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·基础研究·

噬菌体/白细胞介素-4脂质体复合材料预防小鼠上颌扩弓后复发

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【摘要】 **目的** 探讨负载P11噬菌体和白细胞介素-4(IL-4)脂质体(LIP)的新型可注射水凝胶(GelMA/P11/IL4@LIP)预防小鼠上颌扩弓后复发的效果，为其临床应用提供实验依据。**方法** 本研究已获得医院实验动物伦理委员会批准。首先，构建上颌扩弓及复发模型，15只7周龄C57BL/6小鼠随机分为对照组、扩弓后3 d组、扩弓后7 d组、保持14 d组及复发7 d组，每组3只。各组小鼠分别于对应时间点，即0、3、7、21、28 d处死，取上颌骨及前颅部。通过micro-CT测量腭中缝区域骨参数和上颌切牙近中牙槽嵴顶间距(ICD)；组织学染色观察成骨、破骨活动；免疫组织化学染色(IHC)分析巨噬细胞极化标志物(CD86、CD206)、间充质干细胞标志物[胶质瘤相关癌基因同源物1(Gli1)]及成骨相关标志物[Runt相关转录因子2(Runx2)、Osterix(OSX)]的表达量。随后，合成GelMA/P11/IL4@LIP复合材料，应用于小鼠扩弓及复发模型。24只7周龄C57BL/6小鼠随机分为空白对照组、GelMA组、GelMA/P11组及GelMA/P11/IL4@LIP组，每组6只。所有小鼠均进行扩弓。扩弓后7 d，使用树脂固定所有小鼠的扩弓装置，进行14 d的保持。在保持期的第1天，分别向各组小鼠腭中缝区域注射生理盐水、GelMA溶液、GelMA/P11溶液及GelMA/P11/IL4@LIP溶液。14 d的保持期后，每组中随机选择3只小鼠处死；另外3只小鼠去除扩弓装置，经过7 d的复发后处死，取上颌骨及前颅部。通过micro-CT、组织学染色及免疫组化染色，探究GelMA/P11/IL4@LIP复合材料对扩弓后复发的预防作用。**结果** 小鼠上颌扩弓及复发模型中，micro-CT测量结果显示，复发7 d组ICD较保持14 d组下降(P = 0.008)；IHC分析显示，腭中缝区域M1型巨噬细胞持续浸润，$Gli1^+$间充质干细胞数量少，成骨相关标志物(RUNX2、OSX)表达下降(P<0.001)。GelMA/P11/IL4@LIP复合材料腭中缝局部注射后，与空白对照组、GelMA组相比，复发期ICD增大，巨噬细胞M2极化及$Gli1^+$间充质干细胞募集增强，RUNX2和OSX表达量上调(P<0.05)。**结论** 上颌扩弓后复发的机制为腭中缝M1巨噬细胞持续浸润、间充质干细胞募集及成骨分化不足。GelMA/P11/IL4@LIP复合材料可促进口颌面部间充质干细胞募集和成骨分化，并促进巨噬细胞适时向M2极化，增强腭中缝成骨，有效预防上颌扩弓复发。

【关键词】 间充质干细胞； 巨噬细胞； 噬菌体； 噬菌体展示技术； 白细胞介素-4； 上颌扩弓； 上颌横向发育不足； 免疫调节

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Phage/interleukin-4 liposome composite prevents relapse after maxillary expansion in mice

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【**Abstract**】 **Objective** To explore the efficacy of a novel injectable hydrogel (GelMA/P11/IL4@LIP) loaded with P11 bacteriophages and interleukin-4 (IL-4) liposomes (LIP) in preventing relapse after maxillary expansion in mice, providing experimental evidence for its clinical application. **Methods** This study was approved by the experimental animal ethics committee of our hospital. First, 15 7-week-old C57BL/6 mice were used to establish a maxillary expansion model and divided into 5 groups (3 mice in each group): a control group, post expansion day 3 group (PED3 group), post expansion day 7 group (PED7 group), retention for 14 days group (RET group), and relapse for 7 days group (REL group). The mice in each group were sacrificed at their designated time points (day 0, 3, 7, 21, 28), and their maxilla and anterior cranial regions were collected. Bone parameters and the inter-crestal distance (ICD) of maxillary incisor mesial alveolar ridge were measured using micro-computed tomography (micro-CT). Histological staining was performed to evaluate bone formation and resorption, while immunohistochemistry (IHC) was performed for macrophage markers (CD86 and CD206), mesenchymal stem cell markers (glioma-associated oncogene homolog 1 [Gli1]), and osteogenic markers (Runt-related transcription factor 2 [Runx2] and Osterix [OSX]). Next, GelMA/P11/IL4@LIP was synthesized and administered to mouse models of maxillary expansion. A total of 24 7-week-old C57BL/6 mice were divided into 4 groups (6 mice in each group): a blank control group, GelMA group, GelMA/P11 group, and GelMA/P11/IL4@LIP group. All mice underwent palatal expansion. On PED7, the expanders of all 24 mice were cemented with resin to initiate the 14-day retention period. On day 1 of the retention phase, the mice in each group received injections of saline, GelMA, GelMA/P11, or GelMA/P11/IL4@LIP at the midpalatal suture. After the 14-day retention period, three mice in each group were randomly selected and sacrificed, while the other three had their expanders removed and underwent a 7-day relapse before being sacrificed on day 28 (REL). Micro-CT, histological staining, and IHC were performed to evaluate the preventive effect of GelMA/P11/IL4@LIP on post-expansion relapse. **Results** The mice maxillary expansion model exhibited a decreased ICD at REL compared to RET in micro-CT analysis (P = 0.008). IHC analysis demonstrated prolonged M1 macrophage infiltration, scarce $Gli1^+$ mesenchymal stem cells, and insufficient expression of osteogenic markers (RUNX2 and OSX) (P < 0.001). Compared to the blank control and GelMA groups, GelMA/P11/IL4@LIP hydrogel injection in the midpalatal suture led to increased ICD at REL, promoted the timely M2 polarization of macrophages, recruited $Gli1^+$ mesenchymal stem cells, and upregulated the expression of RUNX2 and OSX (P < 0.05). **Conclusion** The mechanism of relapse after maxillary expansion involves the persistent infiltration of M1 macrophages, as well as the inadequate recruitment and insufficient osteogenic differentiation of MSCs in the midpalatal suture. The GelMA/P11/IL4@LIP composite enhanced orofacial mesenchymal stem cell recruitment and promoted the M2 polarization of macrophages, thereby enhancing osteogenesis in the midpalatal suture and preventing post-expansion relapse.

【**Key words**】 mesenchymal stem cells; macrophages; phage; phage display techniques; interleukin-4; maxillary expansion; maxillary transverse deficiency; immunomodulation

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【**Competing interests**】 The authors declare no competing interests.

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上颌横向发育不足会影响口颌系统美观和功能。上颌扩弓是常用的正畸治疗手段，但其常面临腭中缝骨形成不足而造成的复发。上颌扩弓涉及复杂的细胞间相互作用，包括间充质干细胞（mesenchymal stem cells，MSCs）、免疫细胞、软骨细胞、成骨细胞和破骨细胞等[1-2]。其中MSCs是多能干细胞，具有成骨、成软骨、成纤维、成脂分化等潜力，是骨组织工程的重要种子细胞。MSCs还具有免疫调节能力，与巨噬细胞相互作用，维持骨稳态[3]。而巨噬细胞的M1-M2表型转换对应上颌扩弓的早期炎症反应和随后的骨重塑[4-5]。

噬菌体（phage）是特异性感染目标细菌的病

毒。其中,丝状噬菌体不裂解宿主菌,避免了细菌裂解释放的内毒素对人体的危害,被广泛用于生物医药领域[6-8]。本课题组前期利用噬菌体展示肽库技术淘选出了特异性亲和小鼠长骨骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs)的M13噬菌体单克隆P11。P11噬菌体引起巨噬细胞M1极化,同时可趋化BMSCs,并促进其成骨分化[9]。后续研究通过静电纺丝制备了负载P11噬菌体的有序排列的甲基丙烯酰化明胶(gelatin methacryloyl, GelMA)支架,该支架有效促进了小鼠股骨缺损再生[10]。白细胞介素-4(interleukin-4,IL-4)是巨噬细胞M2极化的诱导因子[11]。压电-IL-4程序化免疫调控,使巨噬细胞M1-M2时序性转换,可有效促进骨缺损修复[12]。脂质体(liposome)是理想的药物载体,具有良好的生物相容性、药物缓释性及被动靶向性[13]。

本实验拟在前期研究的基础上,利用P11噬菌体的干细胞募集及IL-4的促巨噬细胞M2极化作用,制备了一种负载P11噬菌体及IL-4脂质体的新型可注射水凝胶(GelMA/P11/IL4@LIP),并将其注射于小鼠扩弓后腭中缝,以评估预防小鼠扩弓后复发的效果,为临床应用提供实验基础。

1　材料和方法

1.1　实验动物

7周龄雄性C57BL/6小鼠购自成都达硕实验动物有限公司,合格证号:SCXK(川)2020-0030。本研究动物实验经四川大学华西口腔医院医学伦理委员会审查批准(批准号:WCHSIRB-D2023-593)。

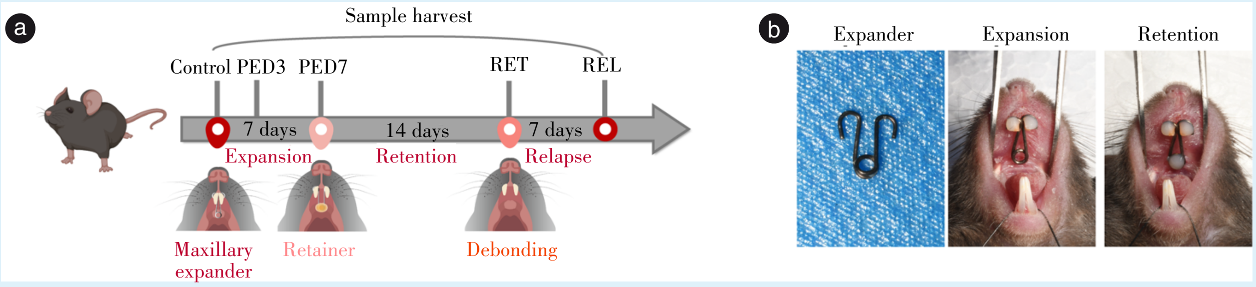
1.2　主要试剂与仪器

戊巴比妥钠盐(P3761,Merck,美国),4%多聚甲醛(BL539A,白鲨,中国),PBS缓冲液(10010072,Gibco,美国),生理盐水(IN9000,Solarbio,中国),苏木素伊红染色试剂盒(G1121,Solarbio,中国),抗酒石酸酸性磷酸酶(tartrate-resistant acid phosphatase,TRAP)染色试剂盒(PMC-AK04F,FUJIFILM,日本),Masson染色试剂盒(G1006-20ML,塞维尔,中国),GelMA试剂盒(EFL GM-90,EFL,中国),胆固醇(C15563101,麦克林,中国),大豆磷脂(L6300,麦克林,中国),重组小鼠IL-4(214-14-5UG,ThermoFisher,美国),氯仿(C166260250,国药,中国),小鼠IL-4 ELISA试剂盒(KE10010,Proteintech,China),一抗兔抗小鼠胶质瘤相关癌基因同源物1(glioma-associated oncogene homolog 1,Gli1)(ET1702-85,华安生物,中国),一抗兔抗小鼠Runt相关转录因子2(Runt-related transcription factor 2,Runx2)(ab192256,Abcam,美国),一抗兔抗小鼠Osterix(OSX)(ab209484,Abcam,美国),一抗兔抗小鼠CD86(ER1906-01,华安生物,中国),一抗兔抗小鼠CD206(ab64693,Abcam,美国),内源性过氧化氢酶阻断液(P0100A,Beyotime,中国),柠檬酸盐抗原修复液(H-3300,Vectorlab,美国),ABC-HRP试剂盒(PK-4000,Vectorlab,美国),DAB显色试剂盒(SK-4100,Vectorlab,美国),0.014英寸不锈钢圆丝(230-100,A.J.Wilcock,澳大利亚),37%磷酸酸蚀剂(Total Etch,Ivociar,德国),正畸粘接系统(Greengloo,Ormco,德国),流体树脂(Z350 XT,3M,美国),GelMA固化光源(EFL-LS-1601-405,EFL,中国),倒置显微镜(IX73,Olympus,日本),Micro-CT系统(μCT50,ScancoMedical,瑞士),石蜡包埋机(HistoCoreArcadiaH,LEICA,德国),石蜡切片机(HistoCoreBIOCUT,LEICA,德国),场发射扫描电子显微镜(SEM,Shimadzu,日本)。

1.3　实验方法

1.3.1　建立小鼠上颌扩弓及复发模型的实验分组　15只7周龄C57BL/6小鼠随机分为5组:对照组、扩弓后3 d(post expansion day 3,PED3)组、扩弓后7 d(post expansion day 7,PED7)组、保持14 d(retention,RET)组及复发7 d(relapse,REL)组,每组3只。对照组不进行扩弓,于0 d时处死;其余4组分别经历3 d扩弓、7 d扩弓、7 d扩弓+14 d保持及7 d扩弓+14 d保持+7 d复发,并于对应时间点处死(3、7、21、28 d)。扩弓、保持及复发时长参考既往文献[14]。戊巴比妥钠腹腔注射(40 mg/kg)麻醉小鼠后,将其仰卧位固定,放入开口器。用0.014英寸不锈钢圆丝制作扩弓簧,开大曲打开1 mm以产生约1 N力,用光固化树脂粘固于双侧切牙,即开始扩弓。针对保持组及复发组,扩弓后7 d时,使用树脂固定开大曲,保持14 d。针对复发组,在保持期结束时取出扩弓装置,进行7 d的复发。模型建立示意图见图1。

1.3.2　GelMA/P11/IL4@LIP的制备　按EFL GM-90试剂盒说明书配制5% GelMA溶液。采用薄膜水化法制备IL-4脂质体:将3.5 mg大豆卵磷脂与1.5 mg胆固醇溶于1 mL氯仿,经37 ℃旋蒸2 h形成脂质薄膜;用5 mL PBS水化,超声震荡10 min;加入1 μg IL-4粉末,经0.45 μm、0.22 μm滤膜3次,获得包被IL-4的脂质体溶液(IL4@LIP)。将IL4@LIP溶液与



a: illustration of mouse maxillary expansion, retention, and relapse; b: photographs showing the opening spring in its activated state, bonded to bilateral incisors to initiate maxillary expansion and secured with light-cure resin for retention

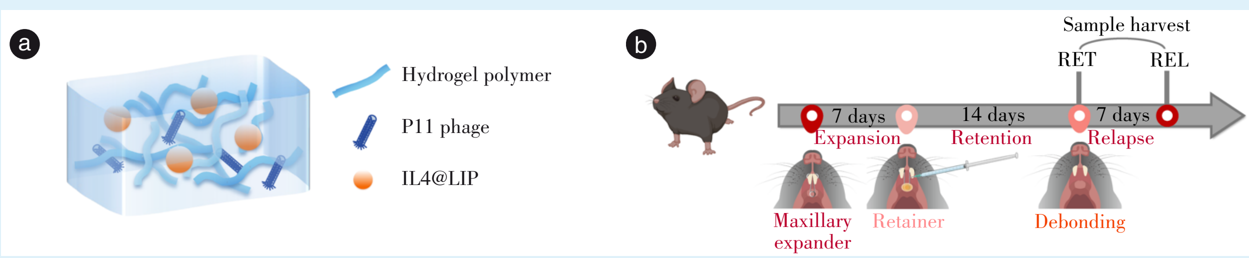
Figure 1　Mouse model of maxillary expansion and relapse

图 1　建立小鼠上颌扩弓及复发模型

5% GelMA 溶液按 1∶1 体积比混合得到 GelMA/IL4@LIP 溶液。将 P11 噬菌体以 10^6 pfu/μL 浓度溶于 GelMA 溶液或 GelMA/IL4@LIP 体系中，得到 GelMA/P11 或 GelMA/P11/IL4@LIP。

1.3.3　GelMA/P11/IL4@LIP 表面形貌观察及 IL-4 释放率检测　使用场发射扫描电子显微镜观察 GelMA/P11/IL4@LIP 的表面形貌。将 1 mL GelMA//P11/IL4@LIP 溶液置于透析袋中，并将之浸入 4 mL PBS 缓冲液中，37 °C 孵育。分别在 1、2、4、8、16、24 和 48 h 取出 1 mL 上清液，并补充等量 PBS 缓冲液。按照说明书，使用小鼠 IL-4 ELISA 试剂盒检测上清液中的 IL-4 蛋白浓度，以计算 IL-4 释放率。

1.3.4　GelMA/P11/IL4@LIP 材料的应用　将 24 只 7 周龄 C57BL/6 小鼠随机分为 4 组：空白对照组、GelMA 组、GelMA/P11 组及 GelMA/P11/IL4 组。24 只小鼠接受扩弓，扩弓后 7 d 时，使用树脂固定扩弓装置，进行 14 d 的保持，并分别于各组小鼠腭中缝区域注射 15 μL 相应材料（无菌生理盐水、GelMA 溶液、GelMA/P11 溶液、GelMA/P11/IL4@LIP 溶液），405 nm 光固化 30 s。21 d（保持期）时，每组随机选取 3 只小鼠处死；并拆除另外 3 只小鼠的扩弓装置，进行 7 d 的复发，最终于 28 d（复发期）处死；取小鼠的上颌骨及前颅部备用（图 2）。



a: schematic of GelMA/P11/IL4@LIP hydrogel. b: illustration of the maxillary expansion model and hydrogel injection. IL4: interleukin-4; LIP: liposome; RET: retention; REL: relapse; GelMA: gelatin methacryloyl

Figure 2　Composition of GelMA/P11/IL4@LIP and its application in the mouse model of maxillary expansion and relapse

图 2　GelMA/P11/IL4@LIP 材料组成及用于小鼠扩弓及复发模型

1.3.5　Micro-CT 分析腭中缝骨形成情况及扩弓量　采用 Micro-CT 扫描上颌骨及前颅部样本（电压 70 kVp、电流 200 μA、精度 10 μm），三维重建，并使用 μCT 50 系统软件测量上颌切牙近中牙槽嵴顶间距（inter-crestal distance，ICD）。根据复发期牙槽嵴顶间距较保持期减小约 50%，相应设置保持组与复发组的兴趣区域（region of interest，ROI）：保持组为 1 mm × 2 mm × 300 μm，复发组为 500 μm × 2 mm × 300 μm。分析 ROI 中的骨体积分数（bone volume/tissue volume ratio，BV/TV）和骨密度（bone mineral density，BMD）。

1.3.6　组织学及 TRAP 染色检测成骨、破骨情况　制取上颌骨及前颅部样本的石蜡切片。按试剂盒说明书行苏木精-伊红（hematoxylin-eosin staining， HE)染色、Masson染色及TRAP染色。

1.3.7　免疫组织化学染色(immunohistochemistry, IHC)检测巨噬细胞极化、干细胞募集及成骨情况　组织切片经脱蜡、复水、抗原修复、内源性过氧化氢酶阻断及5%山羊血清封闭后,4 ℃孵育一抗工作液过夜。一抗工作液浓度为:RUNX2(1∶200)、OSX(1∶400)、CD206(1∶200)、CD86(1∶100)及Gli1(1∶100)。次日室温下孵育相应的二抗工作液,随后ABC反应液孵育30 min,PBS洗净,DAB显色,苏木素复染细胞核。显微镜下观察采图。使用Image Pro Plus 6.0软件(Media Cybernetics,美国)分析。

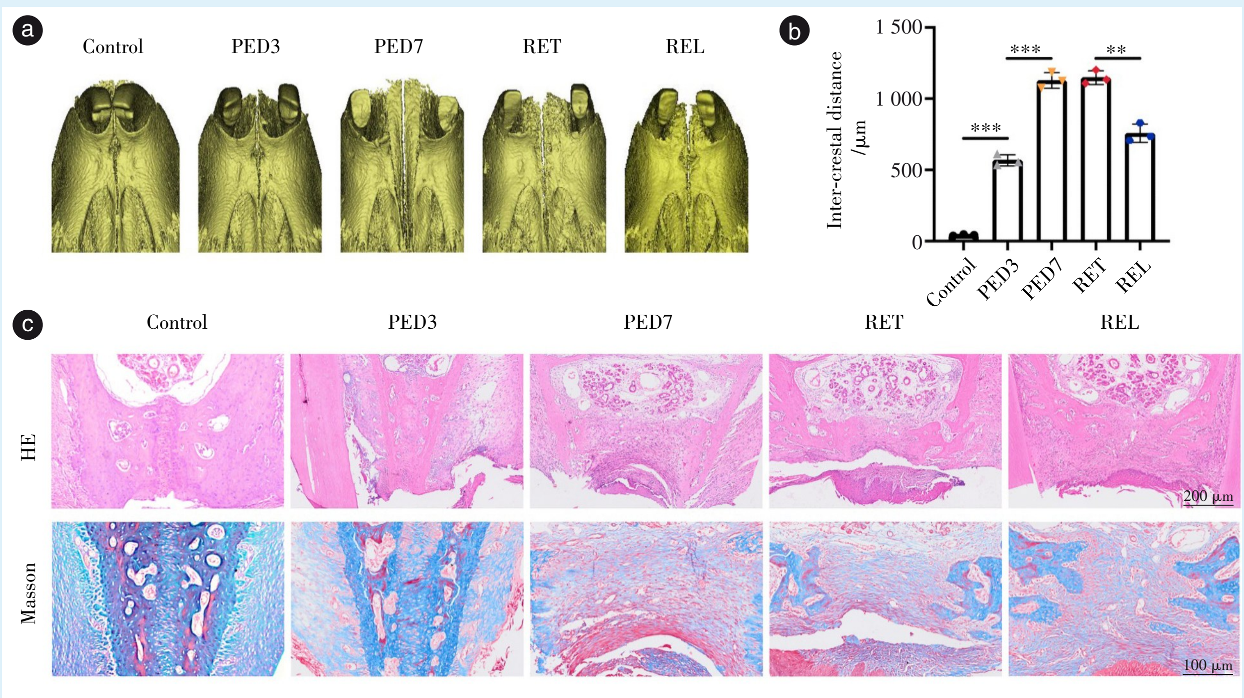
1.4　统计学分析

计量资料用均值±标准差表示。在正态性检验和方差齐性检验后,采用Tukey检验的单因素方差分析(one-way ANOVA)进行组间比较。使用GraphPad Prism 10进行统计分析,以 $P < 0.05$ 为组间差异具有统计学意义。

2　结　果

2.1　小鼠扩弓后出现明显复发

通过micro-CT三维重建,测量小鼠ICD。扩弓后7 d(PED7),ICD明显增加,且保持14 d后(RET)基本稳定;同时,腭中缝在扩弓后3 d及扩弓后7 d时被打开,之后缝隙逐渐变小,说明新骨在双侧腭骨边缘形成。但拆除扩弓装置后7 d(REL),即可观察到ICD较RET时明显缩小,出现复发(图3a&3b)(P =0.008)。H&E及Masson染色显示,扩弓后3 d时,切牙牙周膜间隙在扩弓力下增宽;扩弓后7 d时,腭中缝区域形成大量纤维结缔组织;保持期时,部分纤维结缔组织被新生骨代替;复发期时,腭中缝两侧骨小梁间距明显减小(图3c)。



a: micro-CT 3D reconstruction of the maxillae in different groups. b: inter-crestal distance of maxillary incisor mesial alveolar ridge of mice in different groups. The inter-crestal distance increased during expansion, but declined at relapse. n = 3. c: hematoxylin and eosin and Masson's trichrome staining of coronal sections of the maxillae of mice in different groups. Upper panel scale bar: 200 μm; lower panel scale bar: 100 μm. Control group: without expansion; PED3 group: post expansion day 3; PED7 group: post expansion day 7; RET group: retention; REL group: relapse.**: $P < 0.01$, ***: $P < 0.001$

Figure 3　Micro-CT and histological observation of the mouse model of maxillary expansion

图3　小鼠上颌扩弓模型micro-CT及组织学分析

2.2　小鼠扩弓后腭中缝M1巨噬细胞持续浸润、MSCs募集及成骨分化不足

IHC染色显示,腭中缝区域的 $CD86^+$ M1巨噬细胞数量随着扩弓时间延长逐渐增加,PED7时达到最大值,在保持期及复发期时数量与PED7比较仍无明显下降(P>0.05);而 $CD206^+$M2巨噬细胞数

量仅在保持期及复发期大幅上调（图4a & 4b）。TRAP染色显示，破骨细胞数量在扩弓后3 d即上调（$P < 0.001$），并在PED7、保持期及复发期逐渐回落（$P<0.01$）（图4c & 4d）。扩弓至复发全程，腭中缝区域Gli1⁺细胞数量始终维持在低水平，与对照组相比，差异无统计学意义（$P>0.05$）（图4e & 4f）。扩弓期，RUNX2和OSX表达水平比较低；保持期，RUNX2和OSX蛋白表达水平升高；但直至复发期才大幅上升（图4g & 4h）（$P < 0.001$）。

2.3　GelMA/P11/IL4@LIP的表征

基于小鼠扩弓后腭中缝区域持续性炎症、破骨活跃、MSCs成骨分化不足，拟应用GelMA/P11/IL4@LIP复合材料，靶向调控免疫微环境和成骨-破骨平衡。场发射扫描电子显微镜图像显示GelMA/P11/IL4@LIP表面形貌，呈粗糙多孔的网状结构（图5a）；ELISA检测结果显示复合材料负载的IL-4呈现先快后慢的释放趋势，在24 h达到最大释放量（图5b）。

2.4　GelMA/P11/IL4@LIP注射可减少小鼠上颌扩弓后复发

Micro-CT三维重建显示，保持期时，各处理组间ICD无明显差异。而复发期时，GelMA组与空白对照组ICD无明显差异，均较保持期时下降；而GelMA/P11组及GelMA/P11/IL4@LIP组ICD高于空白对照组，且GelMA/P11/IL4@LIP组数值最高（图6a & 6b）。保持期及复发期，GelMA/P11/IL4@LIP组BMD及BV/TV指数均较空白对照组提升（图6c）。HE及Masson染色显示，GelMA/P11组及GelMA/P11/IL4@LIP组新生骨小梁更多（图6d）。以上结果表明GelMA/P11溶液和GelMA/P11/IL4@LIP复合材料均能有效促进骨形成，以减少复发。

2.5　GelMA/P11/IL4@LIP注射调节局部免疫并促进MSCs募集及成骨分化

通过IHC染色验证复合材料对巨噬细胞、破骨细胞及MSCs的调控作用。在保持期GelMA/P11/IL4@LIP组中CD86⁺巨噬细胞数量明显少于其他3组（$P < 0.001$）。在复发期，GelMA/P11/IL4@LIP组中CD86⁺巨噬细胞数量进一步减少；而GelMA/P11组CD86⁺巨噬细胞数量最多（图7a & 7b）。保持期及复发期，GelMA/P11和GelMA/P11/IL4@LIP处理均上调CD206⁺巨噬细胞数量，差异具有统计学意义（$P < 0.001$）（图7c & 7d）。综上，P11噬菌体促进巨噬细胞M1极化，而IL4@LIP可及时促进巨噬细胞M2极化。保持期时，GelMA/P11/IL4@LIP组TRAP⁺破骨细胞数量最少，而复发期时，GelMA/P11组与GelMA/P11/IL4@LIP组数量相当（图7e & 7f），提示复发期末破骨活动趋于稳定。在保持期及复发期，GelMA/P11组与GelMA/P11/IL4@LIP组的Gli1⁺细胞数均提高，差异具有统计学意义（$P < 0.001$）（图7g & 7h）。GelMA/P11与GelMA/P11/IL4@LIP处理也增强了保持期及复发期RUNX2（图7i & 7j）与OSX（图7k & 7l）的蛋白表达，且GelMA/P11/IL4@LIP组的增强效果更显著。

3　讨　论

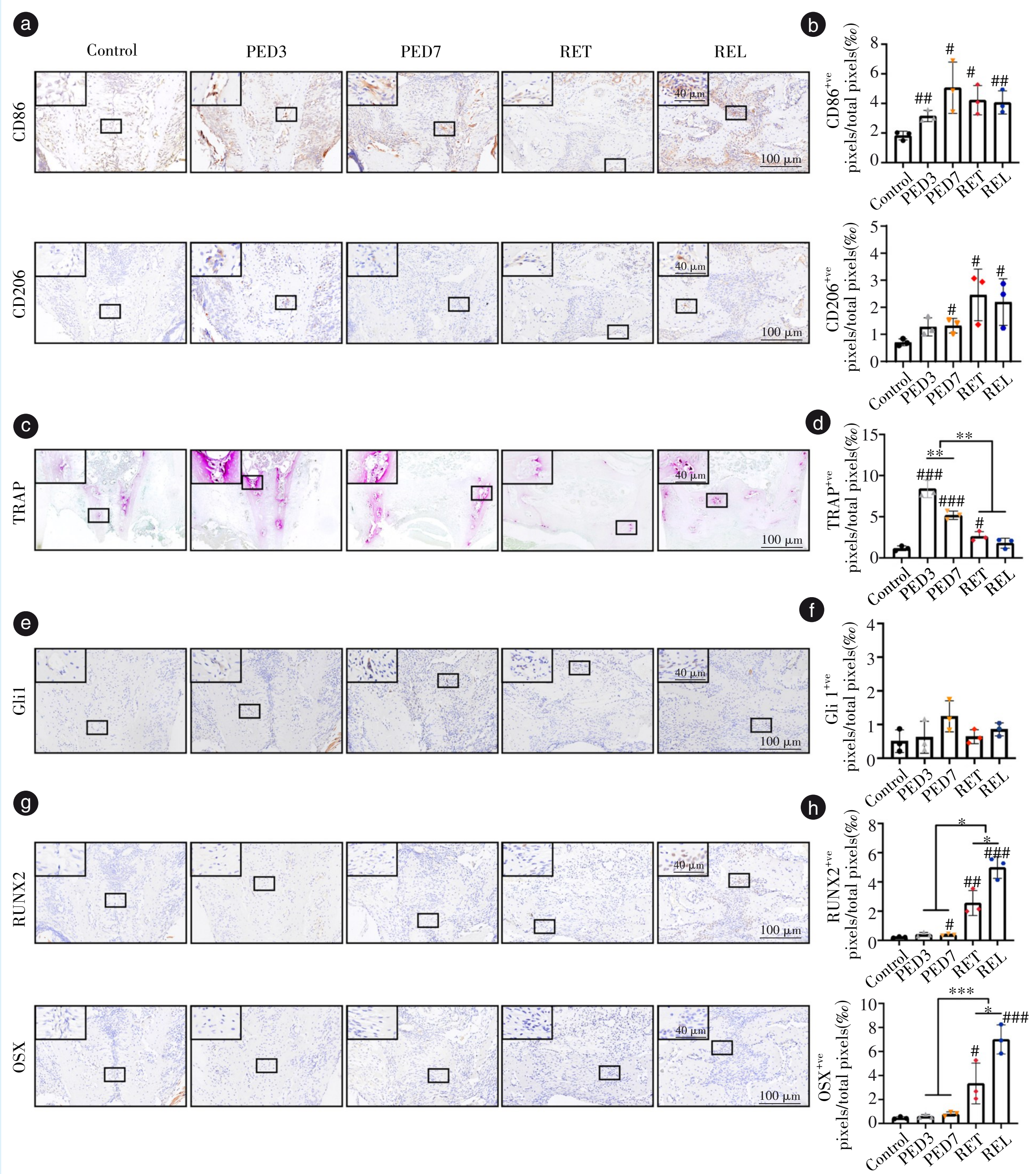
上颌扩弓时，当骨形成大于骨破坏，双侧腭骨边缘新骨沉积，上颌宽度会增加[15]；而骨形成不足时，双侧腭骨在腭部角化龈及颊肌的作用下向中缝复位[16]，则出现复发。为对抗复发，临床常进行过度矫治或延长保持时间，但这会加重患者不适[17]。因此，本研究的重点是如何在较短保持期内加速骨形成。本研究构建小鼠扩弓及复发模型，揭示局部免疫微环境及成骨/破骨活动的变化规律；并针对性合成了GelMA/P11/IL4@LIP复合材料。该材料可有效促进巨噬细胞M2极化、MSCs募集和成骨分化，促进骨形成。

3.1　小鼠扩弓及复发模型的构建

小鼠腭中缝区域主要由纤维细胞、胶原纤维及成骨细胞构成，腭中缝后部多见软骨细胞。传统大鼠上颌扩弓模型对磨牙区施力[15]；而作用于切牙的扩弓，以其长根为支抗，实现前腭中缝牵张成骨，能更准确地模拟青少年的骨膜成骨模式[18]，但既往研究多以大鼠为动物模型[14, 17]。本研究构建小鼠上颌扩弓及复发模型，因小鼠与人类基因的高度相似性[19]，更能模拟人体情况。本研究采用切牙ICD评估扩弓量，以保持期及复发期2次测量的差值代表复发量，可有效排除牙齿倾斜移动的影响[17]。

3.2　GelMA/P11/IL4@LIP促进局部MSCs募集以预防上颌扩弓后复发

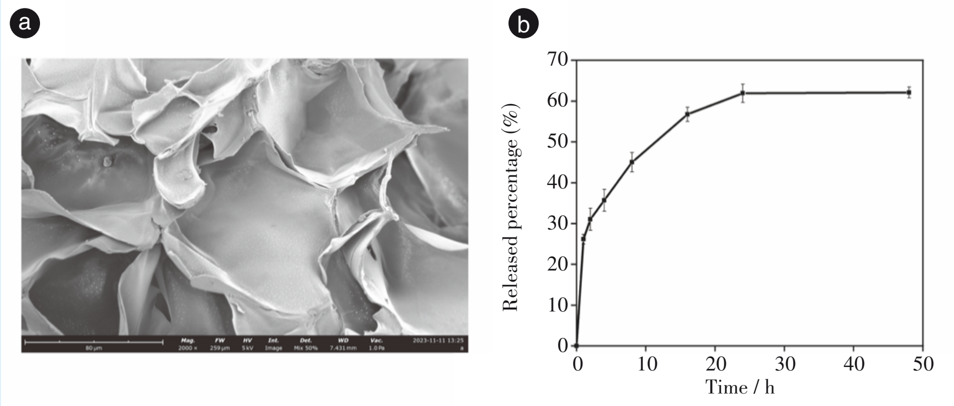
复发期ICD较保持期显著下降。免疫组化染色显示，腭中缝区成骨分化标志物RUNX2及OSX[20]表达量在保持期和复发期才逐步上升，说明成骨迟缓。因此，进一步探究如何在有限保持期内促进成骨以减少复发。既往研究采用多种途径促进腭中缝骨形成，以预防上颌扩弓后复发，如灌服乳铁蛋白溶液[21]，局部注射葛根素[22]和皮下注射甲状旁腺素[23]等。这些方法需要多次给药，



a & b: immunohistochemical staining of CD86 and CD206 and the relative ratio of the positive area; c & d: TRAP staining and ratio of TRAP+ osteoclast area; e & f: immunohistochemical staining of Gli1 and the relative ratio of the positive area; g & h: immunohistochemical staining of RUNX2 and OSX and the relative ratio of positive area; a, c, e, g: the area within the small black box in each image is magnified and shown in the upper left corner. Scale bars: 100 μm (low-magnification view) and 40 μm (magnified view). b, d, f, h: n = 3. CD86: cluster of differentiation 86; CD206: cluster of differentiation 206; TRAP: tartrate resistant acid phosphatase; Gli1: glioma-associated oncogene homolog 1; RUNX2: Runt related transcription factor 2; OSX: osterix. Control group: without expansion; PED3 group: post expansion day 3; PED7 group: post expansion day 7; RET group: retention; REL group: relapse. * indicates pairwise comparison analysis, *: P < 0.05, **: P < 0.01, ***: P < 0.001. Compared with the control group, #: P < 0.05, ##: P < 0.01, ###: P < 0.001

Figure 4　Macrophage polarization, stem cell recruitment, osteogenesis, and osteoclastogenesis in the midpalatal suture area of maxillary expansion in mice

图4　小鼠上颌扩弓腭中缝区域巨噬细胞极化、干细胞募集、成骨及破骨情况



a: GelMA/P11/IL4@LIP observed under scanning electron microscope revealing a rough, porous structure(×2 000); b: IL-4 release rate of GelMA/P11/IL4@LIP. IL-4 was gradually released until plateauing at 24 h

Figure 5　Surface topography and the IL-4 release rate of GelMA/P11/IL4@LIP

图5　GelMA/P11/IL4@LIP复合材料表面形貌和IL-4释放率

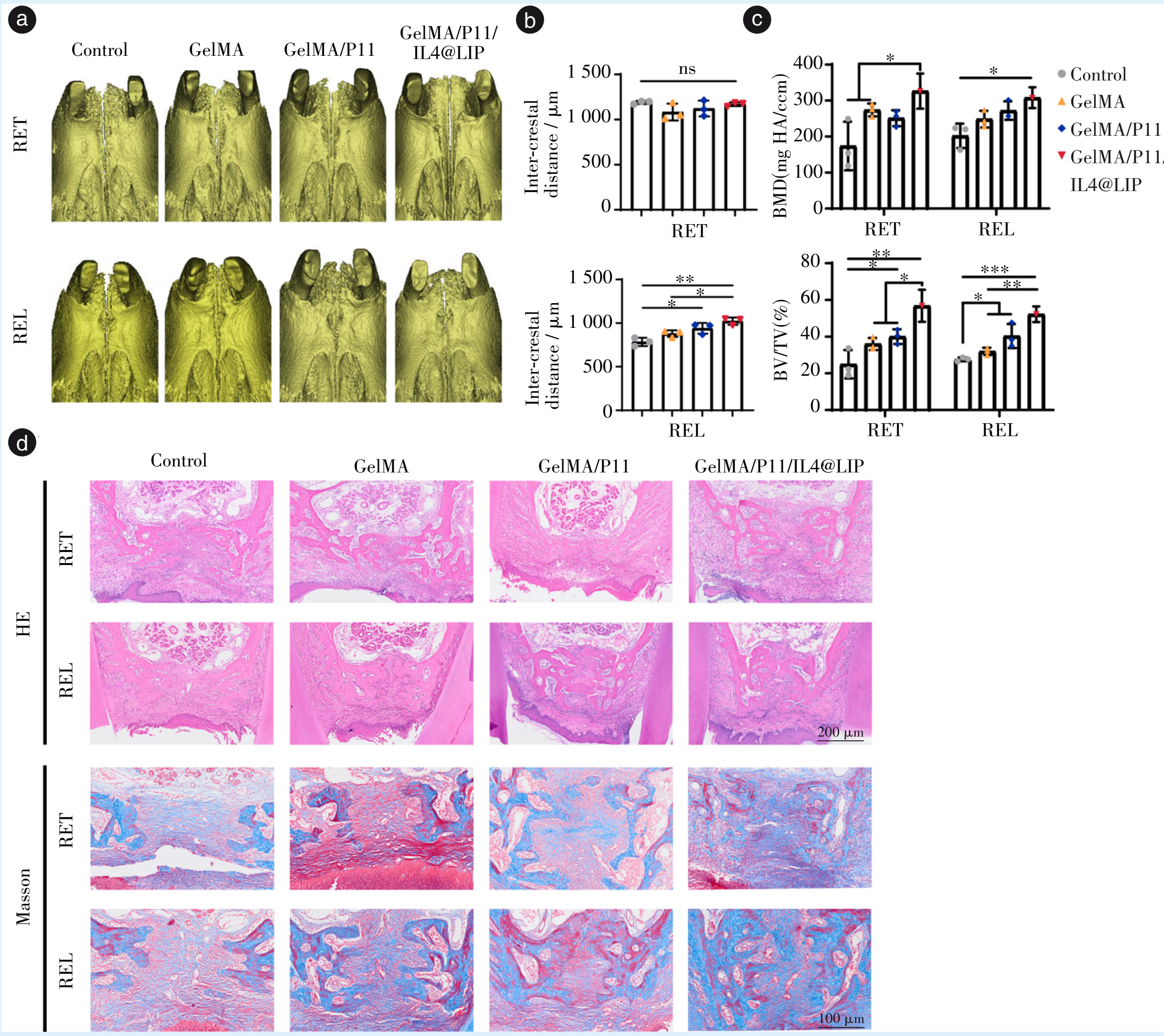
且系统给药方式可能存在全身副作用。而组织工程材料可靶向作用于目标区域，已被应用于上颌扩弓后复发的预防，如介孔生物活性玻璃/纤维蛋白胶复合水凝胶[14]。

上述方法通过注射水凝胶，实现活性因子局部缓释，调节成骨/破骨平衡。但它们未解决局部MSCs募集不足的问题。Gli1是Hedgehog信号的转录激活因子，参与多种细胞生物学过程，是MSCs的理想标志物。Gli1$^+$ MSCs介导颅颌面的骨膜内成骨与软骨内成骨过程[24]。小鼠扩弓过程中，Gli1$^+$ MSCs数量始终较少，这可能是骨形成不足的根本原因。当前基于MSCs的骨组织工程主要采取外源性细胞递送或内源性细胞招募两种策略。外源性细胞存在存活率低、迁移能力差、成本高等问题[25]。因此，更多研究聚焦于能募集内源性MSCs的生物材料。多种细胞因子被用来招募MSCs，包括基质细胞衍生因子-1[26]、P物质[27]、血小板衍生生长因子-BB[28]及白细胞介素-8[29]等。但这些重组生长因子对MSCs的募集缺乏特异性，且价格昂贵、半衰期短。而M13丝状噬菌体生物安全性高、耐受性好且成本低，可用于MSCs招募，这依赖噬菌体展示技术实现[30]。

本课题组前期从M13噬菌体展示肽库中筛选出特异性靶向BMSCs的P11单克隆。P11可促进BMSCs增殖、迁移及成骨分化；也可促进巨噬细胞M1极化，并促使巨噬细胞募集BMSCs[9]。负载P11噬菌体的有序排列GelMA支架能促进小鼠股骨缺损再生[10]。

3.3　GelMA/P11/IL4@LIP促进巨噬细胞M2极化以预防上颌扩弓后复发

炎症反应与扩弓中的骨改建密切相关。骨折时，中性粒细胞及M1巨噬细胞浸润损伤区域，释放促炎细胞因子，并清除组织碎片和死细胞。随后，巨噬细胞在IL-4、Il-10等抗炎因子的作用下向M2极化，炎症消退；MSCs在趋化因子的作用下被募集至损伤区域，促进组织修复[31]。于大鼠腭中缝注射M1巨噬细胞来源的细胞外囊泡混悬液，可促进破骨和腭中缝打开[4]。牵张力促进巨噬细胞M2极化。M2巨噬细胞条件培养基促进腭骨成骨细胞表达碱性磷酸酶(alkaline phosphatase，ALP)及Ⅰ型胶原(type Ⅰ collagen，Col1)，并下调核因子κ-B配体受体致活剂(receptor activator of nuclear factor kappa-B ligand，RANKL)/骨保护素(osteoprotegerin，OPG)比值以抑制破骨活动[5]。这说明M2巨噬细胞在扩弓后期发挥重要作用，M1向M2亚型的转变标志着骨平衡向成骨侧偏移。P11噬菌体可诱导巨噬细胞M1极化[9]。为拮抗P11的免疫原性，引导巨噬细胞适时向M2极化，引入IL-4脂质体。脂质体是常用的药物载体，具有优秀的生物相容性和载药释药性能[32]。IL-4注射可减少大鼠正畸牙移动后的复发[33]。负载IL-4脂质体的聚左旋乳酸微球(IL-4/Ls/PLLA)可诱导巨噬细胞M2极化，促进新西兰兔颅骨缺损及上颌窦骨缺损修复[34]。本研究中，复发期，GelMA/P11组CD86$^+$ M1巨噬细胞数量最多，与前期体外实验相符。保持及复发期，GelMA/P11组较空白及GelMA对照组



a: micro-CT 3D reconstruction of mouse maxillae in retention and relapse phases. b: inter-crestal distance of maxillary incisor mesial alveolar ridge in the retention and relapse phases, respectively. The GelMA/P11/IL4@LIP group showed the widest inter-crestal distance at relapse. *n* = 3. c: bone mineral density and bone volume/tissue volume ratio (BV/TV) of mice maxillae in different groups measured in the retention and relapse phases, respectively. The GelMA/P11/IL4@LIP group showed the highest bone mineral density and BV/TV values at retention and relapse. *n* = 3. d: hematoxylin and eosin and Masson's trichrome staining of coronal sections of the mice maxillae in different groups. Twenty-four 7-week-old C57BL/6 mice were randomly divided into four groups: the control group, the GelMA group, the GelMA/P11 group, and the GelMA/P11/IL4@LIP group. All 24 mice underwent palatal expansion, and 7 days post-expansion, the expansion device was fixed with resin for 14 days of retention. Each group received a 15 μL injection of the corresponding material (sterile saline, GelMA solution, GelMA/P11 solution, or GelMA/P11/IL4@LIP solution) into the palatal suture region. RET: retention; REL: relapse. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$

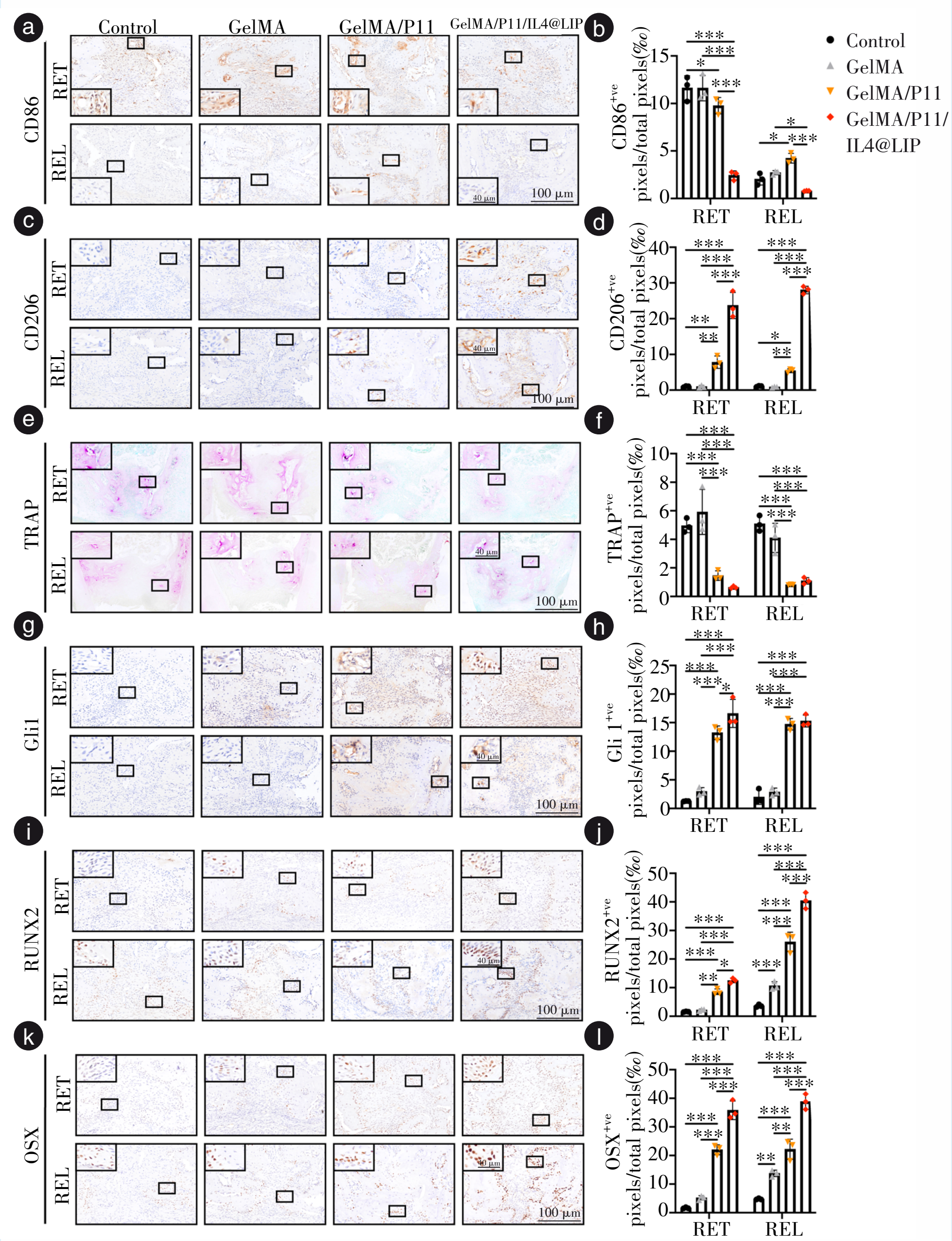
Figure 6　Effect of GelMA/P11/IL4@LIP injection on bone formation in the midpalatal suture area and expansion amount after maxillary expansion in mice

图6　GelMA/P11/IL4@LIP注射对小鼠上颌扩弓后腭中缝区域骨形成情况及扩弓量的影响

$CD206^+$ M2巨噬细胞更多，可能因为P11噬菌体持续募集巨噬细胞，使其总量增多。而GelMA/P11/IL4@LIP组显著下调M1巨噬细胞，并上调M2巨噬细胞数量。综上，GelMA/P11/IL4@LIP复合材料有效促进巨噬细胞M1向M2表型转换。

3.4　P11噬菌体材料在颌面部骨缺损修复中的应用潜力

颅颌面骨与长骨发育及损伤修复方式不同，分别以膜内成骨和软骨内成骨为主。颅颌面骨(除下颌骨髁突及颅底软骨)源自外胚层的神经嵴



a & b: immunohistochemical staining of CD86 and the relative ratio of the positive area. c & d: immunohistochemical staining of CD206 and the relative ratio of the positive area. e & f: TRAP staining and the ratio of the TRAP+ osteoclast area. g & h: immunohistochemical staining of Gli1 and the relative ratio of the positive area. i & j: immunohistochemical staining of RUNX2 and the relative ratio of the positive area. k & l: immunohistochemical staining of OSX and the relative ratio of the positive area. a, c, e, g, i, k: the area within the small black box in each image is magnified and shown in the upper left or lower left corner. Scale bars: 100 μm (low-magnification view) and 40 μm (magnified view). b, d, f, h, j, l: n = 3. CD86: cluster of differentiation 86; CD206: cluster of differentiation 206; TRAP: tartrate resistant acid phosphatase; Gli1: glioma-associated oncogene homolog 1; RUNX2: Runt related transcription factor 2; OSX: osterix. Twenty-four 7-week-old C57BL/6 mice were randomly divided into four groups: the control group, the GelMA group, the GelMA/P11 group, and the GelMA/P11/IL4@LIP group. All 24 mice underwent palatal expansion, and 7 days post-expansion, the expansion device was fixed with resin for 14 days of retention. Each group received a 15 μL injection of the corresponding material (sterile saline, GelMA solution, GelMA/P11 solution, or GelMA/P11/IL4@LIP solution) into the palatal suture region. RET: retention; REL: relapse. *: P <0.05, **: P <0.01, ***: P <0.001

Figure 7　Effects of GelMA/P11/IL4@LIP injection on macrophage polarization, stem cell recruitment, osteogenesis, and osteoclastogenesis in the midpalatal suture region after maxillary expansion in mice

图7　GelMA/P11/IL4@LIP注射对小鼠上颌扩弓后腭中缝区域巨噬细胞极化、干细胞募集、成骨及破骨情况的影响

细胞，而长骨源自轴旁中胚层及侧板中胚层[35-36]。颅骨缺损修复主要依赖膜内成骨[37]；近期研究发现促软骨内成骨的生物材料在颅骨缺损修复也可发挥重要作用[38-39]。长骨缺损修复方式则取决于损伤严重程度和治疗方式。范围小、稳定性强的缺损倾向于膜内成骨；范围大、稳定性弱的缺损倾向于软骨内成骨[40]。骨缝是颅颌面骨的特有结构。腭中缝牵张成骨过程中，腭中缝后份的软骨结构被分开，骨膜细胞迁移至软骨表面，发生膜内成骨[17]。课题组前期研究发现GelMA/P11噬菌体材料可促进小鼠股骨缺损修复[10]。而本研究在小鼠上颌扩弓模型上，验证了P11噬菌体在颌面部的应用潜力。

本研究尚处于初步验证阶段，后续研究将检测该材料的全身安全性，并在大动物扩弓模型中进行验证[41]。此外，后续将利用转录组测序技术，筛选并验证该材料促进口颌面部间充质干细胞成骨分化的关键信号通路，完善该材料发挥作用的分子机制。

本研究构建了基于P11噬菌体和IL-4脂质体的可注射水凝胶，并验证了该材料对上颌扩弓后复发的预防效果。其中，GelMA溶液经光交联形成稳定载体，P11噬菌体募集间MSCs，IL-4脂质体调节局部免疫微环境，共同促进腭中缝骨形成。综上，本研究揭示了临床上颌扩弓后复发的可能机制，并为其预防提供了新策略。

【Author contributions】 Li RZ performed the experiments, analyzed the data and wrote the article. Liu RJ and Wang XM performed the experiments, analyzed the data and revised the article. Pu XM, Yin X and Zou SJ designed the study and revised the article. All authors read and approved the final manuscript as submitted.

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