨组织工程中促骨仿生支架的研究^[1]。然而,通过3D打印技术制作的支架植入体内后,在骨组织再生过程中可能存在生物力学不匹配、组织界面不密合以及细胞分布不均、难以实现血管化等问题^[2]。因此,为了弥补以上不足,4D打印技术在骨缺损修复中具有重要应用前景。4D打印技术于2014年由Skylar Tibbitts教授提出^[3],该技术在3D打印的基础上,将时间作为第四个维度,应用具有对外界刺激响应能力或形状能够发生改变的材料体系,结合智能设计理念及计算机辅助计算,赋予打印物体自组装、可编程和自适应等能力^[4]。与3D打印不同,4D打印物体改变了3D打印静态、逐层堆叠的特点,具有在受到外界因素刺激下实现形态、结构、功能变化的能力^[5]。因此,4D打印产物在修复骨组织缺损领域具有重要研究意义。4D打印产物能够适应复杂的生理环境,可通过对外界刺激响应发生形状变化,使得材料更加匹配骨缺损部位,并在骨骼生长及重塑过程中进行相应的形态调整,有利于长期的骨整合;此外,通过在植入物打印之前进行智能设计,可以有利于生物活性物质的控制释放及血管神经的生长,尤其适用于不规则及大块骨组织缺损的修复^[6]。此外,4D打印技术在未来可能会结合计算机技术、人工智能、模型构建等多领域先进技术,开发一种智能设计程序,该程序能够预测打印支架在人体内的变化及相互作用,选择最合适的骨修复材料及刺激因素,通过精准调控成骨微环境,精确地控制植入物形状、功能、细胞反应和促进新组织的形成^[7]。并通过赋予支架功能化的特点,发挥出减少材料在植入过程中的创伤、降低感染的风险、促进血管的生长等功能。因此,本文从4D打印材料、响应机制及应用三个方面进行综述,为未来骨组织工程材料的开发与研究提供理论基础。

1 4D打印材料

目前用于4D打印研究的材料主要包括形状记忆聚合物(shape memory polymers, SMPs)、压电材料、磁控材料、水凝胶材料以及合金材料等^[8]。这些材料在维持3D打印精度及分辨率的基础上^[9],将不同打印技术与其自身智能化特点相结合,能够在感受外界刺激下充分发挥动态响应能力,更加有利于骨组织缺损的修复^[10]。但是,单一的材料可能存在机械性能与天然骨组织的力学适配性不足、降解速率与骨代谢过程匹配性欠佳、生物活性不足导致的骨再生效率低下等难题,难以获得较为理想的修复效果^[11]。因此,在这类研究工作中,一般会以某种材料作为主体,通过将其与涂层、生物活性分子、纳米颗粒等其他物质结合构成复合材料,从而赋予主体材料更为优良的性能,发挥多重作用,获得更安全、快速的成骨效果。

1.1 形状记忆聚合物及其复合材料

SMPs是一类在一定条件下其形态能够发生改变的高分子聚合物,因具有精准的温度响应特性及可编程的形变恢复能力,在骨组织缺损修复领域拥有重要的研究价值,并在4D打印及定制化骨支架构建方面展现出独特优势^[12]。它通过熔融沉积、生物打印、冷冻成型等技术制备而成,在受到外界环境的刺激后,其形状或内部结构发生改变,这些改变在达到新的平衡或适应性状态后逐渐趋于稳定^[13]。目前用于骨组织缺损修复研究的SMPs主要有聚乳酸^[14]、聚己内酯^[15]、聚氨酯^[16]等,通过精准的计算与设计,赋予该类材料可控的形貌或微结构,在植入体内后发挥形状变换、药物递送等功能,最终促进新骨生成。然而,单一的SMPs可能存在降解速度慢、生物活性单一等问题^[17]。为解决这些问题,可以对支架结构进行功能化设计,将单一的SMPs与具有成骨特性的纳米粒子如羟基磷灰石^[18]、双相磷酸钙^[19],具有成骨作用的生物活性药物如阿仑膦酸钠^[20]等,以及在表面形成

涂层如胶原-地塞米松^[21]等多种技术相结合,发挥多重效应来促进骨组织的生成。

1.2 压电材料及其复合材料

压电材料是一类在压力作用下能够产生电信号的材料。目前,4D生物压电材料的研究主要集中在两个方面。一方面是将脆性较大的压电陶瓷与具有形状记忆功能的水凝胶或压电聚合物混合,获得能够实现形态改变及压电功能的双功能复合材料^[22];另一方面是在具有磁电效应材料的基础上,构建出具有压电效应的新型4D支架^[23]。研究表明,天然骨组织中的压电效应对骨组织生长调节、结构重塑具有重要作用^[24],而压电材料可以通过响应机械应力或超声刺激产生电信号,模拟天然骨的压电效应,通过离子或电荷之间的相互作用,促进细胞黏附,激活生长因子表达、提高细胞增殖和成骨分化^[25]。因此,压电材料在骨组织缺损的修复中具有重要的研究意义。目前应用于骨组织工程的压电材料主要包括压电陶瓷、压电聚合物及压电复合材料。压电陶瓷材料主要包括钛酸钡等,该类材料具有良好的机械性能,但脆性较大,在外力作用下有断裂的风险,因此,常将压电陶瓷与压电聚合物等结合形成压电复合材料,共同应用于骨组织缺损的修复当中。压电聚合物如聚乳酸(poly lactide, PLA)^[26]、聚偏二氟乙烯^[27]等,这些材料具有较好的机械性能,与天然骨组织相匹配。Camarero-Espinosa等^[28]制备了PLA与聚己内酯的共混支架,通过响应外界超声刺激产生机械纳米振动,激活电压门控Ca²⁺离子通道,增强骨髓间充质干细胞(bone mesenchymal stem cells, BMSCs)的增殖、促进骨基质合成和成骨分化。

1.3 水凝胶材料及其复合材料

水凝胶是一种亲水性的网络结构材料。由于链间交联的存在,水凝胶能够在液体环境下吸收较多的水分并在一段时间内保持结构稳定^[29],因其高含水特性与细胞外基质相似,有望实现机体组织在材料内原位成型,使其成为4D打印的理想材料^[30]。此外,另有水凝胶材料能够响应外界刺激,通过控制水凝胶内部的交联梯度,发挥动态细胞负载功能,形成类似天然骨组织排列的骨样组织^[31]。在近期的研究中,通过利用海藻酸钠高溶胀性和形状折叠效应的特点^[32],Lv等^[33]通过采用甲基丙烯酸缩水甘油酯修饰的海藻酸钠作为水凝胶成分,通过紫外光引发梯度交联,形成了上密下

疏的交联密度分布结构,使得下层水凝胶能够具有更大的弯曲率,在与Ca²⁺离子交联时发生弯曲,使得水凝胶更加匹配天然骨组织的形态。但是,单一的水凝胶成分存在机械性能不足、降解速率过快、生物活性差等缺点^[34]。为解决这些难题,学者们采用策略:将水凝胶与机械性能优良的SMPs相结合,通过水凝胶的动态效果与SMPs优良的机械性能实现效果互补^[35];或通过引入成骨活性肽^[36]、基因载体^[37]等方法,增强水凝胶的生物活性;或结合生物制造技术,构建仿生梯度结构,优化孔隙分布,有利于BMSCs黏附与增殖,还可以在水凝胶溶胀后内部产生多孔腔隙,为血管长入提供有利条件,最终加速新骨的生成。

1.4 磁性材料及其复合材料

磁性材料是一种利用外部磁场产生局部机械力或控制材料变形来发挥其功能的材料^[38]。磁性纳米颗粒(如Fe₃O₄)在外磁场作用下产生的局部磁机械力可直接作用于细胞膜表面机械敏感受体,激活下游成骨相关信号通路,促进成骨^[39]。此外,负载磁性纳米颗粒复合材料能够在外加磁场下,实现支架外形及孔隙率的动态调节以适配骨缺损形态并促进成骨分化,在4D打印中具有重要的应用价值。例如,Kuhnt等^[40]合成的各向异性Fe₃O₄纳米颗粒与聚乙二醇二丙烯酸酯水凝胶体系相结合,通过施加特定磁场,调节磁性纳米颗粒在水凝胶中的排列顺序,可实现水凝胶的定向移动,使其与组织贴合更加紧密。此外,磁性材料还能通过施加不同强度的磁场实现药物或生长因子时空特异性释放^[41]。因此,磁性材料通过外加磁场,产生局部机械力、促进成骨分化及靶向控释等多重机制,模拟骨骼微环境,激活成骨相关信号通路,在骨组织工程中极具潜力。

1.5 形状记忆合金材料

形状记忆合金是一种受到机械应力或温度变化时形貌发生变化后,能够恢复初始形状的一种材料,具有良好的记忆功能、生物相容性及耐腐蚀性,在生物打印领域具有重要研究意义^[42]。镍钛(nickel-titanium, NiTi)合金是一种具有良好形状记忆功能、生物相容性、机械性能的智能生物材料,其形貌会随着温度的变化产生相应改变^[43]。它的形状记忆能力使其能够应用于4D打印当中。近年来,随着选区激光熔化(selective laser melting, SLM)技术的发展,NiTi合金的成型技术有了突破性进展。在近期研究中,经SLM技术设计患者特

异性 NiTi 合金网状支架,通过压缩变形,其体积能够降低 30%,将该网状支架植入骨缺损区后,能够响应温度的变化,在体温下使得支架恢复形状并贴合于骨缺损腔隙,这种智能形变不仅为骨组织提供了一定的支撑能力,而且对周围骨组织产生力学刺激,显著促进了骨整合及新骨的生成^[44]。

综上, SMPs 具有形状自适应、可编程性等优点,在修复骨缺损中常常扮演支架基材的角色,但其也存在降解速度慢、生物活性低等缺点;压电材料通过释电信号促进骨组织再生,但是其存在脆性大、电信号不稳定等缺点;水凝胶材料可通过细胞负载、模拟成骨微环境,可作为细胞及生长因

子的载体,在骨组织工程中应用广泛应用,但其存在机械性能不足、降解速度难以与成骨速度相匹配等缺点;磁性材料的远程磁控及动态调节能力使其在骨组织工程中可以发挥精准药物释放及力学刺激功能,但也受到磁场穿透性不足及磁性材料生物相容性欠佳的制约;形状记忆合金具有高强度、形状记忆及良好的承重能力,在大段骨缺损中具有优良的应用前景,但其常受到加工、设计复杂等问题的制约。因此,4D 打印材料在骨组织工程中需根据缺损类型选择合适材料体系,并通过多材料复合策略实现功能互补,获得最大化的成骨效果(图1)。

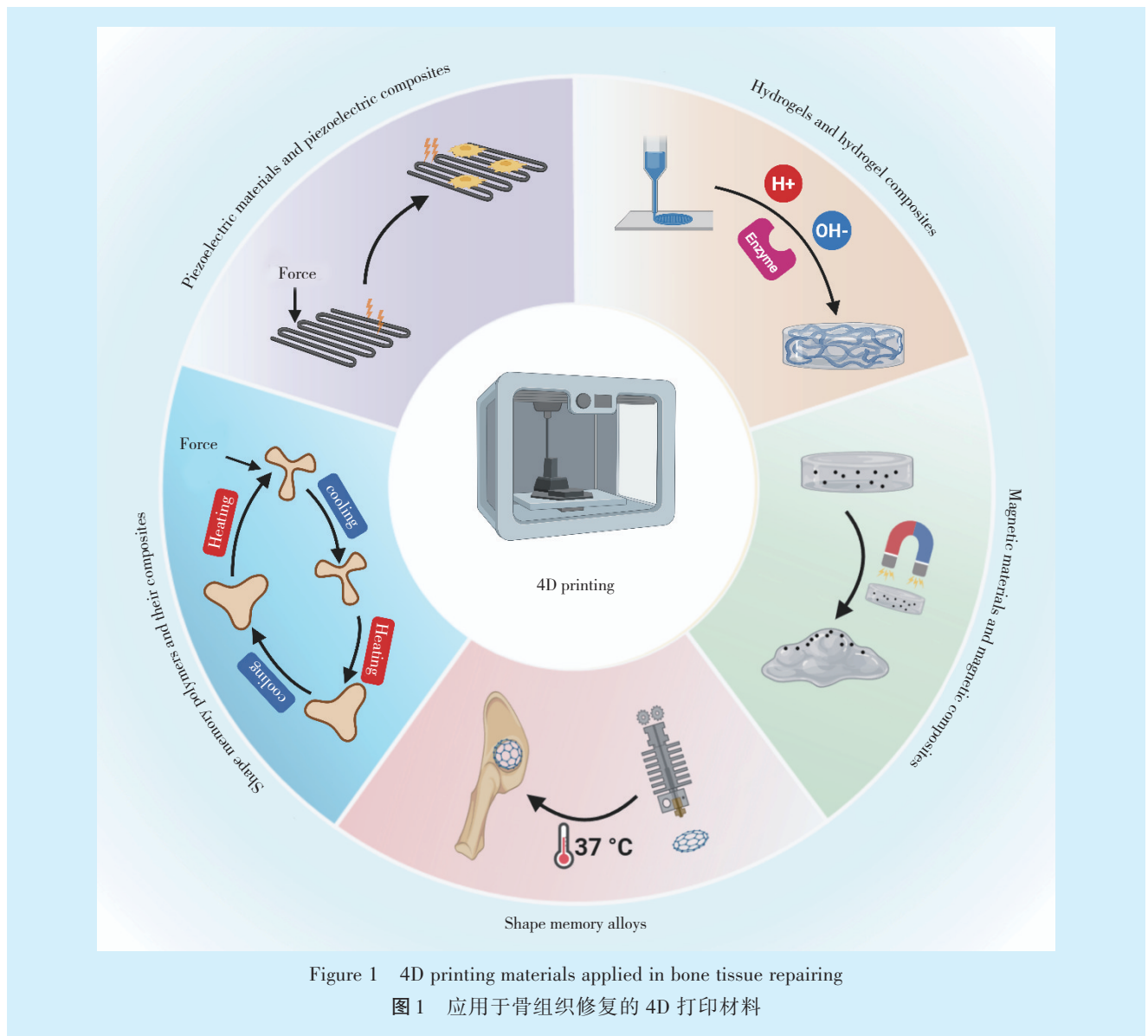


Figure 1 4D printing materials applied in bone tissue repairing

图1 应用于骨组织修复的 4D 打印材料

2 4D打印材料对不同刺激的响应机制

随着4D打印技术的不断进步与材料创新,动态响应性材料的研究取得显著进展,这些材料能

够响应温度、湿度、光、磁场等外源性刺激以及酶、pH值等内源性刺激,产生形状及内部结构的变换,发挥促进组织修复与再生的功能^[45](图2)。

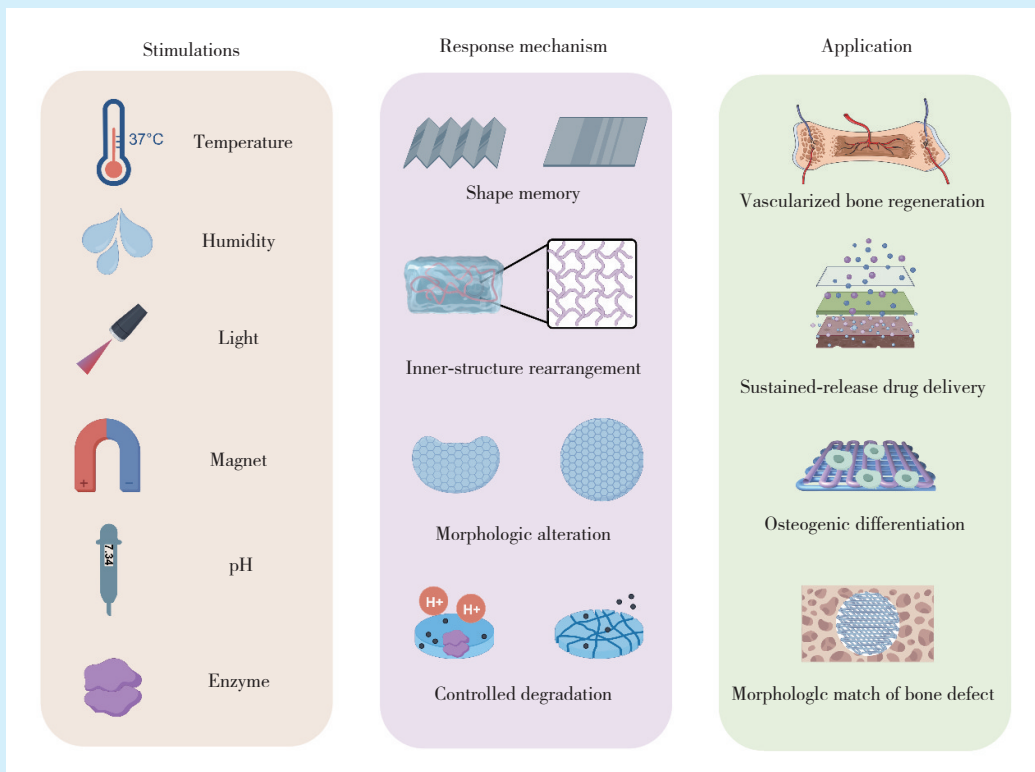


Figure 2 The stimulations, response mechanism and application of 4D printing materials

图2 4D打印材料的刺激因素、响应机制及应用

2.1 外源性刺激

2.1.1 温度 温度作为能够调控形态的物理刺激,在4D打印修复骨组织缺损领域有着重要研究价值^[46]。温度响应性材料在骨缺损修复研究中广泛应用。温度敏感性 SMPs 具有玻璃化转变温度 (glass transition temperature, T_g),当温度超过 T_g 时,材料为软化状态,在施加一定压力后,其形状发生改变,而当温度降至 T_g 之下,材料发生硬化,并最终定型,使其与骨缺损形状更加匹配^[47]。此外,一些温度响应性水凝胶具有较低临界溶液温度 (lower critical solution temperature, LCST),当温度低于 LCST 时,材料处于溶液状态,而当温度高于 LCST 时,其形态或内部结构会发生变化^[48],因此,设计并开发具有低于人体温度的 LCST 的水凝胶具有重要意义。利用这种特性,Hao 等^[49]通过在钛基植入物表面附着一层 LCST 约为 32°C 的聚 (N-异丙基丙烯酰胺) 水凝胶,当该水凝胶处于室温时,其表面丰富的水化层能够阻止细菌黏附;并通

过体外及体内实验证明,当在 37°C 时,植入物表面水凝胶结构改变,表面水化层消失,在表面产生多孔结构有利于骨细胞的黏附,促进骨整合。因此,温度响应性材料可利用热力学相变精准适配骨缺损形态,又能通过温度介导微结构转变调控细胞行为,在骨组织工程领域展现出广阔的应用前景。

2.1.2 湿度 高湿度的人体生理环境为湿度响应性材料的应用创造了理想条件^[50]。其中,湿度响应性水凝胶因其独特的溶胀-收缩特性而成为骨缺损修复领域的研究热点。当水凝胶材料植入体内后,发生溶胀或收缩过程,因此,通过改变具有不同溶胀特性水凝胶的空间分布,在高湿度环境下,依据不同成分的溶胀特点,能够精确调控其形态结构的变化^[51]。此外,为了使水凝胶材料更能符合天然骨组织梯度化结构特性,学者们将不同性质的水凝胶组合在一起,精准调控材料密度与组分比例,实现了时序性骨再生调控:在早期发挥促进 BMSCs 的黏附及增殖作用;在中期通过水凝胶

材料孔隙变化,释放促成骨生物小分子并促进血管长入,为新生骨组织提供优良的生长环境;在后期通过降解较慢的水凝胶形貌发生变化,使得新生骨的形貌更接近于人体正常骨组织结构,从而通过多重作用促进骨组织的恢复^[33]。

2.1.3 光 光响应材料通过捕捉外界光刺激实现光信号—机械响应转换,其作用机制包括通过紫外光(ultraviolet, UV)照射产生光化学驱动^[52]及近红外光(near-infrared light, NIR)照射产生光热驱动^[53]后介导的形态重构或内部结构变化,在4D打印及药物递送系统研究中有广泛的应用。通过UV照射,材料内部的光化学活性基团或分子,通过加成、异构及塑化作用,驱动材料产生宏观变化^[54]。根据这种特性,Zhang等^[55]在材料中引入光交联剂,在打印过程中进行UV照射,赋予SMPs形变记忆能力及自修复特性。NIR响应体系则通过在热响应SMPs中添加光热纳米颗粒,通过NIR照射将光能转变为热能,使局部温度超过T_g,缓慢驱动植入物的形态变化^[56]。NIR驱动的新型复合支架能通过4D打印技术智能调控支架的多孔结构,具有深部组织穿透性与时空精准操控性,并能够发挥局部的抗菌作用^[57]。此外,某些光响应水凝胶在接收光信号后发生分解,实现对材料降解速率及降解位置的精准调控,控释水凝胶内所含成骨相关活性分子,调控骨髓间充质干细胞的成骨分化,促进新骨生成^[58]。

2.1.4 磁 磁响应材料主要含有铁、镍、锰等元素,能够在外加磁场作用下产生特定的运动方向或通过磁滞损耗产生热能,驱动水凝胶材料或SMPs产生形貌或结构变化,在骨组织缺损修复中具有重要的研究价值^[59]。通过施加特定磁场,控制磁响应复合材料的运动方向或使材料形态发生改变,驱动细胞实现有序的空间排列^[60],并对细胞产生一定的机械刺激,最终促进组织的生长^[61]。

2.2 内源性刺激

2.2.1 酶 酶作为生物催化剂,在人体生化反应中发挥重要催化功能。酶响应性材料的设计与合成已成为骨缺损修复领域的重要研究方向,其作用机制源于机体内源性酶对材料的精准调控^[62]。酶响应性材料可以利用肽链的 β -折叠及不同肽链之间的复杂相互作用,在特定酶的作用下,产生不同的微观结构或进行重新组装^[63],也可将形状记忆材料进行修饰,使其能够响应特定的内源性酶,在药物递送系统的开发中具有重要研究价值^[64]。基

质金属蛋白酶(matrix metalloproteinases, MMPs)作为细胞外基质重塑的关键调节因子,已被成功应用于构建智能水凝胶。学者们将MMPs可裂解肽整合到聚乙二醇网络中,并将抗炎药物封装其中,构建了一种MMPs响应性可注射水凝胶,该水凝胶可被MMPs触发,在局部组织产生炎症反应时持续释放抗炎药物,并持续到骨修复时期^[65]。因此,酶响应性水凝胶因其快速交联、降解速率适当以及优良的生物安全性等特点,在组织工程中具有重要的应用价值^[66]。

2.2.2 pH值 成骨微环境中pH动态平衡是生物材料发挥骨再生功能的关键因素,通过影响成骨细胞的增殖、分化,骨基质的分泌及矿化等多种维度调控骨再生进程^[67]。因此,pH响应性材料被应用于骨缺损修复研究中,这些材料通常含有羧基、氨基等化学基团,能够根据pH的变化接受或释放质子,产生结构变化或进行自组装行为^[68]。Zha等^[69]开发了一种新型纳米结构水凝胶,在响应pH值变化后释放锌离子、镓离子和腐植酸,发挥抗菌、抗氧化及促进血管生成、骨生成与神经生成的协同作用,从而加速感染性骨折的愈合。pH响应性材料在药物递送中也发挥着重要作用。聚合物、胶束或脂质体等通过特定化学功能,响应pH值变化,通过产生线性、支化结构或聚合、去聚合作用,广泛应用于药物递送^[70]。因此,pH响应性材料将可调节的形貌及功能化的特点与递送、释放具有成骨功能的生物活性分子的功能相结合,为4D生物打印提供了新的可能。

通过合理设计材料体系及结构,可通过多刺激响应的协同作用,实现骨缺损修复的精准动态调控。Li等^[71]等构建了光-磁双响应的复合支架,通过NIR照射,使得复合支架能够实现形状记忆恢复,并施加静态磁场,使得支架与骨缺损边界更加匹配,并通过体外实验证明该复合支架显著提高了成骨细胞的成骨及矿化能力。此外,Xiu等^[72]构建了一种具有pH响应及光响应的复合水凝胶。在酸性条件下,该复合材料表现出较强的氧化酶和过氧化物酶活性,抑制细菌的增长;在中性条件下,其过氧化氢酶活性增强,有助于减轻局部炎症反应。此外,该材料在近红外光照射下具有良好的光热效应,有利于促进成骨和血管生成。但是,在进行多响应性材料设计时,也要注意不同刺激之间的相互影响。例如酶响应性材料可能会在UV及NIR的照射下失去响应能力以及高湿度环境

下可能会延缓温度响应材料的形变速度等。因此,多刺激响应材料在骨缺损修复中展现出巨大潜力,但需平衡不同刺激间的相互影响,才能精准调控骨组织缺损的修复。

3 4D打印技术在骨组织工程中的应用

3.1 血管化骨再生

近年来,4D打印技术的发展为植入式支架促骨再生提供了新的可能性。利用该技术制作的支架能适应不同形状的骨缺损以及复杂的生理环境,更精确地模拟了天然骨组织的动态变化^[73]。骨骼系统中的血管网络系统对骨骼的形成及修复具有重要作用,能够调节骨细胞的代谢活动及增殖、分化状态^[74]。因此,构建血管系统对于骨组织再生具有重要意义。在血管化骨组织工程中,微血管网络的快速建立是成功的关键。Kirillova等^[75]利用4D打印技术,将小鼠BMSCs与甲基丙烯酸海藻酸盐和透明质酸杂化水凝胶相结合,制备的材料能够动态响应有水微环境,发生自折叠后形成与微小血管相似的中空管腔结构,该结构使得水凝胶中的细胞存活时间超过1周,并能保持细胞活力。Liu等^[76]开发了一种双层仿生骨膜,该双层膜由外层的可编程甲基丙烯酸化水凝胶和内层的人间充质干细胞(human mesenchymal stem cells, hMSCs)细胞片组成。通过4D打印技术,将与骨缺损形状相匹配的智能水凝胶与通过光诱导各向异性细胞片技术构建的hMSCs细胞片相结合,使其具有与天然骨膜相似的定向微结构,并通过体外实验验证了hMSCs细胞片的定向微结构能够促进细胞的迁移和血管生成,并促进hMSCs成骨分化。因此,微小血管的构建及定向技术为4D打印血管化骨组织的制造提供了新的方向。

3.2 药物递送系统

药物递送系统(drug delivery systems, DDS)可实现局部、靶向和连续的药物递送效果,可降低全身毒性^[77],实现精准治疗^[78]。通过4D打印技术将智能材料与动态结构设计相结合,Wu等^[79]研制了一种将光响应与药物递送机制相结合的水凝胶。该水凝胶中掺入光热纳米颗粒,响应NIR刺激,有助于控制部位特异性药物释放,从而提高药物递送精度及功效。因此,通过4D打印技术,使得药物载体能够响应不同的刺激或在体内发生相应的形态转变,从而实现药物的精准递送及可控释放,在修复骨缺损,治疗骨感染性疾病、骨肿瘤等疾病

中能够发挥重要作用。

3.3 促进干细胞成骨分化

近年来,干细胞在骨组织工程中的应用存在多种创新方式:自体源性间充质干细胞(MSCs)既可作为生物墨水直接参与生物打印^[80],也可接种于智能响应型材料实现动态细胞调控^[81],为个性化骨再生提供更多的可能性^[82]。基底微结构的动态调控是组织工程中控制干细胞命运的有效策略。因此,You等^[35]制备了由SMPs层和水凝胶层组成的多重响应型双层变形膜。SMPs层具有可变换的微观结构,可以根据外部加热刺激改变表面形态,从而提供不同的力学信号,可变换的微观结构通过激活Yes相关蛋白信号通路和改变核膜上的核纤层蛋白A/C表达来促进成骨分化。水凝胶层在水中膨胀并形成预定的3D形状,从而与复杂的骨缺损形状相匹配。两层结构发挥双重作用,共同促进新生骨的形成。此外,4D打印建立的仿生骨微环境也会影响BMSCs行为,增强干细胞的分化,加速骨组织的形成^[83]。

3.4 促进软骨修复

软骨再生也是骨组织工程中的重要研究领域^[84]。与骨组织不同,软骨缺乏血管网络和具有再生能力的干细胞,且软骨细胞数量有限,因此软骨在受到破坏后常难进行自我修复^[85]。多项研究报道了4D打印技术在动态软骨组织构建中的应用,这些研究主要集中在通过4D打印技术制造具有自弯曲能力的细胞负载支架,可以提高支架与具有弯曲和多层结构的天然软骨之间的整合,从而改善软骨再生^[86]。此外,通过与其他响应机制结合,4D打印技术在软骨再生的应用中展现出了更大的潜力和可行性。Zhang等^[87]通过将软骨细胞与磁性纳米颗粒水凝胶复合物混合形成生物墨水并通过4D打印技术制备出耳轮廓外形支架,通过施加外部磁场,调控软骨细胞增殖和细胞外基质分泌,最终获得在外观、组织学特征和机械性能等方面与天然软骨高度相似的支架结构。

4 总结与展望

在骨组织工程中,4D打印技术通过把具有优良性能的生物材料与多重响应机制结合,在血管化骨再生、药物递送系统、干细胞增殖及分化以及软骨再生领域取得了丰富的研究成果,为解决加速骨再生等重要难题提供了解决思路。但是,目前4D打印技术在实际应用中仍然存在可用材料较

单一、设计复杂、精确度不足等技术瓶颈,同时该技术目前也只存在于研究及理论阶段,并未向临床进行转化。

在未来,随着计算机科学、材料科学、软件工程及加工技术的发展,4D打印技术有望通过计算机辅助设计及软件开发,综合分析动态响应材料与细胞、组织之间的相互作用,智能选择最合适的修复材料及打印参数,并设计具有时空响应特点的可变换结构。此外,在未来还有望设计可逆化的新型修复材料,通过智能设计可逆化程序,实时监控植入物在人体内的变化,使其在体内能够最大限度促进骨整合。因此,4D打印技术在骨组织工程中的应用前景将更加广阔,其在治疗复杂骨缺损和大块骨缺损等难题方面具有巨大的临床潜力,这无疑将为患者带来新的希望。

【Author contributions】 Wang PY reviewed the references, wrote and revised the article. Shi YR, Sun YF and Xu XW revised the article. All authors read and approved the final manuscript as submitted.

参考文献

- [1] Zhu Y, Li Y, Yang Y, et al. Mechanical stimulus and metabolic responses by cryo-printing anisotropic scaffolds for achieving promoted bone regeneration[J]. *Adv Funct Mater*, 2025, 35(10): 2416546. doi: 10.1002/adfm.202416546.
- [2] Dalfino S, Savadori P, Piazzoni M, et al. Regeneration of critical-sized mandibular defects using 3D-printed composite scaffolds: a quantitative evaluation of new bone formation in *in vivo* studies[J]. *Adv Healthc Mater*, 2023, 12(21): e2300128. doi: 10.1002/adhm.202300128.
- [3] Tibbitts S. 4D printing: multi-material shape change[J]. *Archit Des*, 2014, 84(1): 116-121. doi: 10.1002/ad.1710.
- [4] Sun X, Yue L, Yu L, et al. Machine learning-evolutionary algorithm enabled design for 4D-printed active composite structures [J]. *Adv Funct Mater*, 2022, 32(10): 2109805. doi: 10.1002/adfm.202109805.
- [5] Li H, Zhang B, Ye H, et al. Reconfigurable 4D printing *via* mechanically robust covalent adaptable network shape memory polymer[J]. *Sci Adv*, 2024, 10(20): ead14387. doi: 10.1126/sciadv.adl4387.
- [6] Chen X, Han S, Wu W, et al. Harnessing 4D printing bioscaffolds for advanced orthopedics[J]. *Small*, 2022, 18(36): e2106824. doi: 10.1002/sml.202106824.
- [7] Yarali E, Mirzaali MJ, Ghalayanesfahani A, et al. 4D printing for biomedical applications[J]. *Adv Mater*, 2024, 36(31): 2402301. doi: 10.1002/adma.202402301.
- [8] Mahmood A, Akram T, Chen SG, et al. Revolutionizing manufacturing: a review of 4D printing materials, stimuli, and cutting-edge applications[J]. *Compos Part B Eng*, 2023, 266: 110952. doi: 10.1016/j.compositesb.2023.110952.
- [9] Peng W, Xia H, Wu J, et al. Dynamic boronate ester chemistry facilitating 3D printing interlayer adhesion and modular 4D printing of polylactic acid[J]. *Adv Funct Mater*, 2025, 35(25): 2503682. doi: 10.1002/adfm.202503682.
- [10] Wang J, Zhou J, Xie Z, et al. Multifunctional 4D printed shape memory composite scaffolds with photothermal and magnetothermal effects for multimodal tumor therapy and bone repair[J]. *Biofabrication*, 2025, 17(2): 025032. doi: 10.1088/1758-5090/adc29e.
- [11] Wang J, Zhou D, Wang G, et al. Enhanced bone regeneration with bioprinted GelMA/Bentonite scaffolds inspired by bone matrix[J]. *Virtual Phys Prototyp*, 2024, 19(1): e2345765. doi: 10.1080/17452759.2024.2345765.
- [12] Yang F, He H, Jia J, et al. Composition and layered co-continuous structure co-regulate shape memory properties[J]. *Int J Mech Sci*, 2025, 291: 110187. doi: 10.1016/j.ijmecsci.2025.110187.
- [13] Cooper CB, Nikzad S, Yan H, et al. High energy density shape memory polymers using strain-induced supramolecular nanostructures[J]. *ACS Cent Sci*, 2021, 7(10): 1657-1667. doi: 10.1021/acscentsci.1c00829.
- [14] Zhao W, Huang Z, Liu L, et al. Porous bone tissue scaffold concept based on shape memory PLA/Fe₃O₄[J]. *Compos Sci Technol*, 2021, 203: 108563. doi: 10.1016/j.compscitech.2020.108563.
- [15] Du R, Zhao B, Luo K, et al. Shape memory polyester scaffold promotes bone defect repair through enhanced osteogenic ability and mechanical stability[J]. *ACS Appl Mater Interfaces*, 2023, 15(36): 42930-42941. doi: 10.1021/acscami.3c06902.
- [16] Wang J, Lin X, Wang R, et al. Self-healing, photothermal-responsive, and shape memory polyurethanes for enhanced mechanical properties of 3D/4D printed objects[J]. *Adv Funct Mater*, 2023, 33(15): 2211579. doi: 10.1002/adfm.202211579.
- [17] Bond G, Mahjoubnia A, Zhao W, et al. 4D printing of biocompatible, hierarchically porous shape memory polymeric structures[J]. *Biomater Adv*, 2023, 153: 213575. doi: 10.1016/j.bioadv.2023.213575.
- [18] Wang L, Zeng X, Chen X, et al. Programmable, biodegradable composite scaffolds with variable pore morphology for minimal invasive bone repair[J]. *Compos Part A Appl Sci Manuf*, 2022, 162: 107130. doi: 10.1016/j.compositesa.2022.107130.
- [19] Feng C, Wu Y, Li Q, et al. A novel hollow-tube-biphasic-whisker-modified calcium phosphate ceramics with simultaneously enhanced mechanical strength and osteogenic activity[J]. *Adv Funct Mater*, 2022, 32(44): 2204974. doi: 10.1002/adfm.202204974.
- [20] Zhao Y, Li Y, Wang B, et al. An injectable magnesium-based cement stimulated with NIR for drug-controlled release and osteogenic potential[J]. *Adv Healthc Mater*, 2024, 13(19): e2400207. doi: 10.1002/adhm.202400207.
- [21] Zhou W, Dong X, He Y, et al. *In-vitro* and *in-vivo* studies of 4D printed shape memory scaffolds with bioactive fillers and coating for enhanced bone tissue regeneration[J]. *Smart Mater Struct*, 2022, 31(10): 105002. doi: 10.1088/1361-665X/ac884a.
- [22] Zheng T, Yu Y, Pang Y, et al. Improving bone regeneration with composites consisting of piezoelectric poly(l-lactide) and piezoelectric calcium/manganese co-doped barium titanate nanofibers

- [J]. Compos Part B Eng, 2022, 234: 109734. doi: 10.1016/j.compositesb.2022.109734.
- [23] Shi Y, Wang K, Feng X, et al. Additive manufactured self-powered mechanoelectric sensor as the artificial nucleus pulposus for monitoring tissue rehabilitation after discectomy[J]. Nano Energy, 2022, 96: 107113. doi: 10.1016/j.nanoen.2022.107113.
- [24] Li B, Ma Y, Fatima K, et al. 3D printed shape-memory piezoelectric scaffolds with *in situ* self-power properties for bone defect repair[J]. J Nanobiotechnology, 2025, 23(1): 244. doi: 10.1186/s12951-025-03325-x.
- [25] Wu H, Dong H, Tang Z, et al. Electrical stimulation of piezoelectric BaTiO₃ coated Ti₆Al₄V scaffolds promotes anti-inflammatory polarization of macrophages and bone repair *via* MAPK/JNK inhibition and OXPHOS activation[J]. Biomaterials, 2023, 293: 121990. doi: 10.1016/j.biomaterials.2022.121990.
- [26] Xu Y, Xu C, Song H, et al. Biomimetic bone-periosteum scaffold for spatiotemporal regulated innervated bone regeneration and therapy of osteosarcoma[J]. J Nanobiotechnology, 2024, 22(1): 250. doi: 10.1186/s12951-024-02430-7.
- [27] Chen J, Song L, Qi F, et al. Enhanced bone regeneration *via* ZIF-8 decorated hierarchical polyvinylidene fluoride piezoelectric foam nanogenerator: coupling of bioelectricity, angiogenesis, and osteogenesis[J]. Nano Energy, 2023, 106: 108076. doi: 10.1016/j.nanoen.2022.108076.
- [28] Camarero-Espinosa S, Moroni L. Janus 3D printed dynamic scaffolds for nanovibration-driven bone regeneration[J]. Nat Commun, 2021, 12(1): 1031. doi: 10.1038/s41467-021-21325-x.
- [29] Chuang EY, Lin YC, Huang YM, et al. Biofunctionalized hydrogel composed of genipin-crosslinked gelatin/hyaluronic acid incorporated with lyophilized platelet-rich fibrin for segmental bone defect repair[J]. Carbohydr Polym, 2024, 339: 122174. doi: 10.1016/j.carbpol.2024.122174.
- [30] Wang M, Liu Z, Furukawa H, et al. Fast reverse design of 4D-printed voxelized composite structures using deep learning and evolutionary algorithm[J]. Adv Sci(Weinh), 2025, 12(12): e2407825. doi: 10.1002/advs.202407825.
- [31] Zhou S, Xiao C, Fan L, et al. Injectable ultrasound-powered bone-adhesive nanocomposite hydrogel for electrically accelerated irregular bone defect healing[J]. J Nanobiotechnology, 2024, 22(1): 54. doi: 10.1186/s12951-024-02320-y.
- [32] Ding A, Lee SJ, Ayyagari S, et al. 4D biofabrication *via* instantly generated graded hydrogel scaffolds[J]. Bioact Mater, 2022, 7: 324-332. doi: 10.1016/j.bioactmat.2021.05.021.
- [33] Lv S, Lian X, Feng H, et al. Three-step crosslinking dependent self-bending transformation of a nano-spherical mineralized collagen laden 4D printed sodium alginate scaffold for bone regeneration[J]. Carbohydr Polym, 2025, 355: 123422. doi: 10.1016/j.carbpol.2025.123422.
- [34] Liu Z, Xin W, Ji J, et al. 3D-printed hydrogels in orthopedics: developments, limitations, and perspectives[J]. Front Bioeng Biotechnol, 2022, 10: 845342. doi: 10.3389/fbioe.2022.845342.
- [35] You D, Chen G, Liu C, et al. 4D printing of multi-responsive membrane for accelerated *in vivo* bone healing *via* remote regulation of stem cell fate[J]. Adv Funct Mater, 2021, 31(40): 2103920. doi: 10.1002/adfm.202103920.
- [36] Zhang F, Lv M, Wang S, et al. Ultrasound-triggered biomimetic ultrashort peptide nanofiber hydrogels promote bone regeneration by modulating macrophage and the osteogenic immune microenvironment[J]. Bioact Mater, 2024, 31: 231-246. doi: 10.1016/j.bioactmat.2023.08.008.
- [37] He S, Fang J, Zhong C, et al. Spatiotemporal delivery of pBMP2 and pVEGF by a core-sheath structured fiber-hydrogel gene-activated matrix loaded with peptide-modified nanoparticles for critical-sized bone defect repair[J]. Adv Healthc Mater, 2022, 11(21): e2201096. doi: 10.1002/adhm.202201096.
- [38] Mayorga-Martinez CC, Zelenka J, Klima K, et al. Multimodal-driven magnetic microrobots with enhanced bactericidal activity for biofilm eradication and removal from titanium mesh[J]. Adv Mater, 2023, 35(23): e2300191. doi: 10.1002/adma.202300191.
- [39] Del Bianco L, Spizzo F, Yang Y, et al. Silk fibroin films with embedded magnetic nanoparticles: evaluation of the magnetomechanical stimulation effect on osteogenic differentiation of stem cells[J]. Nanoscale, 2022, 14(39): 14558-14574. doi: 10.1039/d2nr03167a.
- [40] Kuhnt T, Camarero-Espinosa S, Takhsha Ghahfarokhi M, et al. 4D printed shape morphing biocompatible materials based on anisotropic ferromagnetic nanoparticles[J]. Adv Funct Mater, 2022, 32(50): 2202539. doi: 10.1002/adfm.202202539.
- [41] Viteri A, Espanol M, Ginebra MP, et al. Tailoring drug release from skin-like chitosan-agarose biopolymer hydrogels containing Fe₃O₄ nanoparticles using magnetic fields[J]. Chem Eng J, 2025, 517: 164214. doi: 10.1016/j.cej.2025.164214.
- [42] Wu G, Bian P, Xu R, et al. Electro-thermal responses polymer systems with continuous shape memory alloys: merging rapid shape memory and color transitions[J]. Chem Eng J, 2025, 503: 158264. doi: 10.1016/j.cej.2024.158264.
- [43] Zhang Y, Wei D, Chen Y, et al. Non-negligible role of gradient porous structure in superelasticity deterioration and improvement of NiTi shape memory alloys[J]. J Mater Sci Technol, 2024, 186: 48-63. doi: 10.1016/j.jmst.2023.10.053.
- [44] Li Z, Lu M, Lei H, et al. Selective laser melting fabrication of body-temperature shape memory NiTi alloy for 4D-printed orthopedic implants[J]. Virtual Phys Prototyp, 2024, 19(1): e2413181. doi: 10.1080/17452759.2024.2413181.
- [45] Abolhassani S, Fattahi R, Safshekan F, et al. Advances in 4D bio-printing: the next frontier in regenerative medicine and tissue engineering applications[J]. Adv Healthc Mater, 2025, 14(4): e2403065. doi: 10.1002/adhm.202403065.
- [46] Ghosal K, Rashed N, Khamaisi B, et al. Precision 4D printing of multifunctional olive oil-based acrylate photo-resin for biomedical applications[J]. Adv Funct Mater, 2025, 35(13): 2414129. doi: 10.1002/adfm.202414129.
- [47] Jurinovs M, Veseta M, Sabalina A, et al. Sustainable 4D printable biobased shape memory polymers with linear tunability and multi-stimuli actuation for advanced applications[J]. Small Sci, 2025, 5(7): 2500104. doi: 10.1002/smssc.202500104.

- [48] Brissenden AJ, Amsden BG. *In situ* forming macroporous biohybrid hydrogel for nucleus pulposus cell delivery[J]. *Acta Biomater*, 2023, 170: 169-184. doi: 10.1016/j.actbio.2023.08.029.
- [49] Hao X, Zhou J, Xie J, et al. Porous thermosensitive coating with water-locking ability for enhanced osteogenic and antibacterial abilities[J]. *Mater Today Bio*, 2022, 14: 100285. doi: 10.1016/j.mtbio.2022.100285.
- [50] Bai Z, Wang X, Zheng M, et al. Mechanically robust and transparent organohydrogel-based E-skin nanoengineered from natural skin [J]. *Adv Funct Mater*, 2023, 33(15): 2212856. doi: 10.1002/adfm.202212856.
- [51] Liu X, Gao M, Chen J, et al. Recent advances in stimuli-responsive shape-morphing hydrogels[J]. *Adv Funct Mater*, 2022, 32(39): 2203323. doi: 10.1002/adfm.202203323.
- [52] Zhang J, Yin YJ, Wang XW, et al. Adhesive polyelectrolyte coating through UV-triggered polymerization on PLGA particles for enhanced drug delivery to inflammatory intestinal mucosa[J]. *J Nanobiotechnology*, 2025, 23(1): 32. doi: 10.1186/s12951-024-03066-3.
- [53] Pongkulapa T, Yum JH, McLoughlin CD, et al. NIR-induced photoswitching hybrid DNA nanoconstruct-based drug delivery system for spatiotemporal control of stem cell fate[J]. *Small*, 2025, 21(26): e2409530. doi: 10.1002/sml.202409530.
- [54] Chen M, Hou Y, An R, et al. 4D printing of reprogrammable liquid crystal elastomers with synergistic photochromism and photoactuation[J]. *Adv Mater*, 2024, 36(34): e2303969. doi: 10.1002/adma.202303969.
- [55] Zhang B, Li H, Cheng J, et al. Mechanically robust and UV-curable shape-memory polymers for digital light processing based 4D printing[J]. *Adv Mater*, 2021, 33(27): e2101298. doi: 10.1002/adma.202101298.
- [56] Guo S, Agarwal T, Song S, et al. Development of novel multi-responsive 4D printed smart nanocomposites with polypyrrole coated iron oxides for remote and adaptive transformation[J]. *Mater Horiz*, 2025, 12(11): 3907-3917. doi: 10.1039/d4mh01804d.
- [57] Guo W, Zhou B, Zou Y, et al. 4D printed poly(l-lactide)/(FeCl₃ - TA/MgO) composite scaffolds with near-infrared light-induced shape-memory effect and antibacterial properties[J]. *Adv Eng Mater*, 2024, 26(2): 2301381. doi: 10.1002/adem.202301381.
- [58] Zhang Y, Fang C, Zhang S, et al. Controlled osteogenic differentiation of human mesenchymal stem cells using dexamethasone-loaded light-responsive microgels[J]. *ACS Appl Mater Interfaces*, 2021, 13(6): 7051-7059. doi: 10.1021/acsami.0c17664.
- [59] Zhou Y, Liang H, Liu C, et al. A self-assembly strategy for fabricating tough and magneto-responsive scaffolds to promote osteogenesis with enhanced vascularization[J]. *Chem Eng J*, 2025, 514: 163129. doi: 10.1016/j.cej.2025.163129.
- [60] Hwangbo H, Chae S, Ryu D, et al. *In situ* magnetic-field-assisted bioprinting process using magnetorheological bioink to obtain engineered muscle constructs[J]. *Bioact Mater*, 2025, 45: 417-433. doi: 10.1016/j.bioactmat.2024.11.035.
- [61] Guo X, Tao Z, Dai Z, et al. Magnetically guided mechanoactive mineralization scaffolds for enhanced bone regeneration[J]. *Adv Funct Mater*, 2025, 35(38): 2503903. doi: 10.1002/adfm.202503903.
- [62] Chen J, Zhao Q, Tang J, et al. Enzyme-activated biomimetic vesicles confining mineralization for bone maturation[J]. *ACS Appl Mater Interfaces*, 2024, 16(26): 33005-33020. doi: 10.1021/acsami.4c03978.
- [63] Narupai B, Smith PT, Nelson A. 4D printing of multi-stimuli responsive protein-based hydrogels for autonomous shape transformations[J]. *Adv Funct Materials*, 2021, 31(23): 2011012. doi: 10.1002/adfm.202011012.
- [64] Ge C, He J, Gan M, et al. Conformation-switchable polypeptides as molecular gates for controllable drug release[J]. *Biomacromolecules*, 2024, 25(6): 3373-3383. doi: 10.1021/acs.biomac.4c00024.
- [65] Zhang M, Yu T, Li J, et al. Matrix metalloproteinase-responsive hydrogel with on-demand release of phosphatidylserine promotes bone regeneration through immunomodulation[J]. *Adv Sci(Weinh)*, 2024, 11(20): e2306924. doi: 10.1002/advs.202306924.
- [66] Han Z, Wang M, Hu Z, et al. Tracking the enzyme-response mechanism of tannic acid-embedded chitosan/ γ -polyglutamic acid hydrogel[J]. *Commun Mater*, 2024, 5: 137. doi: 10.1038/s43246-024-00577-2.
- [67] Wang Q, Gao Y, Chen Y, et al. Synergistic enhancement of antibacterial and osteo-immunomodulatory activities of titanium implants *via* dual-responsive multifunctional surfaces[J]. *Adv Healthc Mater*, 2025, 14(4): e2404260. doi: 10.1002/adhm.202404260.
- [68] Parimita S, Kumar A, Krishnaswamy H, et al. 4D printing of pH-responsive bilayer with programmable shape-shifting behaviour[J]. *Eur Polym J*, 2025, 222: 113581. doi: 10.1016/j.eurpolymj.2024.113581.
- [69] Zha K, Hu W, Xiong Y, et al. Nanoarchitecture-integrated hydrogel boosts angiogenesis-osteogenesis-neurogenesis tripling for infected bone fracture healing[J]. *Adv Sci(Weinh)*, 2024, 11(43): e2406439. doi: 10.1002/advs.202406439.
- [70] Zhang B, Zhang H, Sun Y, et al. Functionalized bone implant inspired by lattice defense strategy: grid management, precise and effective multiple-prevention of osteomyelitis recurrence and promote bone regeneration[J]. *Adv Healthc Mater*, 2025, 14(6): e2403058. doi: 10.1002/adhm.202403058.
- [71] Li Y, You J, Lv H, et al. 4D-printed dual-responsive bioscaffolds for treating critical-sized irregular bone defects[J]. *Chem Eng J*, 2024, 489: 151205. doi: 10.1016/j.cej.2024.151205.
- [72] Xiu H, Yang K, Dong L, et al. Near-infrared light-responsive Cu₂MoS₄@GelMA hydrogel with photothermal therapy, antibacterial effect and bone immunomodulation for accelerating infection elimination and fracture healing[J]. *Adv Healthc Mater*, 2025, 14(2): e2403205. doi: 10.1002/adhm.202403205.
- [73] Shen C, Shen A. 4D printing: innovative solutions and technological advances in orthopedic repair and reconstruction, personalized treatment and drug delivery[J]. *Biomed Eng Online*, 2025, 24(1): 5. doi: 10.1186/s12938-025-01334-3.
- [74] Dзамukova M, Brunner TM, Miotla-Zarebska J, et al. Mechanical forces couple bone matrix mineralization with inhibition of angio-

- genesis to limit adolescent bone growth[J]. *Nat Commun*, 2022, 13(1): 3059. doi: 10.1038/s41467-022-30618-8.
- [75] Kirillova A, Maxson R, Stoychev G, et al. 4D biofabrication using shape-morphing hydrogels[J]. *Adv Mater*, 2017, 29(46): 1703443. doi: 10.1002/adma.201703443.
- [76] Liu C, Lou Y, Sun Z, et al. 4D printing of personalized-tunable biomimetic periosteum with anisotropic microstructure for accelerated vascularization and bone healing[J]. *Adv Healthc Mater*, 2023, 12(22): e2202868. doi: 10.1002/adhm.202202868.
- [77] Khodaei A, Nawaz Q, Zhu Z, et al. Biomolecule and ion releasing mesoporous nanoparticles: nonconvergent osteogenic and osteoimmunogenic performance[J]. *ACS Appl Mater Interfaces*, 2024, 16(49): 67491-67503. doi: 10.1021/acsami.4c17540.
- [78] Sadraei A, Naghib SM. 4D printing of physical stimuli-responsive hydrogels for localized drug delivery and tissue engineering[J]. *Polym Rev*, 2025, 65(1): 104-168. doi: 10.1080/15583724.2024.2427184.
- [79] Wu Y, Xie X, Luo G, et al. Photothermal sensitive nanocomposite hydrogel for infectious bone defects[J]. *Bone Res*, 2025, 13(1): 22. doi: 10.1038/s41413-024-00377-x.
- [80] Jeon O, Park H, Leach JK, et al. Biofabrication of engineered tissues by 3D bioprinting of tissue specific high cell-density bioinks[J]. *Mater Today*, 2025, 86: 172-182. doi: 10.1016/j.mat-tod.2025.03.021.
- [81] Wang Y, Cui H, Wang Y, et al. 4D printed cardiac construct with aligned myofibers and adjustable curvature for myocardial regeneration[J]. *ACS Appl Mater Interfaces*, 2021, 13(11): 12746-12758. doi: 10.1021/acsami.0c17610.
- [82] Hwangbo H, Lee H, Roh EJ, et al. Bone tissue engineering *via* application of a collagen/hydroxyapatite 4D-printed biomimetic scaffold for spinal fusion[J]. *Appl Phys Rev*, 2021, 8(2): 021403. doi: 10.1063/5.0035601.
- [83] Ding A, Jeon O, Cleveland D, et al. Jammed micro-flake hydrogel for four-dimensional living cell bioprinting[J]. *Adv Mater*, 2022, 34(15): 2109394. doi: 10.1002/adma.202109394.
- [84] Deng Y, Zhang F, Liu Y, et al. 4D printed shape memory polyurethane-based composite for bionic cartilage scaffolds[J]. *ACS Appl Polym Mater*, 2023, 5(2): 1283-1292. doi: 10.1021/ac-sapm.2c01833.
- [85] Shu C, Qin C, Chen L, et al. Metal-organic framework functionalized bioceramic scaffolds with antioxidative activity for enhanced osteochondral regeneration[J]. *Adv Sci(Weinh)*, 2023, 10(13): e2206875. doi: 10.1002/advs.202206875.
- [86] Rajzer I, Kurowska A, Janusz J, et al. Four-dimensional printing of β -tricalcium phosphate-modified shape memory polymers for bone scaffolds in osteochondral regeneration[J]. *Materials(Basel)*, 2025, 18(2): 306. doi: 10.3390/ma18020306.
- [87] Zhang H, Hua S, He C, et al. Application of 4D-printed magnetoresponsive FOGS hydrogel scaffolds in auricular cartilage regeneration[J]. *Adv Healthc Mater*, 2025, 14(9): e2404488. doi: 10.1002/adhm.202404488.

(编辑 周春华)



Open Access

This article is licensed under a Creative Commons
Attribution 4.0 International License.

Copyright © 2025 by Editorial Department of Journal of
Prevention and Treatment for Stomatological Diseases



官网