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·基础研究·

负载西格列汀的可注射水凝胶促进糖尿病小鼠皮肤创面愈合

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【摘要】　目的　探讨负载西格列汀（STG）的可注射四臂聚乙二醇（tetra-PEG）水凝胶（简称PEG-STG水凝胶）对糖尿病小鼠皮肤创面愈合的作用，为其后续应用于糖尿病患者口腔颌面部皮肤及软组织创面一期愈合的局部治疗材料研发提供实验依据。**方法**　采用四臂聚乙二醇琥珀酰亚胺戊二酸酯（PEG-SG）与四臂聚乙二醇胺（PEG-NH_2）制备PEG水凝胶，进一步负载STG制备PEG-STG水凝胶。通过扫描电镜观察PEG-STG水凝胶微观结构，检测其成胶、可注射性、压缩、溶胀、降解性能及体外药物释放性能。采用小鼠成纤维细胞系L929、人脐静脉内皮细胞系（HUVECs）进行体外细胞实验，实验分为4组：NC组为正常培养基对照组；Glu组为30 mmol/L葡萄糖培养基处理组；PEG组为高糖条件下加入PEG水凝胶浸提液处理组；PEG-STG组为高糖条件下加入PEG-STG水凝胶浸提液处理组。通过CCK-8、细胞死/活染色、溶血实验评估材料生物相容性；划痕实验、Transwell迁移实验、qRT-PCR及Western blot评估PEG-STG水凝胶对高糖环境下细胞功能的影响。获得单位实验动物福利伦理委员会批准，进一步建立C57BL/6J小鼠糖尿病小鼠皮肤缺损模型，实验分为3组：NC组为正常小鼠皮肤缺损对照组；Glu组为糖尿病小鼠皮肤缺损模型组；PEG-STG组为糖尿病小鼠皮肤缺损后给予PEG-STG水凝胶原位处理组，通过创面大体观察、创面愈合率统计分析及HE染色评价PEG-STG水凝胶对创面愈合和组织修复的影响。**结果**　PEG-STG水凝胶可在室温下快速成胶，具有良好的可注射性和较均一的多孔结构。相较于PEG水凝胶，PEG-STG水凝胶的最大压缩强度显著增加，溶胀率和降解速率均有所提高（$P < 0.05$）。体外药物释放实验结果显示，STG在释放早期呈现较快释放趋势，随后释放速度逐渐减缓，并在观察期内保持持续释放。CCK-8、细胞死/活染色及溶血实验结果表明，PEG-STG水凝胶具有良好的生物相容性和血液相容性。体外细胞实验结果显示，相较于NC组，Glu组可明显抑制HUVECs和L929的迁移能力，PEG组细胞迁移能力无明显改善，而PEG-STG组上述指标明显改善。此外，PEG-STG组HUVECs血小板-内皮细胞黏附分子1（CD31）、血管内皮生长因子（VEGF）和血管性血友病因子（VWF）的mRNA表达水平升高，VEGF和CD31的蛋白表达水平亦升高。糖尿病小鼠皮肤缺损模型实验结果表明，术后14 d，PEG-STG组大体组织创面愈合程度显著优于Glu组和NC组，HE染色镜下观察，相比NC组和PEG组，PEG-STG组创面再上皮化程度提高，肉芽组织形成更明显，组织结构恢复较好。**结论**　PEG-STG水凝胶具有良好的可注射性和生物相容性，可改善高糖环境下内皮细胞和成纤维细胞功能，促进糖尿病小鼠皮肤创面愈合，可为后续开发适用于糖尿病患者口腔颌面部皮肤及软组织创面一期愈合的局部治疗材料提供实验依据。

【关键词】　水凝胶；　西格列汀；　糖尿病；　皮肤创面；　软组织愈合；　四臂聚乙二醇；　局部给药
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Injectable hydrogel loaded with sitagliptin promotes wound healing of diabetic skin defects in mice　WANG Qirui, YU Yi, LIU Dawei, YU Tingting.　Department of Orthodontics, School and Hospital of Stomatology, Peking Uni-

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【**Abstract**】 **Objective** To investigate the effect of injectable tetra-polyethylene glycol (PEG) hydrogels loaded with sitagliptin (STG) (abbreviated as PEG-STG hydrogels) on skin wound healing in diabetic mice, providing an experimental basis for the subsequent development of local therapeutic materials for primary healing of oral and maxillofacial skin and soft tissue wounds in patients with diabetes. **Methods** PEG hydrogels were fabricated via the reaction of four-arm PEG succinimidyl glutarate (PEG-SG) and four-arm PEG amine (PEG-NH_2). Subsequently, PEG hydrogels loaded with STG were prepared. The microstructure, gelation, injectability, compression properties, swelling, degradation, and *in vitro* drug release profiles were characterized. *In vitro* cellular experiments were conducted using the mouse fibroblast cell line L929 and human umbilical vein endothelial cells (HUVECs), which were divided into four groups: an NC group (normal medium control), Glu group (30 mmol/L high glucose medium), PEG group (high glucose medium with PEG hydrogel extracts), and PEG-STG group (high glucose medium with PEG-STG hydrogel extracts). Biocompatibility was evaluated via CCK-8 assays, live/dead staining, and hemolysis tests. The impact of the PEG-STG hydrogels on cellular function under hyperglycemic conditions was assessed using scratch assays, Transwell migration assays, qRT-PCR, and western blotting. Furthermore, approved by the Institutional Animal Care and Use Committee of the affiliated institution, a diabetic C57BL/6J mouse skin defect model was established and divided into three groups: an NC group (normal mice control), Glu group (diabetic model control), and PEG-STG group (treated with PEG-STG hydrogel *in situ*). Wound healing was evaluated through gross observation, wound healing rate analysis, and histological assessment via H&E staining. **Results** The PEG-STG hydrogels exhibited rapid gelation at room temperature, excellent injectability, and a uniform porous structure. Compared with the PEG hydrogels, the PEG-STG hydrogels showed a significantly increased maximum compressive strength, swelling ratio, and degradation rate ($P < 0.05$). *In vitro* release profiles indicated an initial burst release of STG followed by a sustained release phase. Biocompatibility assessments confirmed that the PEG-STG hydrogels possessed good cytocompatibility and hemocompatibility. *In vitro* cellular experiments demonstrated that high glucose significantly inhibited the migration of the HUVECs and L929 cells, which was not ameliorated by the PEG group but was notably improved by the PEG-STG group. Moreover, the PEG-STG hydrogels upregulated the mRNA expression levels of platelet-endothelial cell adhesion molecule-1 (PECAM-1/CD31), vascular endothelial growth factor (VEGF), and von Willebrand factor in HUVECs, along with increased protein expression of VEGF and CD31. *In vivo* results revealed that at 14 days post-operation, the PEG-STG group exhibited significantly enhanced wound closure compared with the Glu and NC groups. H&E staining showed improved re-epithelialization, increased granulation tissue formation, and better tissue structure restoration in the PEG-STG group. **Conclusion** PEG-STG hydrogels possess favorable injectability and biocompatibility. They can improve endothelial cell and fibroblast function under hyperglycemic conditions and promote diabetic skin wound healing, providing a experimental basis for developing localized therapeutic materials for oral and maxillofacial wounds in patients with diabetes.

【**Key words**】 hydrogel; sitagliptin; diabetes mellitus; skin wound; soft tissue healing; tetra-polyethylene glycol; local drug delivery
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糖尿病患者创面愈合障碍是临床常见问题。长期高糖状态可导致微血管病变、氧化应激增强、炎症反应延迟消退、血管生成不足及成纤维细胞迁移和增殖能力下降，使皮肤及软组织创面再上皮化、肉芽组织形成和基质重塑过程受阻，严重时可发展为慢性难愈合创面[1]。因外伤、感染清创、肿瘤切除等造成的口腔颌面部皮肤创面具有形态不规则、解剖结构复杂、局部活动频繁、邻近口腔微生物环境的特点，同时患者对功能和美观修复要求高，因此治疗难度大。在高血糖状态下，口腔颌面部皮肤及软组织创面更易出现感染风险增加、愈合延迟及一期愈合质量下降等问题，进而增加再次换药、抗感染治疗或二次处理的需求，严重影响患者进食、社交活动及生活质量[2-3]。因此，探索适用于糖尿病高糖微环境下口腔颌面部皮肤及软组织创面修复的局部治疗材料，具有重要临床意义。

西格列汀（sitagliptin，STG）是临床常用的二肽

基肽酶-4(dipeptidyl peptidase-4,DPP-4)抑制剂,近年研究表明其除降糖作用外,还可通过调节巨噬细胞极化、改善局部血管生成等途径促进糖尿病相关组织修复[4-5]。有研究表明,可以通过构建丝素蛋白/STG可注射凝胶促进高血糖骨缺损修复;采用纳米颗粒、静电纺丝支架、3D打印多孔支架等材料,可将STG递送至创面促进高血糖皮肤创面愈合及瘢痕防治,但因其合成材料复杂且制备过程涉及多基团修饰,工艺繁琐,在一定程度上限制了临床转化应用[6-9]。

四臂聚乙二醇(tetra-polyethylene glycol,tetra-PEG)水凝胶(简称PEG水凝胶)具有较好的生物相容性和原位成胶特性,可在局部形成湿性覆盖环境,并作为药物递送载体实现药物的局部负载和持续释放,同时tetra-PEG具有较好的可塑性以及可注射性,能够适应颌面部复杂缺损形态和功能活动,有利于颌面部创面临床应用[10-19]。目前,关于将STG负载于tetra-PEG水凝胶并适用于糖尿病患者颌面部皮肤缺损修复的研究尚未见报道。本研究构建了负载STG的四臂聚乙二醇(PEG-STG)可注射水凝胶,在验证材料性能、释药特征、生物相容性基础上,探索了PEG-STG水凝胶局部改善糖尿病高糖微环境下修复相关细胞功能并促进皮肤创面愈合的可行性,为后续拓展至糖尿病患者口腔颌面部复杂形态、活动度较大的皮肤及软组织创面一期愈合相关治疗提供实验依据。

1　材料和方法

1.1　主要仪器与试剂

扫描电子显微镜(SU3500,Hitachi,日本)、倒置荧光显微镜(IX73,Olympus,日本)、生物安全柜(1300 Series A2,Thermo Fisher Scientific,美国)、二氧化碳细胞培养箱(Heracell VIOS 160i,Thermo Fisher Scientific,美国)、酶标仪(Multiskan SkyHigh,Thermo Fisher Scientific,美国)、荧光定量PCR仪(CFX Connect,Bio-Rad,美国)、冷冻干燥机(Lyo-Quest,Telstar,西班牙)、精密电子分析天平(EX223,OHAUS,美国)、万能材料试验机(5944,Instron,美国)、台式高速离心机(Centrifuge 5424 R,Eppendorf,德国)、电泳仪(Mini-PROTEAN Tetra Cell,Bio-Rad,美国)、湿式转膜仪(Mini Trans-Blot Cell,Bio-Rad,美国)及化学发光成像系统(Chemi-Doc MP Imaging System,Bio-Rad,美国)。

四臂聚乙二醇琥珀酰亚胺戊二酸酯[4-arm poly(ethylene glycol) succinimidyl glutarate,PEG-SG]和四臂聚乙二醇胺[4-arm poly(ethylene glycol) amine,PEG-NH_2](厦门赛诺邦格生物科技有限公司,中国)、西格列汀(Sigma-Aldrich,美国)、DMEM培养基(Gibco,美国)、胎牛血清(Gibco,美国)、青霉素-链霉素双抗(Gibco,美国)、细胞计数试剂盒-8(cell counting kit-8,CCK-8)(上海碧云天生物技术有限公司,中国)、磷酸盐缓冲液(phosphate-buffered saline,PBS)(Solarbio,中国)、死/活细胞染色试剂盒(Invitrogen,美国)、4% 多聚甲醛组织细胞固定液(Solarbio,中国)、链脲佐菌素(streptozotocin,STZ)(Sigma-Aldrich,美国)、柠檬酸盐缓冲液(Solarbio,中国)、苏木精-伊红染色试剂盒(Solarbio,中国)、RIPA裂解液、BCA蛋白定量试剂盒、SDS-PAGE凝胶制备试剂盒、蛋白上样缓冲液、PVDF膜、脱脂奶粉、Tris缓冲盐溶液含吐温-20(Tris-buffered saline with Tween-20,TBST)、ECL化学发光试剂(上海碧云天生物技术有限公司,中国)。Western blot实验所用一抗包括兔抗小鼠VEGFA多克隆抗体(19003-1-AP,Proteintech,中国)、兔抗小鼠血小板-内皮细胞黏附分子-1(platelet endothelial cell adhesion molecule-1,CD31)多克隆抗体(11265-1-AP,Proteintech,中国)和兔抗小鼠β-actin多克隆抗体(20536-1-AP,Proteintech,中国);二抗为HRP标记山羊抗兔IgG(H+L)(SA00001-2,Proteintech,中国)。

1.2　细胞与实验动物

体外细胞实验采用小鼠成纤维细胞系L929、人脐静脉内皮细胞系(human umbilical vein endothelial cells,HUVECs)(北京亿奥邦生物科技有限公司)。本实验遵守动物研究指南:体内实验报告(The Animal Research: Reporting of In Vivo Experiments,ARRIVE)指南2.0(https://arriveguidelines.org),并且已获得北京大学口腔医院实验动物福利伦理委员会批准(审批号:LA2022560),动物实验方案按伦理委员会批准的方案执行(未进行注册)。实验动物选用SPF级、4~6周龄雌性C57BL/6J小鼠,购自北京斯贝福实验动物技术有限公司,小鼠生产合格证号为SCXK(京)2019-0010。所有动物饲养及实验操作均在北京大学口腔医院SPF级实验动物中心完成,饲养环境温度20~26 ℃(日温差≤4 ℃),相对湿度30%~70%,12 h光/暗循环,自由摄食饮水,每日监测动物体重、活动状态。

1.3　PEG-STG水凝胶的制备

根据PEG水凝胶是否负载STG，实验分为PEG组和PEG-STG组，每组均设置3个样本。PEG组先将四臂聚乙二醇琥珀酰亚胺戊二酸酯（PEG-SG）和四臂聚乙二醇胺（PEG-NH_2）分别溶于超纯水，配制成质量分数15%的前体溶液，取等体积的两种溶液混合并涡旋，室温条件下即可形成PEG水凝胶。PEG-STG组综合Xiang等[9]的研究与预实验结果，结合细胞生物相容性及促伤口愈合效果，确定STG初始负载量为0.5%，即每1 mL水凝胶前体溶液添加5 mg STG，将STG溶解于质量分数15%的PEG-NH_2 PBS溶液中，再与等体积PEG-SG溶液混合，静置反应后制得载药PEG-STG水凝胶。

实验采用倾斜法检测2组水凝胶成胶时间，将各组对应的两种前体溶液等体积混合并快速涡旋，装入离心管后置于室温环境，每隔5 s倾斜离心管观察混合液流动状态。若样品倾斜后不再出现明显流动，且离心管恢复直立后凝胶形态可稳定保持，即判定为成胶，记录从溶液混合至完全成胶的时间。

1.4　PEG-STG水凝胶的材料性能与释药特征检测

1.4.1　SEM观察微观结构　分组及样本数同1.3。水凝胶经液氮速冻后冻干3 d，取样固定于样品台，表面喷金处理后，置于扫描电子显微镜下，加速电压3 000 V，观察2组水凝胶孔隙结构是否均匀。测量孔隙直径并计算孔隙率，孔隙率=孔隙面积/总面积×100%。

1.4.2　水凝胶压缩、溶胀、降解特征检测　水凝胶压缩、溶胀、降解性能检测实验的分组同1.3。

将水凝胶制备为直径10 mm、高8 mm的圆柱形试样，每组3个样本。采用万能材料试验机以2 mm/min速率进行压缩测试，根据应力-应变曲线计算压缩弹性模量和断裂应力，实验独立重复3次。

溶胀实验中，将水凝胶称取初始质量$W_{初}$后，置于37 ℃PBS中孵育。分别于1、3、6、12、24、48、96、168 h取出3份样品，吸去表面液体后称重，记录溶胀质量$W_{胀}$。溶胀率（%）= 100% ×（$W_{胀}$ −$W_{初}$）/$W_{初}$。

降解实验中，将水凝胶称取初始质量$W_{初}$后，置于37 ℃PBS中孵育，并于前述相同时间点取出3份样品，冻干或吸干后称重，记录剩余质量$W_{剩}$。本研究降解环境未加入胶原酶或其他酶组分。降解率（%）= 100% ×（$W_{初}$−$W_{剩}$）/$W_{初}$。

1.4.3　水凝胶释药特征检测　制备完成的PEG-STG水凝胶置于PBS中充分洗涤，设置3个样本，收集洗涤液，采用紫外分光光度法于267 nm处检测洗涤液中未包封STG的吸光度，根据STG标准曲线计算未包封STG质量。根据初始加入STG质量、凝胶中实际载药量及释放液检测结果计算包封率和载药量。

包封率（%）= 凝胶中实际包封的STG质量/初始加入STG质量× 100%。凝胶中实际包封的STG质量按初始加入STG质量减去未包封STG质量计算。载药量（%）= 凝胶中实际包封的STG质量/载药凝胶总质量× 100%。

将制备好的PEG-STG水凝胶置于含PBS的离心管中，设置3个样本。于37 ℃恒温条件下孵育。释放介质体积为10 mL；分别于1、3、6、12、24、48、96、168 h取出1 mL释放液，并补加等体积新鲜PBS。采用紫外分光光度法在267 nm波长处检测释放液中STG含量，并根据STG标准曲线计算各时间点药物释放量。标准曲线线性范围为5~100 μg/mL，线性方程为 A = 0.008C + 0.0042，R^2为0.993。

1.5　PEG-STG水凝胶对高糖环境下修复相关细胞功能的影响

1.5.1　细胞增殖活性检测、死/活染色及溶血实验　采用CCK-8检测不同处理条件对HUVECs和L929增殖活性的影响。细胞分为4组：NC组为正常培养基对照组；Glu组为30 mmol/L葡萄糖培养基处理组；PEG组为高糖条件下（30 mmol/L葡萄糖培养基处理）加入PEG水凝胶浸提液处理组；PEG-STG组为高糖条件下加入PEG-STG水凝胶浸提液处理组。将细胞5 000个/孔接种于96孔板，每个时间点各组设3个复孔，分别培养1、4、7 d后检测450 nm处OD值。

采用死/活染色评价PEG-STG水凝胶浸提液处理后细胞的存活情况。实验分为2组：NC组为正常培养基对照组；PEG-STG组为高糖条件下（30 mmol/L葡萄糖培养基处理）加入PEG-STG水凝胶浸提液处理组。每组3个样本。细胞贴壁后更换对应处理培养基或水凝胶浸提液，共培养24 h后按照试剂盒说明进行染色，并在荧光显微镜下观察。

采用溶血实验评价水凝胶的血液相容性。实验分为4组：PEG组、PEG-STG组、ddH_2O组和PBS组，每组3个样本。取健康小鼠外周血，经抗凝处理后离心收集红细胞，并用PBS洗涤后配制成2%红细胞悬液。PEG组和PEG-STG组分别加

入灭菌后的PEG水凝胶和PEG-STG水凝胶，ddH_2O组加入去离子水作为阳性对照，PBS组加入PBS作为阴性对照。各组均与2%红细胞悬液于37 ℃孵育1 h，离心后取上清，于540 nm检测吸光度。样品组吸光度记为A_{sample}，阴性和阳性对照组吸光度分别记为$A_{negative}$和$A_{positive}$，按公式计算溶血率。溶血率(%)=(A_{sample} − $A_{negative}$)/($A_{positive}$ − $A_{negative}$)×100%。以溶血率低于5%评价材料具有良好的血液相容性。

1.5.2　细胞划痕及迁移实验　分组及样本数同1.5.1。将HUVECs和L929接种于12孔板，待细胞融合形成单层后，采用200 μL枪头垂直划痕，随后用PBS轻柔清洗去除脱落细胞，并更换为含1% FBS的对应处理培养基。分别于0、12、24 h拍照，记录划痕闭合情况，并计算划痕闭合率。

Transwell迁移实验分组及样本数同1.5.1。将HUVECs和L929接种于Transwell上室，下室加入含20% FBS的对应处理培养基或水凝胶浸提液。共培养24 h后，取出小室，固定、染色，并在显微镜下计数迁移至下膜面的细胞数量。

1.5.3　伤口愈合相关基因CD31、VEGF和VWF的mRNA、蛋白表达检测　qRT-PCR实验分组及样本数同1.5.1，检测CD31、血管内皮生长因子(vascular endothelial growth factor，VEGF)和血管性血友病因子(von Willebrand factor，VWF)的mRNA表达。采用总RNA提取试剂盒提取各组HUVECs RNA，测定260 nm和280 nm的OD值评价浓度及纯度。取2 μg RNA进行逆转录合成cDNA。反应体系包括2×SYBR Green Master Mix、上下游引物及cDNA模板。反应程序为95 ℃预变性10 min，随后40个循环：95 ℃ 5 s，60 ℃ 1 min。以GAPDH为内参，采用$2^{-\Delta\Delta Ct}$法计算VEGF、CD31和VWF的相对表达量。引物序列如表1。

表1　PCR引物序列

Table 1　PCR primer sequences

Genes	5'-3'	3'-5'
GAPDH	ACTGAGGACCAGGTTGTC	TGCTGTAGCCGTATTCATTG
CD31	AACAGTGTTGACATGAAGAGCC	TGTAAAACAGCACGTCATCCTT
VWF	GCAGTGGAGAACAGTGGTG	GTGGCAGCGGGCAAAC
VEGF	GTGAGGTTTGATCCGCATGAT	GACCCTGGCTTTACTGCTGTA

GAPDH: glyceraldehyde-3-phosphate dehydrogenase; CD31: platelet endothelial cell adhesion molecule-1; VWF: von Willebrand factor; VEGF: vascular endothelial growth factor

Western blot实验分组及样本数同1.5.1。收集各组处理后的HUVECs，加入RIPA裂解液提取总蛋白，并采用BCA法测定蛋白浓度。每孔取20 μg总蛋白样品进行SDS-PAGE电泳分离，随后转移至PVDF膜。PVDF膜经5%脱脂奶粉室温封闭1 h后，分别加入VEGF、CD31及β-actin一抗，于4 ℃孵育过夜。一抗稀释比例分别为：VEGFA 1∶1 000、CD31 1∶1 000、β-actin 1∶5 000。次日用TBST洗膜后，加入HRP标记山羊抗兔IgG二抗，稀释比例为1∶5 000，室温孵育1 h。随后采用ECL化学发光法显影，并使用Image J软件分析条带灰度值。以β-actin作为内参，计算目的蛋白相对表达量。

1.6　糖尿病小鼠皮肤缺损模型建立及伤口愈合情况评价

采用单次腹膜注射链脲佐菌素(STZ)40 mg/kg构建Ⅰ型糖尿病小鼠模型。STZ溶于pH 4.5柠檬酸盐缓冲液，注射后给予20 mmol/L葡萄糖水喂养7 d预防低血糖[20]。7 d后测定尾静脉空腹血糖，空腹血糖浓度>8.3 mmol/L且伴随多饮、多尿或体重下降趋势者纳入高糖模型实验。该阈值用于本研究中筛选STZ处理后处于持续高糖状态的小鼠，并非严格临床糖尿病诊断标准。经腹腔注射戊巴比妥钠(50 mg/kg)麻醉去除小鼠背部毛发并消毒，使用打孔器制备双侧6 mm全层皮肤缺损。

按照预实验结果设定每组样本量，将小鼠按照随机数字法分为Glu组和PEG-STG组，每组3只。另设NC组为对照组，每组3只。NC组为同品系、同性别、同周龄且未接受STZ处理的正常小鼠皮肤缺损对照组，仅制备同样大小全层皮肤缺损，不给予水凝胶处理；Glu组为Ⅰ型糖尿病小鼠皮肤缺损模型组；PEG-STG组为糖尿病小鼠皮肤缺损后给予PEG-STG水凝胶原位处理组。评估人员单盲。

分别于术后0、3、7、10、14 d拍摄创面照片，使用ImageJ软件测量创面面积，并按公式计算创面愈合率：创面愈合率(%)=(术后0 d创面面积－各时间点创面面积)/术后0 d创面面积×100%。

术后14 d CO_2吸入后颈椎脱臼处死小鼠。取创面及周围组织，置于4%多聚甲醛中固定。经梯度乙醇脱水、石蜡包埋后，沿创面中央区域连续切片。切片经脱蜡、水化后，按照HE染色试剂盒说明进行染色，随后脱水、透明、封片，并在光学显微镜下观察创面组织结构、再上皮化、炎症细胞浸润及肉芽组织形成情况。

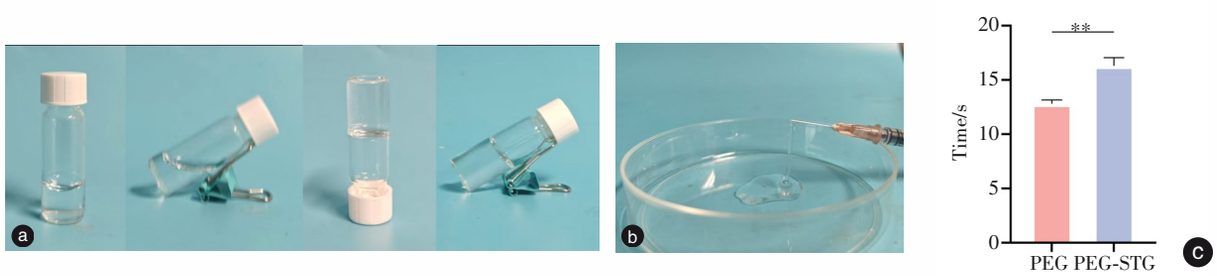
1.7　统计学分析

细胞学实验均分别进行3次独立生物学重复。n值代表独立实验次数、每组样本数或每组单个小鼠数量。采用SPSS 24.0软件进行统计学分析。采用Shapiro-Wilk检验对数据进行正态性检验，符合正态分布的计量资料以均值±标准差($\bar{x}\pm s$)表示。两组间比较采用独立样本t检验，多组比较使用单因素方差分析及Tukey多重比较。以P<0.05为差异具有统计学意义。

2　结　果

2.1　水凝胶的成胶性能

PEG-STG水凝胶大体观及成胶过程见图1a。将PEG-STG水凝胶两组分前体混合后加入1 mL医用无菌注射器中，可顺利挤出黏稠的预凝胶化混合物，说明PEG-STG水凝胶具有良好的可注射性(图1b)，有利于其覆盖不规则皮肤伤口部位。PEG组和PEG-STG组水凝胶的成胶时间见图1c。相较于PEG组水凝胶，PEG-STG组水凝胶的成胶时间更长，提示STG的加入可能影响水凝胶的成胶过程。



a: gelation state after mixing PEG-NH2 and PEG-SG precursor solutions. Gelation was evaluated using the tube inversion method; gel formation was defined as the absence of obvious flow after tilting and the maintenance of a fixed gel shape after returning the tube to an upright position. b: good injectability of the PEG-STG hydrogel. c: gelation time of the PEG and PEG-STG hydrogels. n=3 independent hydrogel samples per group . Statistical analysis used t-test. **P <0.01. PEG group: tetra-polyethylene glycol (PEG) hydrogel; PEG-STG group: sitagliptin-loaded tetra-PEG (PEG-STG) hydrogel

Figure 1　Synthesis and gelation properties of the PEG-STG hydrogel

图1　PEG-STG水凝胶的合成与成胶性能

2.2　水凝胶的材料性能及释药特征检测结果

SEM图像显示，PEG组和PEG-STG组水凝胶均具有较均匀的孔隙结构(图2a)，PEG和PEG-STG水凝胶孔隙直径分别为(18.8±1.7) μm和(18.5±2.4) μm，孔隙率分别为47.2%±3.8%和52.8%±3.1%。2组水凝胶的孔隙直径和孔隙率差异均无统计学意义(P>0.05，图2b、2c)。

PEG-STG组最大压缩强度显著高于PEG组(图3a)，PEG-STG组水凝胶的溶胀率和降解率较PEG组增加(图3b、3c)。

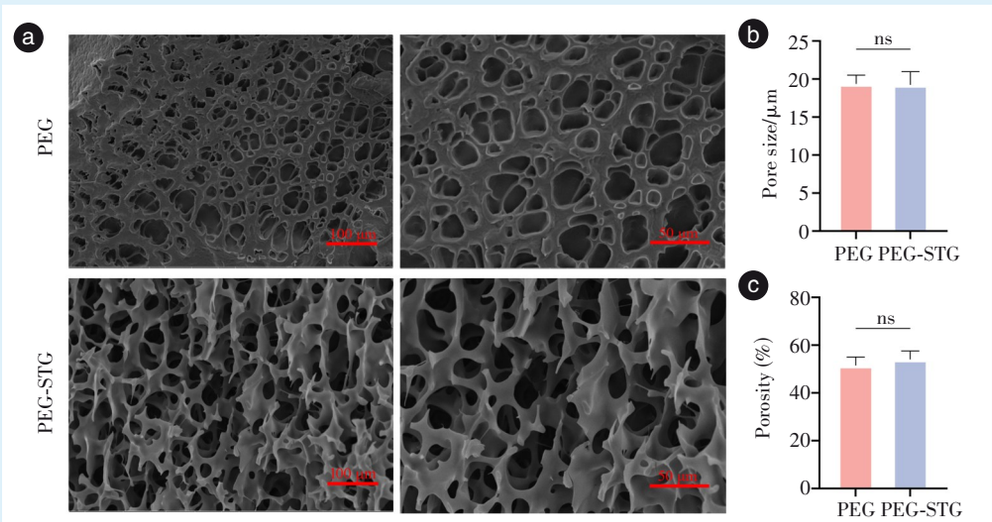
PEG-STG水凝胶的包封率为82.1%±5.23%，载药量为10.3%±3.13%。

体外释放实验显示，STG在释放早期呈现一定快速释放趋势，随后释放速度逐渐减缓，并在观察期内保持持续释放。至168 h，STG累计释放率达到86.3%±3.1%(图3d)。

2.3　PEG-STG水凝胶改善高糖环境下细胞功能

2.3.1　细胞增殖实验、死/活染色及溶血实验结果

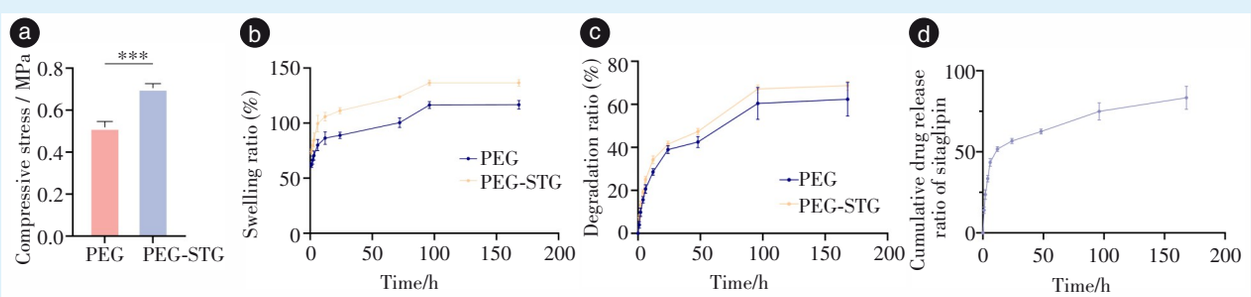
CCK-8结果显示，与NC组相比，Glu组细胞活性降低；PEG组与Glu组相比未见明显改善；PEG-STG组细胞活性高于Glu组，提示PEG-STG水凝胶浸提液可在一定程度上改善高糖环境对细胞活



a: representative SEM images of the PEG and PEG-STG hydrogels. Both hydrogels exhibited relatively uniform porous structures. b: quantitative analysis of pore diameter. c: quantitative analysis of porosity. *n*=3 independent hydrogel samples per group (b, c). Statistical analysis used *t*-test. *ns*: not statistically significant. PEG group: tetra-polyethylene glycol (PEG) hydrogel; PEG-STG group: sitagliptin-loaded tetra-PEG hydrogel. SEM: scanning electron microscopy

Figure 2　SEM observations of the PEG and PEG-STG hydrogels

图 2　PEG 和 PEG-STG 水凝胶的扫描电镜观察



a: the PEG-STG hydrogel exhibited a higher maximum compressive strength than the PEG hydrogel. b: the PEG-STG hydrogel exhibited a higher swelling rate than the PEG hydrogel. c: the PEG-STG hydrogel exhibited a higher degradation rate than the PEG hydrogel. d: cumulative *in vitro* release profile of STG from the PEG-STG hydrogel. STG release was relatively rapid at the initial stage, gradually slowed thereafter, and remained sustained for up to 168 h. PEG group: tetra-polyethylene glycol (PEG) hydrogel; PEG-STG group: sitagliptin-loaded tetra-PEG (PEG-STG) hydrogel. *n*= 3 independent hydrogel samples per group (a, b, c, d). Statistical analysis used *t*-test. ***$P < 0.001$ (a)

Figure 3　Compressive, swelling, degradation, and *in vitro* release properties of the PEG and PEG-STG hydrogels

图 3　PEG 和 PEG-STG 水凝胶的压缩、溶胀、降解及体外释放性能

性的抑制作用(图 4a)。

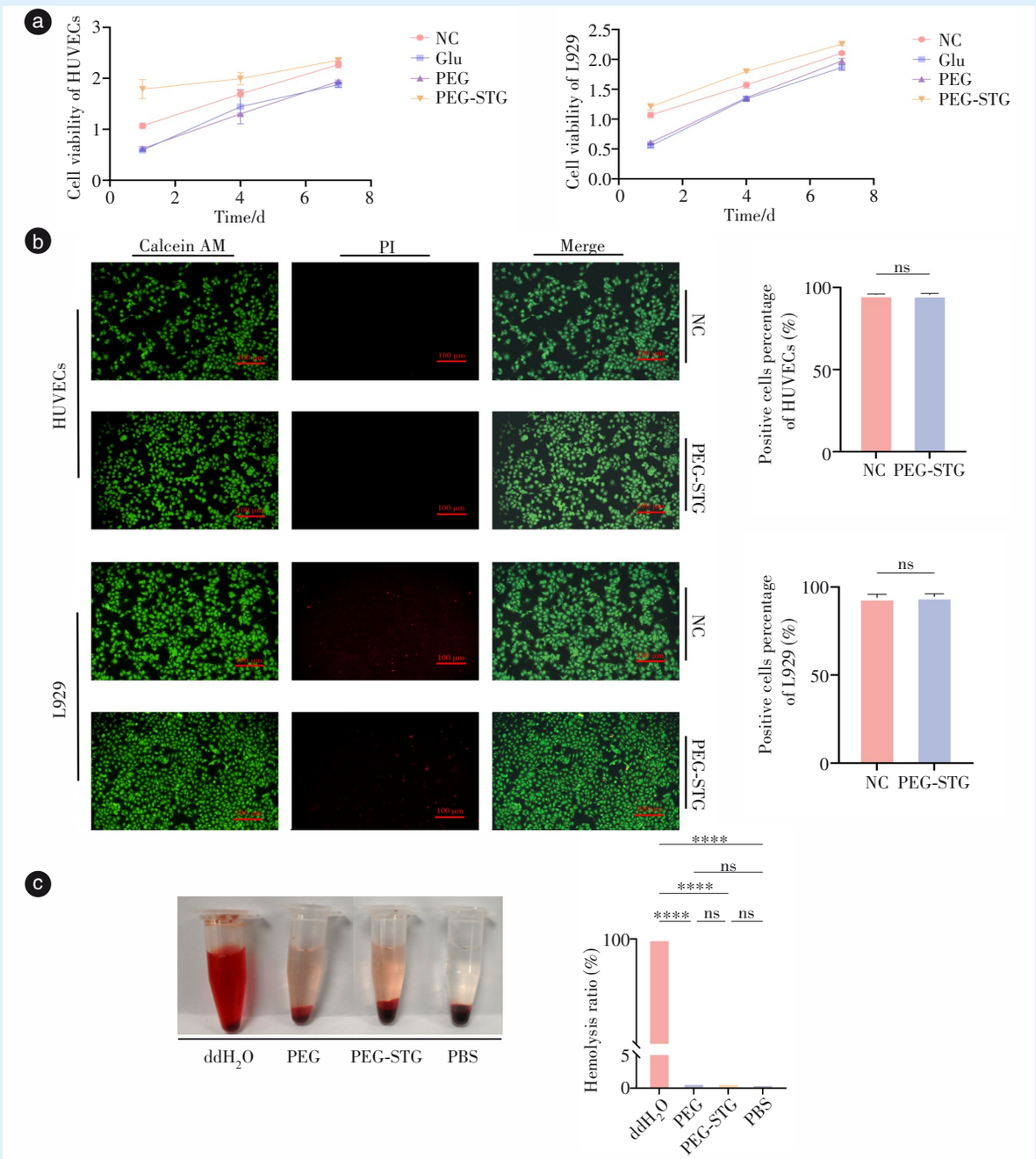
死/活染色结果显示,NC 组和 PEG-STG 组视野内死细胞均较少,两组间差异无统计学意义(图 4b)。

溶血实验结果显示(图 4c),PEG 组和 PEG-STG 组均具有良好的血液相容性,其溶血率与 PBS 组相比差异无统计学意义,ddH_2O 组红细胞破裂明显,溶血率显著升高。

综上,细胞增殖实验、死/活染色及溶血实验结果表明,PEG-STG 水凝胶具有良好的生物相容性,对 HUVECs 和 L929 细胞无明显细胞毒性。

2.3.2　细胞划痕及迁移实验结果　划痕实验结果显示,与 NC 组相比,Glu 组 HUVECs 和 L929 的划痕闭合率均降低;PEG 组与 Glu 组相比未见明显改善;PEG-STG 组 HUVECs 和 L929 在 12 h 和 24 h 的划痕闭合率均较 Glu 组显著升高(均 $P<0.001$,图 5a)。

Transwell 细胞迁移实验结果显示,与 NC 组相



a: CCK-8 assay results of the HUVECs and L929 cells. Cell viability was reduced in the Glu group compared with the NC group, was not markedly improved in the PEG group compared with the Glu group, and was increased in the PEG-STG group compared with the Glu group. NC group: normal culture control. Glu group: high-glucose treatment. PEG group: tetra-polyethylene glycol (PEG) hydrogel extract treatment under high-glucose conditions. PEG-STG group: sitagliptin-loaded tetra-PEG (PEG-STG) hydrogel extract treatment under high-glucose conditions. *n*= 3 biologically independent replicates. b: representative fluorescence images of dead/live staining and quantitative analysis of the HUVECs and L929 cells. The NC and PEG-STG groups exhibited high viability (green fluorescence) with negligible cell death (red fluorescence), and no significant differences were observed between the groups. *n*=3 biologically independent replicates. Statistical analysis used t-test. ns: not statistically significant. NC group: normal culture control. PEG-STG group: PEG-STG hydrogel extract treatment under high-glucose conditions. c: representative images of hemolysis assay and quantitative analysis showing that the hemolysis rates of both the PEG and PEG-STG groups were below 5%, indicating good hemocompatibility. *n*=3 biologically independent replicates. Statistical analysis used one-way ANOVA with Tukey's test for multiple groups. ns: not statistically significant. ****P < 0.000 1. PBS group: negative control; ddH_2O group: positive control, PEG group: treated with tetra-PEG hydrogel; PEG-STG group: treated with PEG-STG hydrogel.

Figure 4　Biocompatibility of the PEG and PEG-STG hydrogels

图 4　PEG 和 PEG-STG 水凝胶的生物相容性

比，Glu 组 HUVECs 和 L929 的迁移细胞数均减少；PEG 组迁移细胞数与 Glu 组相比未见明显增加；PEG-STG 组两类细胞的迁移细胞数均较 Glu 组显著增加（均 $P<0.001$，图 5b）。

2.3.3　PEG-STG 水凝胶上调高糖环境下 HUVECs 血管生成相关基因及蛋白表达　qRT-PCR 结果显示，与 NC 组相比，Glu 组 CD31、VEGF 和 VWF 的 mRNA 表达显著下调（均 $P<0.05$）；PEG 组与 Glu 组相比未见明显改变；PEG-STG 组 CD31、VEGF 和 VWF 的表达均较 Glu 组显著升高（均 $P<0.05$，图 6a）。

Western blot 结果进一步显示，Glu 组 VEGF 和 CD31 蛋白表达较 NC 组降低，提示高糖处理可抑制 HUVECs 血管生成相关功能。与 Glu 组相比，PEG 组 VEGF 表达有所上调，而 CD31 表达未见明显变化，说明单纯 PEG 水凝胶浸提液可能对高糖环境下内皮细胞的促血管生成信号具有一定改善作用，但其对内皮细胞表型恢复的影响有限。相比之下，PEG-STG 组 VEGF 和 CD31 蛋白表达均较 Glu 组升高，提示 STG 负载后可进一步增强水凝胶体系对高糖环境下内皮细胞功能的改善作用（图 6b）。

2.4　PEG-STG 水凝胶对糖尿病小鼠皮肤缺损愈合的影响

PEG-STG 水凝胶对糖尿病小鼠皮肤缺损愈合及组织学修复的影响如图 7 所示。

实验结果显示，术后 0 d 各组创面面积大致一致。随观察时间延长，3 组创面面积均逐渐缩小，但不同组别的创面闭合速度存在差异（图 7a）。与 NC 组相比，Glu 组在术后 3、7、10、14 d 创面闭合程度均较低，提示糖尿病状态可延缓皮肤创面愈合。与 NC 组相比，PEG-STG 组在 3、10、14 d 的创面愈合率更高，而在 7 d 二者无明显差异。与 Glu 组相比，PEG-STG 组在各观察时间点创面面积缩小更明显，术后 3、7、10、14 d 创面愈合率均升高，提示 PEG-STG 水凝胶可促进糖尿病小鼠皮肤缺损修复。术后 14 d，PEG-STG 组创面接近完全愈合，创面愈合率显著高于 Glu 组（$P<0.000\ 1$）和 NC 组（$P=0.021\ 4$）；NC 组创面愈合率亦显著高于 Glu 组（$P<0.000\ 1$）。各时间点组间比较的单因素方差分析结果见表 2。

术后 14 d 创面组织 HE 染色如图 7b 所示。结果显示，NC 组创面组织结构较完整，再上皮化程度较高，炎症细胞浸润较少，肉芽组织形成较充分；Glu 组创面组织结构破坏较明显，再上皮化不连续，炎症细胞浸润较多，肉芽组织形成不足；PEG-STG 组创面组织结构较 Glu 组明显改善，再上皮化程度提高，炎症细胞浸润减少，肉芽组织形成更充分。上述组织学结果与创面大体愈合结果基本一致。

上述结果表明，PEG-STG 水凝胶可促进糖尿病小鼠皮肤缺损创面的愈合，提示其对糖尿病皮肤创面的促修复作用。

3　讨　论

3.1　糖尿病创面修复障碍与局部递药策略

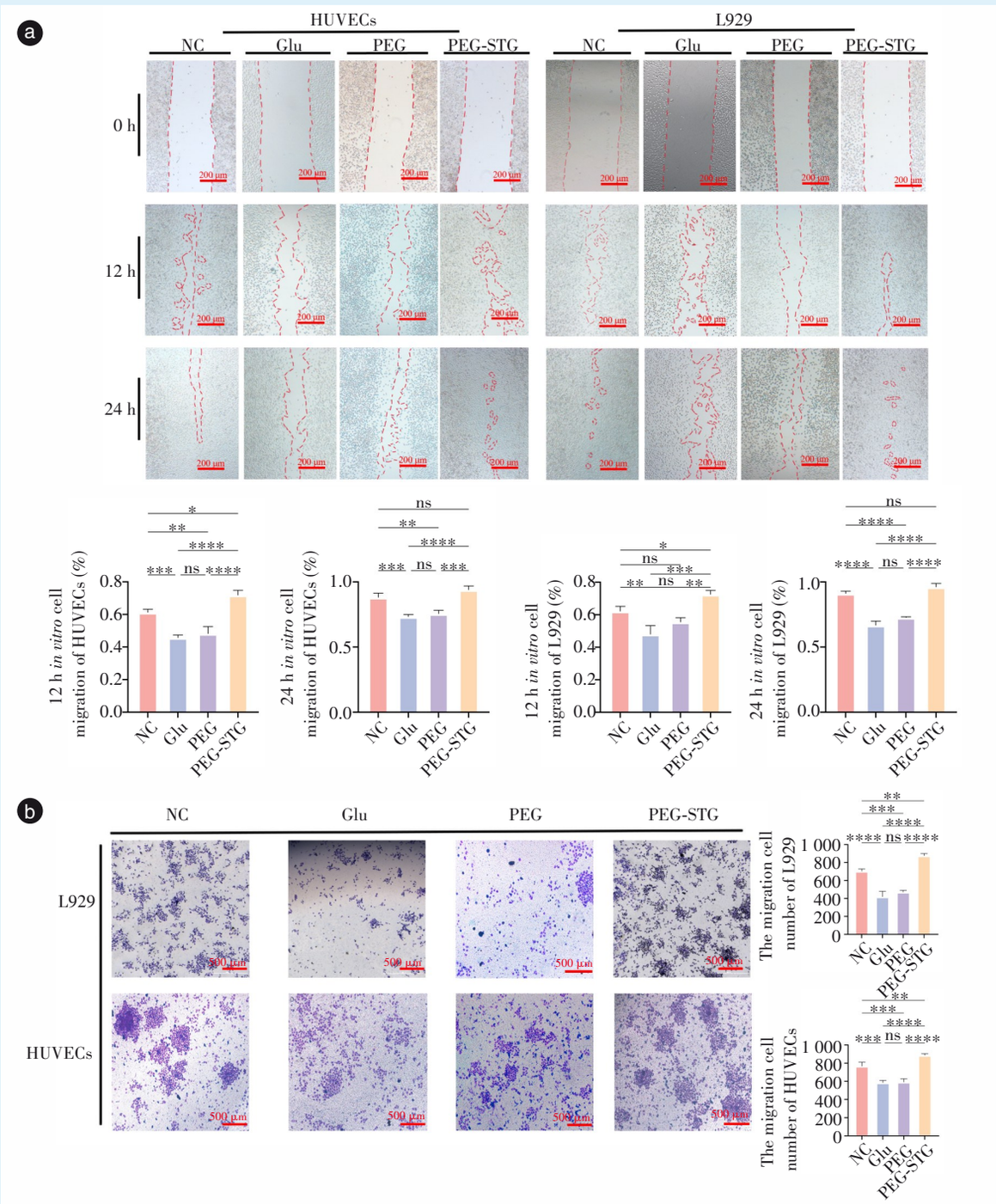
糖尿病创面愈合障碍是多因素共同作用的结果，其病理基础涉及持续高糖状态、氧化应激增强、炎症反应延迟消退、血管生成不足、成纤维细胞迁移及增殖能力下降等过程[21-22]。在糖尿病微环境下，创面局部细胞功能受损，肉芽组织形成和再上皮化过程延迟，常导致创面长期处于慢性炎症和低效修复状态[23]。对于口腔颌面部创面，糖尿病可影响拔牙后牙槽窝愈合、牙周创面及颅颌

表 2　各组小鼠创面愈合率及单因素方差分析结果

Table 2　Wound healing rates and one-way ANOVA results for each group

Group	3 d	7 d	10 d	14 d
NC	22.86%±1.36%^{b}	45.75%±3.62%^{a}	63.25%±1.75%^{b}	82.25%±3.02%^{b}
Glu	16.46%±1.10%^{c}	28.30%±0.43%^{b}	51.68%±1.23%^{c}	59.43%±3.01%^{c}
PEG-STG	37.90%±0.77%^{a}	48.76%±1.07%^{a}	73.22%±2.76%^{a}	90.08%±1.04%^{a}
F	297.8	76.1	85.71	118.4
P	<0.000 1	<0.000 1	<0.000 1	<0.000 1

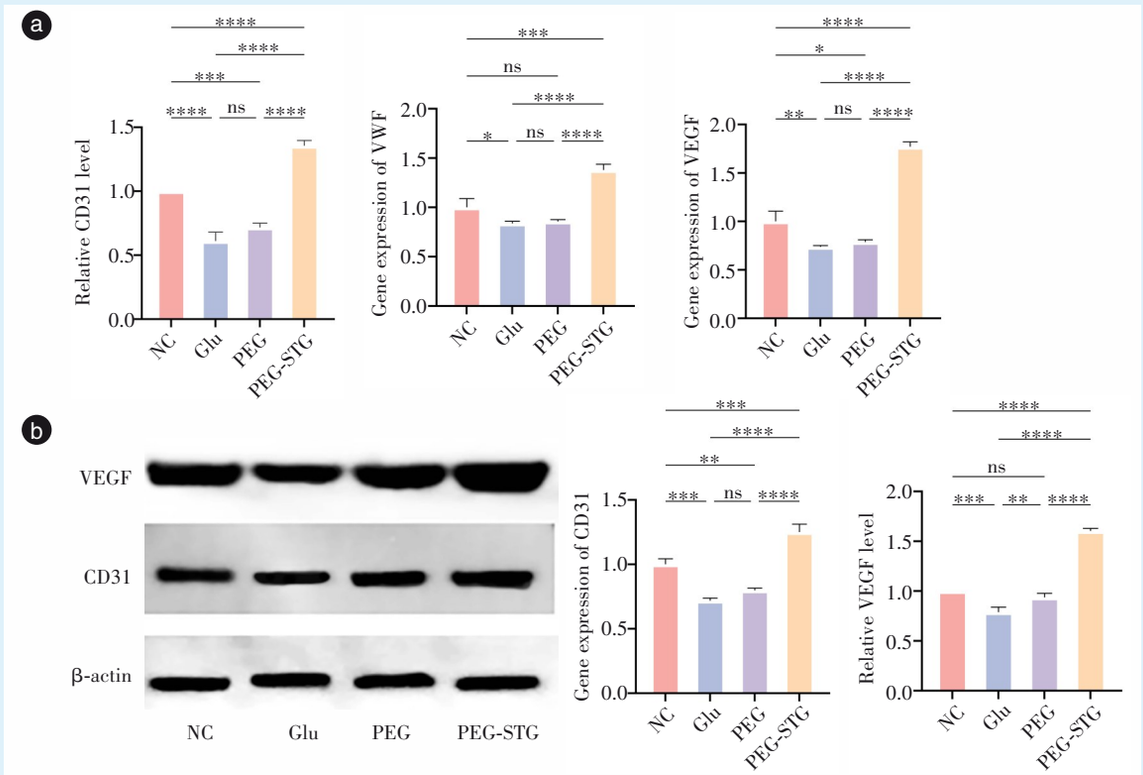
Different lowercase superscript letters within the same row indicate significant between-group differences (Tukey's multiple-comparison test, $P<0.05$). Wound areas on postoperative day 0 were normalized to baseline; therefore, no between-group comparison was performed. NC group: normal culture control; Glu group: high-glucose treatment; PEG-STG group: sitagliptin-loaded tetra-polyethylene glycol (PEG-STG) hydrogel extract treatment under high-glucose conditions



a: scratch assays of the HUVECs and L929 cells and a quantitative analysis showing that scratch closure rates were reduced in the Glu group compared with the NC group, were not markedly improved in the PEG group compared with the Glu group, and were increased in the PEG-STG group compared with the Glu group. Dashed lines indicate the initial scratch boundaries. b: Transwell migration assays of the HUVECs and L929 cells and a quantitative analysis showing that the number of migrated cells was reduced in the Glu group and increased in the PEG-STG group compared with the Glu group. n = 3 biologically independent replicates (a, b). Statistical analysis used one-way ANOVA with Tukey's test for multiple groups for cratch assays (a) and Transwell migration assays (b). *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.000 1; ns, not statistically significant. ns, not statistically significant. NC group: normal culture control. Glu group: high-glucose treatment. PEG group: tetra-polyethylene glycol (PEG) hydrogel extract treatment under high-glucose conditions. PEG-STG group: sitagliptin-loaded tetra-PEG (PEG-STG) hydrogel extract treatment under high-glucose conditions

Figure 5　Improvement of scratch closure and migration of HUVECs and L929 cells by the PEG-STG hydrogel extract under high-glucose conditions

图 5　PEG-STG 水凝胶浸提液改善高糖环境下 HUVECs 和 L929 细胞的划痕闭合及迁移能力



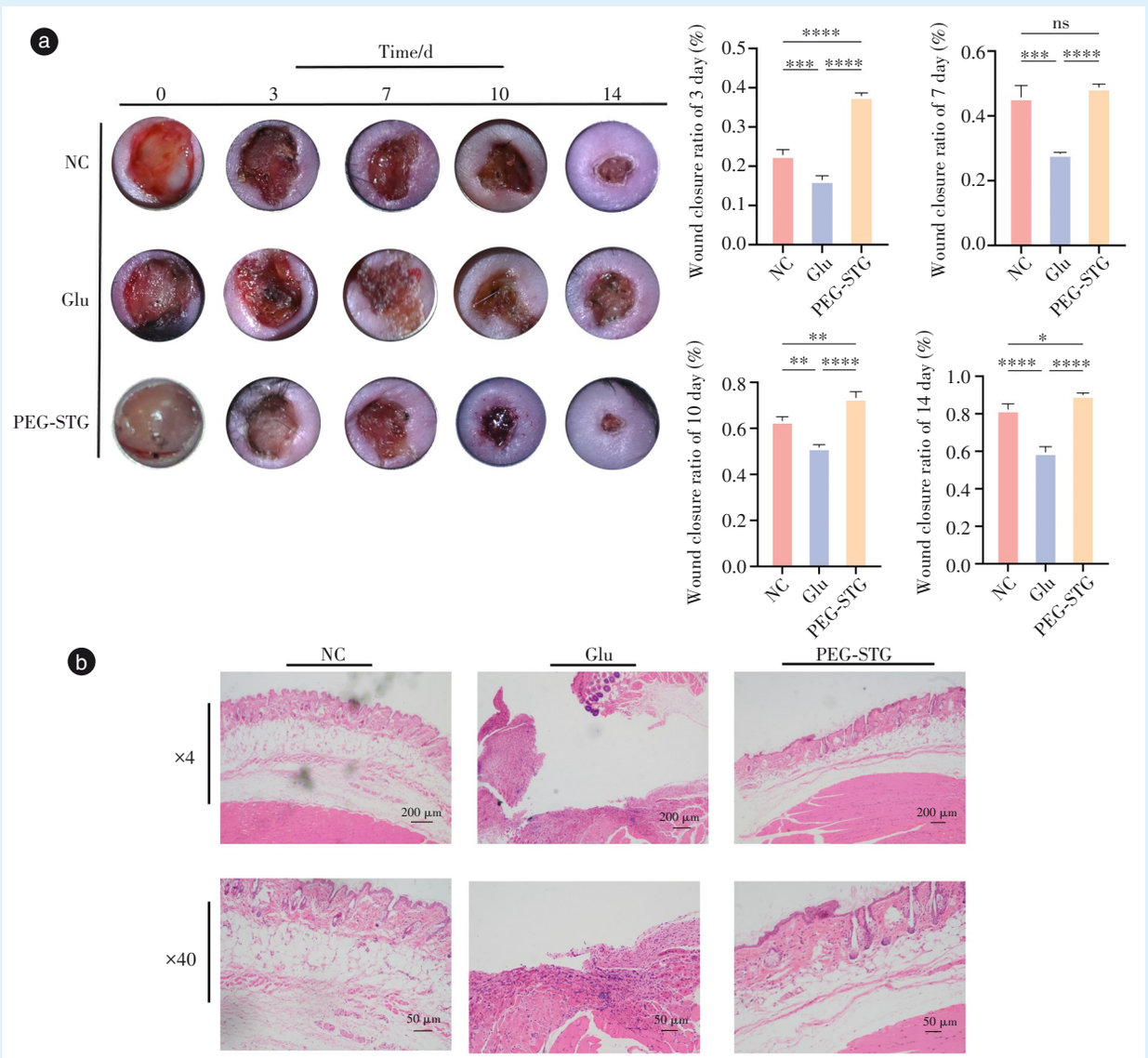
a: qRT-PCR and quantification analysis showed that, compared with the NC group, the Glu group exhibited reduced mRNA expression of platelet endothelial cell adhesion molecule-1(CD31), von Willebrand factor (VWF), and vascular endothelial growth factor (VEGF) in HUVECs. No marked changes were observed in the PEG group compared with the Glu group, whereas the PEG-STG group exhibited increased expression of these genes. b: representative western blot analysis images and grayscale quantification showed that, compared with the NC group, the Glu group exhibited reduced protein expression of VEGF and CD31 in HUVECs. Compared with the Glu group, the PEG group exhibited increased VEGF expression but no marked change in CD31 expression, whereas the PEG-STG group exhibited increased expression of both VEGF and CD31. $n = 3$ biologically independent replicates (a, b). Statistical analysis used one-way ANOVA with Tukey's test for multiple groups for qRT-PCR (a) and Western blot (b). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.000\ 1$; ns, not statistically significant. NC group: normal culture control. Glu group: high-glucose treatment. PEG group: tetra-polyethylene glycol (PEG) hydrogel extract treatment under high-glucose conditions. PEG-STG group: sitagliptin-loaded tetra-PEG hydrogel extract treatment under high-glucose conditions

Figure 6　Upregulation of angiogenesis-related gene and protein expression in HUVECs by the PEG-STG hydrogel extract under high-glucose conditions

图 6　PEG-STG 水凝胶浸提液上调高糖环境下 HUVECs 血管生成相关基因及蛋白表达

面组织缺损修复，延迟愈合可能增加感染风险并影响后续口腔功能恢复[2-3]。此外，口腔黏膜及颌面部创面常处于湿润、活动频繁及形态不规则的局部环境中，对敷料的可塑性、可注射性和持续递药能力提出更高要求[10-12]。因此，构建兼具可塑性、可注射性、持续药物递送的功能性敷料，是糖尿病创面治疗研究的重要方向[24-29]。本研究构建PEG-STG 可注射水凝胶，通过材料性能、体外细胞实验及糖尿病小鼠皮肤缺损修复实验，验证了材料应用于糖尿病创面修复潜能。

此外，既往 STG 相关创面研究多关注系统给药、微针递送或较复杂的响应性递药体系[30-32]，本研究将 STG 负载于相对简洁、可快速原位成胶的PEG 水凝胶中，有利于临床转化应用。同时，PEG 水凝胶虽已被广泛用于药物释放和组织修复等研究[17-19]，但其与 STG 结合后用于高糖微环境下相关细胞功能改善及糖尿病皮肤缺损修复的研究仍相对较少。在此基础上，本研究从材料性能、细胞功能和体内创面修复三个层面初步验证 PEG-STG 水凝胶的促修复潜力，构建一种简洁可注射的 STG 局部递药水凝胶体系，并为其后续用于糖尿病相关皮肤及口腔颌面部软组织创面修复提供依据[33-34]。



a: gross images and a quantitative analysis showed that wound areas were comparable among the groups on postoperative day 0 and gradually decreased over time. Wound closure was more evident in the PEG-STG group than in the Glu group, and wounds in the PEG-STG group were nearly completely healed on postoperative day 14. n = 3 mice (3 biologically independent replicates). Statistical analysis used one-way ANOVA with Tukey's test for multiple groups. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.000 1; ns, not statistically significant. b: representative HE staining images of wound tissue from 3 mice per group on postoperative day 14. The Glu group showed incomplete epidermal continuity, evident inflammatory cell infiltration, and insufficient granulation tissue formation. Compared with the Glu group, the PEG-STG group exhibited improved re-epithelialization, more evident granulation tissue formation, and better tissue structural restoration. ns, not statistically significant. NC group: normal culture control; Glu group: high-glucose treatment; PEG-STG group: sitagliptin-loaded tetra-polyethylene glycol (PEG) hydrogel extract treatment under high-glucose conditions

Figure 7　Effect of the PEG-STG hydrogel on skin defect healing and histological repair in diabetic mice

图 7　PEG-STG 水凝胶对糖尿病小鼠皮肤缺损愈合及组织学修复的影响

3.2　PEG-STG 水凝胶的材料性能与释药特征

以往研究显示，PEG 水凝胶呈多孔结构，有利于水分交换、营养物质扩散及药物释放[13,15]，本研究中 PEG-STG 水凝胶在室温下可通过注射方式快速成胶，具有覆盖不规则创面的潜力。扫描电镜结果显示 PEG 水凝胶与 PEG-STG 水凝胶均呈多孔结构。负载 STG 后，水凝胶成胶时间延长，溶胀和降解速度增加，同时压缩强度增强。负载 STG 可能在一定程度上改变水凝胶的水分进入和降解行为，同时并未削弱其整体抗压性能，后续研究仍需

结合流变学检测进一步评价其流变性能，通过优化组分进一步优化材料的力学性能，构建更加适合临床应用的材料。

本研究发现，PEG-STG水凝胶可实现体外持续释放STG，可能是由于水凝胶吸水膨胀后，内部网络间隙增加，有利于药物从凝胶内部向外扩散；同时，材料逐渐降解也可进一步促进STG释放。对于糖尿病创面而言，局部持续释放有助于延长药物在创面区域的作用时间，减少游离药物快速扩散所导致的局部浓度不足。

3.3　PEG-STG水凝胶对高糖环境下修复相关细胞功能的影响

本研究采用30 mmol/L葡萄糖模拟高糖微环境，结果显示Glu组显著抑制HUVECs和L929的细胞活性及迁移能力，与既往研究结果相符[22,35-36]。PEG-STG组中，两类细胞的增殖和迁移能力均有所改善，进一步检测血管新生因子VEGF、内皮细胞标记物CD31和VWF的相关基因[37-38]发现，PEG-STG可上调HUVECs中VEGF、CD31和VWF的表达，提示PEG-STG可能通过改善高糖环境下内皮细胞功能和血管生成相关基因表达，为创面修复提供有利条件。

作为DPP-4抑制剂，STG在系统给药条件下可通过改善糖代谢状态间接影响创面愈合；同时影响炎症和组织修复相关过程[39-40]，还可能与氧化应激相关通路调控有关[4,41]，本研究采用局部水凝胶递送、高糖环境下HUVECs和L929的体外功能验证PEG-STG水凝胶可通过局部效应促进皮肤缺损修复，但体内实验中，STG系统降糖作用对创面愈合的影响仍需要进一步研究。

3.4　PEG-STG水凝胶对糖尿病小鼠皮肤创面愈合的影响

体内实验结果显示，PEG-STG水凝胶可促进糖尿病小鼠皮肤缺损愈合。术后14 d，PEG-STG组创面愈合率高于Glu组，提示其在糖尿病病理微环境下具有一定促修复效果。以往文献表明，仅水凝胶覆盖可以加速创面愈合，但在糖尿病环境下，单纯水凝胶治疗对创面愈合效果有限，主要依赖其中负载药物的治疗效果，本研究中单纯PEG水凝胶的促愈合效果仍需进一步研究。

糖尿病患者口腔颌面部皮肤及软组织创面的一期愈合依赖充分的局部血供、稳定的创面保护、适宜的细胞迁移和组织重塑过程；本研究结果提示，PEG-STG水凝胶可通过局部覆盖和持续递药改善高糖环境下相关细胞功能，为糖尿病患者口腔颌面部创面一期愈合提供参考。

3.5　局限性与后续研究方向

本研究采用小鼠背部皮肤缺损模型进行体内验证，该模型创面形态稳定、重复性较好，适用于创面修复材料的初步评价[16,42-43]，但口腔颌面部皮肤及软组织创面在局部活动、湿润环境、微生物暴露和美学修复要求等方面具有特殊性。后续仍需在颌面部皮肤缺损、口腔黏膜缺损或拔牙窝愈合等更接近口腔颌面部临床情境的模型中进一步验证其组织适应性、局部驻留能力、促一期愈合效果及降解产物的长期生物相容性[44]。

综上，本研究构建了负载西格列汀的PEG-STG可注射水凝胶。该水凝胶具有良好的理化性能和生物相容性，可在高糖环境下改善血管内皮细胞和成纤维细胞功能，并促进糖尿病小鼠皮肤创面愈合。研究结果证实了PEG-STG水凝胶具有作为糖尿病创面局部递药材料的临床应用价值，可为后续开发适用于糖尿病患者口腔颌面部皮肤创面愈合的局部治疗材料提供依据。未来仍需在颌面部特异性创面模型中进一步探索其促愈合机制。

【Author contributions】 Wang QR designed and performed the experiments and wrote the article. Yu Y analyzed the data and revised the article. Liu DW, Yu TT designed the study and reviewed the article. All authors read and approved the final manuscript as submitted.

【Ethics Statement】 All animal procedures were carried out in compliance with the ARRIVE guidelines (https://arriveguidelines.org) and adhered to the guidelines for the care and use of laboratory animals issued by the China Animal Research Council. All animal experiments were approved by the Experimental Animal Ethics Committee of Peking University School and Hospital of Stomatology (Approval ID: LA2022560).

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【Data availability statement】 The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author upon reasonable request.

【Generative AI statement】 The authors declared that generative AI was not used in the creation of this manuscript.

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