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·基础研究·

人脐带间充质干细胞培养上清液促口腔黏膜愈合

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[摘 要] **目的** 探讨人脐带间充质干细胞(hUCMSCs)培养上清液对口腔黏膜愈合的促进作用。**方法** 取1例足月生产健康产妇的新鲜脐带,分离hUCMSCs并培养,获取hUCMSCs培养上清液。取20只SD大鼠,在其口腔黏膜内局部注射顺铂注射液制备口腔黏膜炎模型,共18只造模成功。将造模成功的大鼠按照随机数字表法分为上清液治疗组(n=9)和对照组(n=9),分别予以hUCMSCs培养上清液、生理盐水治疗。观察干预前后溃疡数量、总溃疡面积和干预后溃疡愈合率,并采用HE染色观察2组残留溃疡组织病理改变。**结果** 细胞形态学和分子表型流式细胞仪测试结果证实hUCMSCs分离成功。与干预前比较,干预后对照组溃疡数量、总溃疡面积变化无统计学差异(P>0.05),上清液治疗组溃疡数量减少、总溃疡面积缩小(P<0.05),且干预后上清液治疗组溃疡数量少于对照组、总溃疡面积小于对照组、溃疡愈合率高于对照组(P<0.05)。上清液治疗组大鼠口腔黏膜细胞层次基本恢复、界限清晰,小血管数目多;对照组上皮全层丧失,符合顺铂导致的口腔黏膜炎病理改变。**结论** hUCMSCs培养上清液可促进化疗所致的口腔黏膜炎大鼠创面愈合,减轻病理改变。

[关键词] 人脐带间充质干细胞;口腔黏膜炎;溃疡面积;溃疡愈合
[中图分类号] R363.1+3;R781.5+1 [文献标志码] A [收稿日期] 2025-04-11

Human umbilical cord mesenchymal stem cell culture supernatant promotes oral mucosal healing

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Abstract: Objective To explore the promoting effect of human umbilical cord mesenchymal stem cells (hUCMSCs) culture supernatant on oral mucosal healing. **Methods** Fresh umbilical cord tissue was obtained from one healthy full-term parturient. hUCMSCs were isolated and cultured, and then the culture supernatant of hUCMSCs was collected. Twenty SD rats were selected, and the model of oral mucositis was established by local injection of cisplatin into the oral mucosa. A total of 18 rats were successfully modeled. The rats with successful modeling were divided into the supernatant treatment group (n=9) and the control group (n=9) according to the random number table method, and were treated with hUCMSCs culture supernatant and normal saline, respectively. The number of ulcers, the total ulcer area

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before and after the intervention, and the ulcer healing rate after the intervention were observed. HE staining was used to observe the pathological changes of the residual ulcer tissues in the two groups. **Results** The results of flow cytometry tests on cell morphology and molecular phenotype confirmed the successful isolation of hUCMSCs. Compared with before intervention, the changes in the number of ulcers and total ulcer area in the control group after intervention showed no statistically significant difference ($P>0.05$). In the supernatant treatment group, the number of ulcers decreased and the total ulcer area shrank ($P<0.05$). Moreover, after intervention, the number of ulcers in the supernatant treatment group was less than that in the control group, the total ulcer area was smaller than that in the control group, and the ulcer healing rate was higher than that in the control group ($P<0.05$). In the supernatant treatment group, the layers of rat oral mucosal cells were basically restored with clear boundaries and an increased number of small blood vessels. In the control group, the entire epithelium was lost, consistent with the pathological changes of cisplatin-induced oral mucositis. **Conclusion** The hUCMSCs culture supernatant can promote wound healing and alleviate pathological changes in rats with chemotherapy-induced oral mucositis.

Keywords: human umbilical cord mesenchymal stem cells; oral mucositis; ulcer area; ulcer healing

口腔黏膜炎是化疗患者常见的不良反应,发生率为40%~70%,其中持续和反复发作者超50%,可影响进食及营养状态,加重患者的痛苦[1]。但是目前针对口腔黏膜炎常用的细胞因子、激光、冷冻、抗氧化剂与抗微生物肽疗法的效果难以令人满意[2-3],仍需探索新的治疗方案。人脐带间充质干细胞(human umbilical cord mesenchymal stem cells,hUCMSCs)是一类多能干细胞,具有高度自我更新能力,还可多向分化,且hUCMSCs较骨髓间充质干细胞及其他组织来源间充质干细胞的生物学特性更佳,在组织修复方面已得到了应用与肯定[4-5]。有报道指出,hUCMSCs条件培养基可促进白血病患儿口腔黏膜炎的创面愈合,且其效果优于重组人粒细胞巨噬细胞刺激因子凝胶[6];也有研究证实,hUCMSCs的细胞外囊泡可促进大鼠口腔黏膜炎愈合[7];另有研究表明,间充质干细胞条件培养液存在抗炎、促进细胞增殖等作用,在炎症性疾病中的应用效果确切[8]。据此推测,将hUCMSCs培养上清液用于治疗化疗引起的口腔黏膜炎可能有利于促进口腔黏膜愈合,但该推论仍需验证,且其作用机制也需要进一步探讨。基于此,本研究开展大鼠实验分析上述问题,旨在为化疗所致的口腔黏膜炎的临床防治研究提供新思路。

1 材料与方法

1.1 材料

健康产妇1例,28岁,单胎,足月经阴道分娩(孕周40周),取脐带于一次性无菌袋中保存备用。本研究已经过我院伦理委员会审批(批准号:院准字2023年第014号)。孕妇本人对本研究知情同意。

20只SD大鼠,雌雄各半,6~9周龄,体质量180~270 g,购自北京希诺因生物技术有限公司[许可证号:SCXK(京)2022-0006],常规适应性喂养1周。本实验已经过甘肃省实验动物管理委员会审批(批准号:GSPEAMC2023-007)。

顺铂注射液(江苏豪森药业,批号:202305118);DMEM培养基(美国Gibco公司,批号:2304125071);胎牛血清(上海一研生物科技有限公司,批号:C2023011);乙醇溶液(国药集团化学试剂有限公司,批号:u202302603);磷酸盐缓冲液(phosphate buffer saline,PBS;深圳子科生物科技有限公司,批号:2317133A);胰蛋白酶-乙二胺四乙酸溶液(深圳子科生物科技有限公司,批号:2023147C);藻红蛋白(phycoerythrin,PE)荧光素(上海士锋生物科技有限公司,批号:2301052);苏木素-伊红(hematoxylin-eosin,HE)染色试剂盒(武汉百浩天生物科技有限公司,批号:2212157)。

HF90/HF240型CO_2培养箱(上海力申科学仪器有限公司);CTL535R型离心机(湖南湘立科学仪器有效公司);primovert. iLED型倒置显微镜(卡尔蔡司上海管理有限公司);流式细胞仪(美国BD公司);MDF-86v588型超低温冰箱(安徽中科都菱商用电器股份有限公司);OLYMPUS BX43型光学显微镜(奥林巴斯中国有限公司)。

1.2 方法

hUCMSCs的分离、培养与鉴定方法:产妇分娩完成后取新鲜脐带1 cm,4 h内采用含10%胎牛血清的DMEM培养基于4 ℃、5%CO_2培养箱中培养。于超净工作台将脐带组织浸入75%乙醇溶液30 s,PBS重复冲洗,去除表面的血液、脂肪和杂质。按照上述条件继续培养,剔除血管与内膜组织并用PBS冲洗数次。将组织块剪碎,大小约1 mm^3,接种于15 cm直径的大培养皿。加入上述培养液5 mL,于37 ℃、5% CO_2培养箱中过夜。次日加入上述培养液10 mL,继续同等条件下培养3~5 d。待组织块贴壁后,半量换液,每7 d更

换1次培养液,14 d后将组织块剔除。全血细胞贴壁融合至80%时,取胰蛋白酶-乙二胺四乙酸消化细胞,按照1∶3传代培养。细胞融合度达90%时,再传代培养至第5代。取第3代细胞于倒置显微镜下观察形态,并用流式细胞仪检测分子表型,撇去培养液,消化、收集细胞,加入PBS,以1 000 r/min离心5 min,弃上清,重复2次。重悬细胞,测定分子表型,包括CD19、CD34、CD45、CD73、CD90、CD105,均以PE荧光素标记分子抗体,振荡混匀后避光孵育20 min,上机检测,设对应荧光素标记的鼠IgG抗体为同型对照。

hUCMSCs培养上清液制备:将生长良好的hUCMSCs接种于细胞培养瓶内,细胞融合度达80%后加入无血清DMEM培养液,于37 ℃、5% CO_2培养箱中培养72 h。取上清液经0.22 μm滤膜过滤、分装,于-80 ℃超低温冰箱保存备用。

化疗所致口腔黏膜炎模型制备:取20只SD大鼠,在每只大鼠右侧口腔颊膜黏膜内注射顺铂注射液1.25 mg/kg,每只注射50 μL[9]。禁食24 h,观察口腔溃疡形成情况,共18只造模成功,仅注射等量生理盐水的8只大鼠均未见口腔溃疡形成。

样本量计算、分组及干预:本实验属于优效性检验,样本量计算公式:$n=(Z_{\alpha/2}+Z_{\beta})^2\times p\times(1-p)/\triangle^2$,其中$Z_{\alpha/2}$、$Z_{\beta}$查表可得(分别取值1.96、0.84),p为预计事件发生概率[根据预实验取溃疡愈合率为0.529(18/34)],△为预期效应的最小差异(取0.35),脱落率设为10%,故n至少为18。本研究中共18只大鼠造模成功,符合上述样本量计算结果,因此研究结果可靠。将造模成功的18只大鼠按照随机数字表法分为上清液治疗组和对照组,每组9只大鼠。上清液治疗组予以hUCMSCs培养上清液均匀涂抹于大鼠口腔溃疡处和周围组织,对照组予以生理盐水均匀涂抹于大鼠口腔溃疡处和周围组织,每天3次,共7 d。统计干预前后溃疡数量、总溃疡面积和干预后溃疡愈合率。

干预后残留溃疡组织病理改变观察:取各组残留的口腔溃疡组织置于福尔马林中固定24 h,脱水后制成石蜡组织块并切片(片厚4 μm)。HE染色试剂盒染色,氨水返蓝,苏木精复染,PBS冲洗,光学显微镜下观察残留溃疡组织病理改变情况。

1.3 统计学分析

数据采用SPSS 21.0软件分析。以*K-S*法检验计量资料的正态性分布,服从正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用独立样本t检验,组内比较采用配对t检验。不服从正态分布的计量资料以中位数(四分位间距)[$M(Q_1,Q_3)$]表示,组间比较采用秩和检验,组内比较采用配对设计的秩和检验。计数资料以率(%)表示,组间比较采用χ^2检验。$P<0.05$为差异有统计学意义。

2 结果

2.1 hUCMSCs的鉴定

倒置显微镜下可见细胞呈长梭形、多边型、纺锤样,符合典型间充质干细胞形态,见图1;流式细胞仪检测发现,细胞CD19、CD34、CD45表型均呈低表达(1.08%、0.76%、2.78%),而CD73、CD90、CD105表型均呈高表达(89.39%、90.28%、88.43%),见图2。

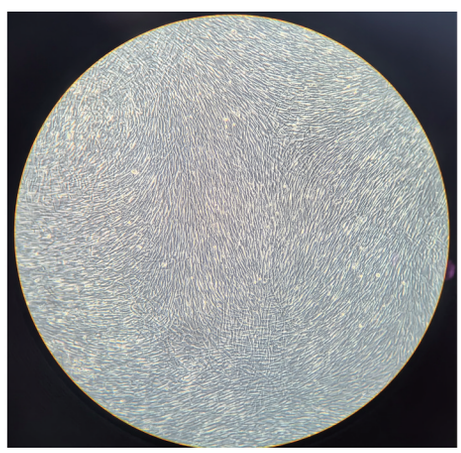


图1 细胞形态学观察(×100)

2.2 2组大鼠干预前后溃疡数量、总溃疡面积和干预后溃疡愈合率比较

与干预前比较,干预后对照组大鼠溃疡数量、总溃疡面积变化无统计学差异($P>0.05$),上清液治疗组大鼠溃疡数量减少、总溃疡面积缩小($Z=4.583$,$P=0.026$;$t=7.697$,$P<0.001$),且干预后上清液治疗组大鼠溃疡数量少于对照组,总溃疡面积小于对照组,溃疡愈合率高于对照组($P<0.05$),见表1。

2.3 2组大鼠干预后残留溃疡组织病理改变情况比较

上清液治疗组大鼠口腔黏膜结构基本正常,有增厚,上皮钉突多,细胞层次基本恢复,界限清晰,小血管数目多,有散在炎性细胞;对照组大鼠上皮全层丧失,棘细胞层崩解,钉突不明显,溃疡底部深入肌层,肌纤维灶性坏死,部分血管扩张,有点状出血灶,在坏死灶周围有大量炎性细胞浸润,见图3。

3 讨论

顺铂是常用的化疗药物,但是在杀灭癌细胞的同时也会对正常细胞造成损伤,不仅能阻断口腔上皮细

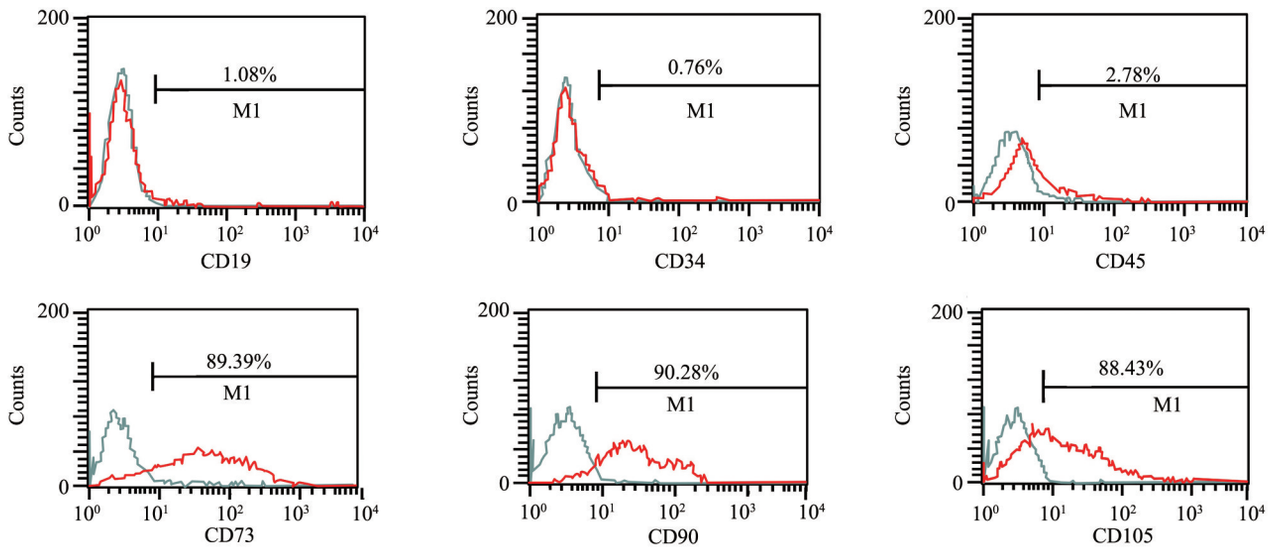
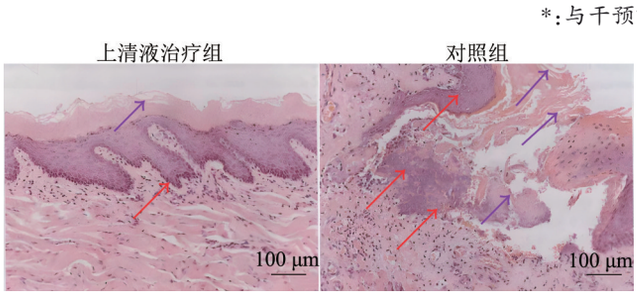


图2 细胞分子表型鉴定

表1 干预前后大鼠溃疡数量、总溃疡面积和干预后溃疡愈合率比较

组别	n	溃疡数量(个)		总溃疡面积(cm^2)		溃疡愈合[个(%)]
		干预前	干预后	干预前	干预后	
上清液治疗组	9	4(3.0,4.0)	0(0,1.0)*	1.15±0.22	0.53±0.10*	30/34(88.24)
对照组	9	4(3.0,4.5)	3(3.0,4.0)	1.09±0.20	0.98±0.18	6/34(17.65)
$Z/t/\chi^2$		0.176	4.769	0.605	6.556	34.000
P		0.854	0.024	0.553	<0.001	<0.001

*:与干预前比较,P<0.05



紫色箭头:上皮层;红色箭头:炎性细胞浸润

图3 干预后大鼠残留溃疡组织病理改变观察

胞生长和增殖,还会影响口腔黏膜上皮细胞的分裂与增殖,进而引起口唇、双颊、口底和上颚等部位黏膜溃疡[10-12]。本研究中对照组大鼠干预后残留口腔溃疡组织HE染色结果符合化疗所致口腔黏膜炎的病理特征[13],也证实了本研究采用顺铂注射法可建立化疗所致的口腔黏膜炎模型。

本研究中细胞形态学观察和流式细胞仪检测结果均证实hUCMSCs被成功分离,同时本研究还发现,hUCMSCs培养上清液可促进化疗所致的口腔黏膜炎创面修复,减小溃疡面积,促进溃疡愈合。hUCMSCs可激活体内本处于休眠状态的干细胞,参与受氧化或有害代谢物质损伤的组织修复,并调控自由基应激反应,使得损伤组织快速愈合[14];hUCMSCs还可分泌营养因子,促使损伤组织内细胞增殖,迅速恢复组织功能,并能通过调节免疫功能减轻创伤组织的炎症反应[15]。另外,hUCMSCs可调节代谢,提高机体的代谢效率,进而加快代谢废物运转与排泄,并促进营养因子吸收和利用,这也是修复创伤组织的重要途径。本研究中HE染色结果也显示,hUCMSCs上清液治疗可减轻口腔黏膜炎形态学改变,与上述报道及相关分析一致。既往多采用hUCMSCs修复外伤创面、促进牙再生[16-18],也有研究发现hUCMSCs可通过Wnt通路加速肠干细胞与上皮细胞再生、并促进结肠炎肠黏膜愈合[19],但利用hUCMSCs培养上清液修复口腔黏膜炎溃疡创面的报道鲜见,本研究在该方面具有创新性。分析hUCMSCs培养上清液发挥疗效的原因,可能是由于上清液中不仅含有hUCMSCs,具有促进创面愈合的能力,并且还存在大量的生物活性因子,包括碱性成纤维细胞生长因子、转化生长因子、血管内皮生长因子、肝细胞生长因子、胰岛素样生长因子等,而且hUCMSCs培养上清液中还有大量外泌体,其中含有大量蛋白质、mRNA与miRs,不仅能传递遗传信息,还可调控靶细胞功能,从而促进创面愈合[20-21]。

综上,本研究成功分离了hUCMSCs,hUCMSCs培养上清液可促进化疗所致的口腔黏膜炎大鼠创面愈合,减轻病理改变。然而本研究仍有一些不足:hUCMSCs培养上清液促进口腔黏膜炎大鼠溃疡愈合

的具体作用机制仍有待进一步探讨,可作为后续的研究方向;同时,本研究未观察远期疗效,该方案的远期疗效尚不能确定,后续应延长观察时间以评价其远期疗效(如瘢痕形成、功能恢复等);化疗所致的口腔黏膜炎动物模型与患者有明显不同,如各种生长因子及细胞因子的序列与结构差异等,可能会干扰研究结果,故hUCMSCs培养上清液在化疗所致的口腔黏膜炎患者中应用的可行性仍需要进一步探讨;本研究仅取1例产妇的新鲜脐带进行实验,可能存在样本选择偏倚,且实验结果也受个体差异的影响,建议后续扩充临床样本,以获得更可靠的结果。

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