

智能响应水凝胶在糖尿病伤口修复中的研究进展

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摘 要

糖尿病伤口因其复杂的病理微环境(如高血糖、异常pH波动、活性氧过载及基质金属蛋白酶过表达等)而难以愈合, 传统敷料因药物释放模式单一难以实现精准治疗。水凝胶作为一种新兴的伤口敷料, 在治疗不规则创面时具有其独特优势。而近年来, 智能响应水凝胶通过动态调控药物释放机制, 在糖尿病伤口治疗中展现出显著优势。目前水凝胶的响应主要通过内源环境响应与外源刺激两种形式。内源环境响应的药物控释水凝胶可响应糖尿病伤口的环境变化, 达到药物按需释放的效果: 高血糖响应水凝胶、pH敏感水凝胶、活性氧响应、基质金属蛋白酶响应水凝胶感知糖尿病伤口的微环境变化, 动态释放抗炎、抗菌药物以促进伤口进入正常愈合流程。此外, 外源性物理刺激(如电场和超声)通过调控凝胶溶胀、电泳迁移或结构崩解增强药物渗透与控释能力。这些多模态药物释放系统通过时空匹配创面微环境动态变化, 协同调控炎症、抗菌、血管生成和组织重塑等关键环节, 显著提升药物生物利用度并规避耐药风险, 有望推动智能敷料的临床转化。

关键词

糖尿病伤口, 水凝胶, 药物释放, 精准医学

Research Progress on Advanced Responsive Hydrogels for Diabetic Wound Healing

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Abstract

Diabetic wounds are difficult to heal due to their complex pathological microenvironment (e.g., hyperglycemia, abnormal pH fluctuations, reactive oxygen species overload, and overexpression of matrix metalloproteinases). Conventional dressings, which rely on a single drug release mode, are inadequate for achieving precision therapy. Hydrogels, as an emerging class of wound dressings, offer unique advantages in treating irregular wounds. In recent years, smart responsive hydrogels have demonstrated significant advantages in diabetic wound therapy by dynamically modulating drug release mechanisms. Currently, the responsiveness of hydrogels is primarily achieved through two forms: endogenous environmental responses and exogenous stimuli. Endogenously responsive drug-controlled release hydrogels can sense environmental changes in diabetic wounds to achieve on-demand drug release: glucose-responsive hydrogels, pH-sensitive hydrogels, reactive oxygen species-responsive hydrogels, and matrix metalloproteinase-responsive hydrogels perceive the microenvironmental changes in diabetic wounds and dynamically release anti-inflammatory and antibacterial agents to promote the wound to enter a normal healing process. In addition, exogenous physical stimuli (e.g., electric field and ultrasound) enhance drug penetration and controlled release capability by modulating gel swelling, electrophoretic migration, or structural disintegration. These multimodal drug delivery systems, by spatiotemporally matching the dynamic changes of the wound microenvironment, synergistically regulate key processes including inflammation, antibacterial activity, angiogenesis, and tissue remodeling, significantly improving drug bioavailability and circumventing the risk of drug resistance, and are expected to promote the clinical translation of smart dressings.

Keywords

Diabetic Wound, Hydrogel, Drug Release, Precision Medicine

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1. 背景资料

糖尿病伤口愈合障碍已成为全球公共卫生领域的重大挑战。随着糖尿病患病率的持续攀升,糖尿病伤口治疗也正以惊人的速度加剧医疗系统的负担。流行病学数据显示,全球约 5.89 亿成年人受糖尿病困扰,其中 19%~34% 的患者将发展为糖尿病足溃疡(Diabetic Foot Ulcer, DFU) [1]。

创面敷料在伤口治疗中起着重要的作用,但传统创面敷料在糖尿病伤口管理中面临显著局限性[2]。传统敷料无法主动调节创面修复进程,且其药物释放模式缺乏可控性[3],常规联合使用的抗生素等治疗剂常发生突释效应(Burst effect) [4],既可能因剂量不足影响疗效,又可能因过量释放而诱发耐药性[5]。

糖尿病创面特有的高糖微环境、异常升高的基质金属蛋白酶(如 MMP-9),活性氧(ROS)积聚及复杂 pH 变化构成动态复杂的病理微环境[6]-[8],而现有的临床伤口敷料难以针对上述多维病理特征建立响应性药物释放机制[9]。传统的药物递送模式导致治疗药物难以精准匹配微环境动态变化,最终导致创面修复关键环节的调控失效[10]。

在本综述中,将总结现有治疗糖尿病伤口的水凝胶如何控制药物释放,促进糖尿病伤口的愈合。

2. 糖尿病伤口特征

2.1. 糖尿病伤口异常炎症状态

糖尿病伤口的微环境呈现出高度复杂且动态失衡的病理特征, 其独特的理化性质与分子生物学改变共同构成了阻碍组织修复的恶性循环[11]。长期高血糖状态作为核心诱因, 通过非酶糖基化反应产生大量糖化末端产物(AGEs) [6], 这些产物与细胞表面受体结合后, 不仅触发核因子 κ B 信号通路介导的慢性炎症反应, 更通过破坏巨噬细胞极化平衡, 使 M1 型促炎表型持续占优[12], 导致炎症消退延迟。糖尿病伤口因微血流减少而导致组织缺氧, 而组织缺氧会进一步加剧线粒体功能障碍和氧化应激水平升高, 促使活性氧(ROS)在创面过度蓄积。正常水平的 ROS 作为许多免疫细胞和非淋巴细胞的次级信使, 可以促进血管生成和抵抗细菌感染[13]。然而, 长期过量的 ROS 水平可在微环境中引起慢性炎症和不可逆的细胞损伤, 使创面更加脆弱, 抑制内源性干细胞和巨噬细胞的功能, 阻碍创面愈合, 形成抑制细胞迁移与血管新生的氧化损伤微环境[14]。

2.2. 糖尿病伤口常伴发感染

创面 pH 值的动态变化显著影响着愈合进程[15]。随着病程进展, 细菌代谢产生的乳酸与局部缺血导致的糖酵解增强, 可能使创面转为反常的持续酸性状态(pH 5.5~6.5) [16], 这种异常酸化不仅抑制角质形成细胞迁移[17], 更通过激活基质金属蛋白酶(MMPs)加剧细胞外基质降解[18]。基质金属蛋白酶家族成员在糖尿病创面呈现差异化表达特征, MMP-2、MMP-9 的过度活化导致胶原合成与降解失衡, 最终使得创面陷入持续性上皮化停滞状态[19]。

2.3. 糖尿病伤口愈合面临的挑战

正常伤口愈合是一个组织良好的过程, 分为四个重叠的阶段: 止血、炎症、增殖和重塑[4]。虽然在糖尿病等病变情况下, 伤口愈合过程也由这四个阶段组成, 但糖尿病伤口复杂的微环境(如高血糖、异常 pH 波动、活性氧过载及基质金属蛋白酶过表达等)会阻碍进展会形成异常炎性环境, 干扰胶原纤维的正常合成而导致慢性伤口的形成。

3. 新型伤口敷料——智能响应水凝胶的研究现状

糖尿病伤口存在多维度、多层次的微环境紊乱, 使得传统敷料难以满足动态治疗需求。传统伤口敷料采用被动药物释放, 而糖尿病患者伤口的微环境并非一成不变。糖尿病患者伤口常伴随着感染; 创面渗出液中异常升高的炎症介质与蛋白酶, 不仅加速药物失活, 更可能逆向影响敷料理化性质[20]; 而缺氧与氧化应激时空交错, 则对药物的递送提出了精准调控要求[21]。因此亟待开发一种可控药物释放的伤口敷料, 以应对糖尿病患者复杂的伤口微环境[22]。

目前基于智能水凝胶通而实现的药物精准控释, 主要分为内源微环境响应型和外源调控型两大方向。内源响应系统通过感知伤口局部生化特征触发药物释放: 高血糖响应型水凝胶针对糖尿病伤口高血糖环境, 实现了血糖浓度与药物释放速率的动态匹配; pH 敏感型水凝胶针对糖尿病伤口并发感染后出现的酸性环境, 实现抗生素按需递送, 避免细菌耐药发生; 对于氧化应激微环境与基质金属蛋白酶过表达, ROS 响应型水凝胶与基质金属蛋白酶水凝胶可精准清除过量 ROS, 平衡细胞外基质代谢。在外源调控领域, 电场响应型水凝胶通过聚电解质溶胀、电泳迁移或电化学腐蚀等机制实现药物精准控释, 超声响应技术则利用空化效应破坏 Ca^{2+} 交联网络, 使水凝胶结构塌陷进而释放药物。

这些智能药物控释系统通过时空匹配创面愈合不同阶段的病理特征, 在炎症期快速释放抗炎药物, 在增殖期持续递送促血管生成因子, 并根据感染情况按需释放抗菌药物, 促进糖尿病伤口进入正常愈合轨道。

4. 内源环境响应的水凝胶

4.1. 高血糖响应水凝胶

糖尿病伤口愈合中, 高糖环境是伤口无法进入正常愈合过程的关键因素, 也是糖尿病伤口的最显著特征。下述两项研究均利用苯硼酸基元与葡萄糖的分子相互作用实现了局部糖浓度驱动的药物控释[2]。

槲皮素(quercetin)是一种中药成分, 已被证明有抗炎, 促进血管生成的作用, 而左氧氟沙星(levofloxacin)则是早已被证明的广谱抗菌药物。Liu 等人构建的疏水水凝胶 QL@MAB 通过(3-丙烯酰胺苯基)硼酸(AAPBA)与槲皮素(Q)形成动态硼酸酯键[9], 模拟皮肤汗孔的开闭机制。当伤口微环境中葡萄糖浓度升高时, 葡萄糖分子与 AAPBA 的竞争性结合导致硼酸酯键断裂, 触发“汗孔”通道扩张, 使抗氧化剂 Q 和抗生素左氧氟沙星(L)的释放量在 24 小时内提升至 51.8% (vs PBS 环境 25.0%), 实现长达 16 天的持续释放[23]。

Guo 等人构建微针水凝胶 Gel-AFPBA-ins 则采用氟化苯硼酸(AFPBA)与葡萄糖酸修饰胰岛素的动态结合, 当葡萄糖浓度从 100 mg/dL 升至 400 mg/dL 时, 胰岛素释放速率提升 2.1 倍。这种糖响应机制源于苯硼酸在高糖环境下释药孔隙增大, 通过渗透压变化扩大凝胶孔径(400 mg/dL 时孔径增加 42%), 促进药物扩散。

上述两种药物系统均实现了通过伤口微环境调控药物释放。不仅如此, 前者通过疏水层相分离形成表皮屏障延缓药物流失[24], 而后者利用微针结构增强组织粘附确保持续作用。这些智能释放系统通过局部糖浓度监测 - 响应 - 释放的闭环调控, 有效解决了传统水凝胶药物突释和生物利用度低的问题, 为高糖环境下伤口胰岛素的精准递送提供了新策略。

4.2. pH 响应水凝胶

耐甲氧西林金黄色葡萄球菌(Methicillin-resistant *Staphylococcus Aureus*, MRSA)是一种高度侵袭性的革兰氏阳性病原菌。它是皮肤伤口感染的主要病原体[25]。MRSA 的快速增殖导致大量乳酸在感染伤口中蓄积[26]。这就产生了酸性微环境(pH 5.5), 其酸性明显高于生理环境(pH 7.4)。

透明质酸(HA)作为生物相容性良好的材料, 常用于模拟细胞外基质。Wang 等人开发的 CG-HA-Zn 水凝胶[27], 利用 HA 羧酸基团的 pH 依赖性去质子化特性, 在酸性感染微环境下通过增强聚合物链静电斥力, 显著提升溶胀率, 促使阿魏酸(FA)和 Zn^{2+} 释放速率提升 40%, 有效抑制耐药菌并缓解炎症。

目前研究表明锌离子具有抗菌效果[27], 而 Zhang 团队设计的 CS-PBA/PEG-DA/ ZnO -P-TA 水凝胶则针对糖尿病伤口固有酸性环境, 通过 ZnO 纳米颗粒的酸降解(pH 5.5 下 Zn^{2+} 释放量 2.73 ppm)和单宁酸(TA)酚羟基的 pH 响应性解离, 协同发挥抗菌和抗氧化作用[28]。上述两项研究分别通过金属 - 酚配位键解离和金属氧化物溶解, 实现差异化的 pH 响应窗口以精准响应糖尿病伤口的酸性微环境。值得关注的是, Zn^{2+} 的双重功能在两种系统中均得到体现——既作为交联增强剂, 又在特定 pH 下通过膜破坏作用增强抗菌效果[29], 其释放动力学与伤口 pH 变化呈正相关[30]。上述智能释放系统通过伤口微环境驱动, 有效协调了抗菌、抗氧化、免疫调节和血管生成的多重需求[31], 不仅实现了药物的精准控释, 还避免了传统施用抗生素过量导致的细菌耐药。

值得一提的是, 花青素(Anthocyanin)作为一种抗炎, 抗氧化药物, 同时还具备在不同 pH 下变色的能力, 实现了伤口 pH 的可视化监测[31]-[34]。目前已有研究将食物源性花青素作为用于感染监测的可视 pH 探针整合到聚乙二醇水凝胶中, 以开发一种可视化的智能伤口敷料[35]。这种方法制备的水凝胶敷料可在 pH 4.5~10 的范围内实现 pH 的可视化检测, 并精准调控抗生素的释放[36]。

4.3. ROS 响应水凝胶

线粒体功能障碍、糖化末端产物(AGEs)积累以及持续性炎症反应导致 ROS 过度生成, 打破氧化还原平衡。过量的 ROS 通过氧化损伤细胞功能, 抑制细胞增殖和迁移能力, 激活 NF- κ B 信号通路, 诱导 TNF- α 、IL-6 等促炎因子持续性释放, 形成“炎症-氧化应激”恶性循环[37], 因此亟待开发通过伤口微环境的氧化应激水平动态调控药物递送的伤口敷料。

以 Li 等人开发的 SA-RhB 水凝胶和 Liang 团队设计的 CF gel 为例[13], 前者通过 RhB-AC 传感器识别 HClO/CIO⁻, 导致凝胶网络解体并释放负载的牙囊干细胞外囊泡(DFSC-sEVs), 同时水凝胶自身清除 ROS, 形成抗氧化-药物释放协同效应[13]; 而 CF gel 则利用二茂铁(Fc)与环糊精(CD)的主客体相互作用, 在高 ROS 环境下 Fc 被氧化为亲水性 Fc⁺, 破坏超分子交联结构, 释放包载小檗碱的 F127 胶束。这种 ROS 浓度依赖的药物释放机制实现了精准的时空控制——在糖尿病伤口炎症期(ROS 水平峰值期)快速释放抗炎成分(如 DFSC-sEVs 中的抗氧化酶或小檗碱), 而在愈合后期 ROS 下降时减缓释放, 实现了按需给药。这种响应性释放显著提高了疏水药物的生物利用度, 并通过降低局部 ROS 和 AGE 水平, 协同促进巨噬细胞向 M2 极化, 从而打破炎症的恶性循环。

4.4. MMPs 响应水凝胶

糖尿病伤口中, 糖化末端产物的增加会引起基质金属蛋白酶浓度变化。局部 MMP-9 浓度的动态变化可通过酶响应性水凝胶系统实现药物的智能释放调控。

MMPs 的过度表达会导致细胞外基质的降解, 而明胶微球可模拟天然的细胞外基质。在 Zhang 等人开发的 CBP/GMs@Ccl&INS 水凝胶中, 明胶微球作为 MMP-9 的天然底物, 在创面 MMP-9 浓度升高时, 明胶链被特异性酶解, 促使抗炎药物塞来昔布从微球中缓释。体外实验显示, 当 MMP-9 浓度从 0 nM 升至 50 nM 时, 塞来昔布 120 小时累积释放率从 18%提升至 40%, 而在同时存在 5 mg/mL 葡萄糖的协同作用下, 释放率进一步增至 62.3%, 表明微环境双重刺激可加速药物释放动力学[38]。

而 Yang 等人构建的 HA-Gel 水凝胶则通过明胶-己二酸二酰肼交联网络, 在 MMP-9 介导的酶解作用下持续释放 TRPA1 激动剂肉桂醛(CA)。动物实验证实该体系在糖尿病创面中响应炎症相关的 MMP-9 过表达(25~100 nM), 实现 CA 的按需释放, 显著抑制内皮细胞铁死亡并促进血管新生[39]。基于 MMP-9 浓度梯度设计的酶响应水凝胶可精准匹配糖尿病创面的病理特征, 通过酶解动力学调控药物释放速率, 防止细胞外基质过度降解, 为伤口愈合提供稳定环境, 促进伤口正常进入增殖期和重塑期。

5. 依靠外源刺激的响应水凝胶

5.1. 电场响应水凝胶

内源性电刺激(ES)本身对伤口愈合存在一定促进作用[40], 目前研究发现可通过外源电场调控药物释放。电场调控药物释放机制主要包括材料溶胀, 电泳迁移, 电化学腐蚀[41]。

当施加电场时, 聚电解质水凝胶的离子化基团(如羧酸根或氨基)与电场相互作用, 引发凝胶体积或形态的变化, 从而驱动药物释放。例如, 聚丙烯酸(PAA)等聚阴离子凝胶在阳极附近因局部 pH 下降导致羧酸基团质子化, 聚合物链间斥力减弱, 凝胶脱水收缩, 通过挤压作用将药物随水分同步排出。这种释放模式与电场强度密切相关, 但受凝胶电阻变化的影响, 高电压下的释放效率可能逐渐降低。此外, 若凝胶处于非接触电极的环境中, 电场可能仅在表面诱导形成致密“皮层”, 阻碍内部药物的扩散, 此时断电后凝胶重新溶胀反而促进药物释放, 形成“反向调控”现象[42]。

对于带电药物分子, 电泳迁移是另一重要机制。阳离子药物(如乙丙噻)在电场中向阴极迁移, 同时阳极产生的 H⁺离子可置换药物与凝胶网络的静电结合, 进一步加速释放。这种机制使带电药物的释放速率

显著高于中性分子(如氢化可的松)。而当药物为大分子(如胰岛素)时, 扩散作用占主导地位[43]。

电化学腐蚀也为某些复合凝胶提供了独特的释放途径。例如, 聚乙烯基恶唑啉/聚甲基丙烯酸(PEO/PMAA)复合物在阴极附近因 OH^- 离子升高破坏氢键, 导致凝胶表面逐层腐蚀, 药物(如肝素)以零级动力学释放。此类机制的优势在于释放速率稳定, 但腐蚀过程不可逆, 适用于单次脉冲给药[42]。值得注意的是, 电场关闭时, 凝胶可能因吸水膨胀导致小分子药物回流, 这一现象在微球体系中尤为明显, 需通过优化药物分子量与凝胶孔径的匹配性加以规避[3][44]。目前前沿研究聚焦于设计多响应性凝胶(如引入温度或 pH 敏感单元)增强释放可控性[45], 以解决凝胶疲劳、生物相容性及体内电场传递效率等挑战, 以推动电响应水凝胶在智能给药系统中的实际应用。

5.2. 超声响应水凝胶

超声(ultrasound)本是一种临床诊断手段[46], 但目前已有关于通过超声调控水凝胶药物释放的研究出现。释放超声响应水凝胶的载药释放机制主要依赖于超声能量对材料结构的动态调控作用。在 Zhang 等人构建的 HBD 肽复合水凝胶体系中, 超声通过物理 - 化学双重作用触发药物的可控释放: 一方面, 超声波的机械振动和空化效应直接破坏由 Ca^{2+} 离子交联形成的水凝胶三维网络结构, 导致聚合物链间的配位键断裂, 促使水凝胶发生结构坍塌, 这一过程不仅加速了加载的 HBD 肽纳米颗粒和银离子的释放, 还通过降低间质压力增强了药物在深层组织的渗透能力[47]; 另一方面, 超声诱导的局部微环境扰动(如温度波动和微流效应)进一步促进药物扩散动力学, 同时空化效应产生的微泡破裂可产生瞬时剪切力, 有效破坏生物膜基质屏障, 使释放的抗菌成分能够穿透至约 $400\text{ }\mu\text{m}$ 的创面深层[48]。这种结构崩解与功能释放的协同效应, 使得水凝胶在维持长效药物递送的同时, 实现了按需触发的精准治疗, 特别适用于糖尿病创面复杂的病理微环境。

6. 小结

智能水凝胶作为糖尿病伤口治疗的新型敷料, 通过动态响应创面微环境的多维病理特征, 实现了药物的精准控释与协同治疗。现有研究不仅将药物释放与微环境动态变化时空匹配, 显著提升了药物的生物利用度, 同时规避了传统敷料的突释效应和耐药风险, 同时外源性物理刺激(如电场、超声)的引入进一步拓展了药物控释的时空精度, 通过调控凝胶结构或增强组织渗透性优化治疗效果。

糖尿病伤口治疗水凝胶的智能药物释放系统已展现出突破性潜力, 但其临床转化仍面临多重挑战。首先当前单一响应机制(如仅响应葡萄糖浓度或 pH)难以全面匹配糖尿病伤口动态变化的病理特征, 未来需开发多刺激协同响应的药物递送系统。其次, 电场/超声等外源调控技术需向便携式、无创化发展, 目前现已出现非植入式无线电用于伤口治疗[43]。同时, 现有药物系统多依赖被动响应, 实时监测与缺乏自适应调控能力。未来可融合柔性电子技术与水凝胶载体: 嵌入花青素类比色传感器或荧光探针(如前文提到 pH 可视化体系)[36], 通过图像分析实时追踪创面 pH、ROS 等参数, 并与超声促进药物释放联动, 构建“感知 - 分析 - 响应”智能闭环。

糖尿病伤口治疗中的药物递送正从“单一响应”向“智能闭环”演进, 其未来必将走向多机制协同、实时反馈、个体化适配的新阶段。通过材料创新、技术整合与临床验证的深度融合, 智能水凝胶有望突破现有敷料的静态局限, 成为糖尿病创面精准医学的革新性载体, 最终实现从糖尿病伤口微环境调控的跨越式突破。

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