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不同氧浓度对骨髓源内皮祖细胞分泌促血管新生相关生长因子的影响*

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摘要 目的:观察培养环境不同氧浓度对骨髓源内皮祖细胞分泌促血管新生相关生长因子的影响。**方法:**利用密度梯度离心技术分离 SD 大鼠骨髓单个核细胞,向内皮祖细胞进行诱导分化、扩增、培养和鉴定。然后在不同氧浓度(1%,5%,21%)的环境中培养,于第3天,7天,10天采用酶联免疫吸附试验检测内皮祖细胞分泌血管内皮生长因子(Vascular endothelial growth factor, VEGF)、基质细胞衍生因子-1 α (Stromal-derived factor-1 α , SDF-1 α)、胰岛素样生长因子 I(Insulin-like growth factor-I, IGF-I)等生长因子的水平。**结果:**第3天,不同氧浓度下各组 EPC 分泌 VEGF、SDF-1 α 、IGF-I 无明显差异(P 均 >0.05)。第7天和第10天,各组 EPC 分泌 IGF-I 无明显差异(P 均 >0.05);但是和21%氧浓度相比,相对低氧浓度(1%和5%)能够明显增强 EPC 分泌 VEGF 和 SDF-1 α (P 均 <0.001)。**结论:**适当时间的低氧环境培养能够显著刺激内皮祖细胞分泌 VEGF 和 SDF-1 α ,进而增强其促血管新生能力。

关键词:氧浓度;低氧;骨髓干细胞;内皮祖细胞;重度肢体缺血

中图分类号:R-33;R329.2;Q813.11;R654.4 **文献标识码:**A **文章编号:**1673-6273(2018)17-3214-04

Effect of Different Oxygen Concentration on Neovascularization related Secretion Characteristics of Bone Marrow-derived Endothelial Progenitor Cells*

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ABSTRACT Objective: This study was to evaluate the effect of different oxygen concentration on EPCs' secretion of neovascularization growth factors. **Methods:** Bone marrow mononuclear cells of SD rat were acquired with density gradient centrifugation method and cultured, induced, and differentiated to EPCs. Then they were cultured respectively under three different oxygen concentration (1%, 5% and 21%). On days 3, 7 and 10, the effect of different oxygen concentration (1%, 5% and 21%) on EPCs' secretion (secreting VEGF, SDF-1 α and IGF-I) were evaluated by means of ELISA. **Results:** On days 3, different oxygen concentration (1%, 5% and 21%) did not have effect on EPCs' secretion (secreting VEGF, SDF-1 α and IGF-I) (all $P>0.05$). On days 7 and 10, there was no difference among three groups for IGF-I (all $P>0.05$). However, compared with 21% oxygen concentration, hypoxia condition (1% and 5% oxygen concentration) can stimulate EPCs to secrete VEGF and SDF-1 α ($P<0.001$). **Conclusions:** Appropriate hypoxia condition culture can stimulate EPCs to secrete VEGF and SDF-1 α , and enhance their neovascularization function.

Key words: Oxygen concentration; Hypoxia; Bone marrow derived stem cell; Endothelial progenitor cells; Critical limb ischemia

Chinese Library Classification(CLC): R-33; R329.2; Q813.11; R654.4 **Document code:** A

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前言

慢性严重下肢缺血临床治疗困难,是血管外科医师面临的挑战,截肢常常是这类病人不得不面对的残酷现实。干细胞移植为这些病人提供了一个治疗机会^[1,2],我科于2003年在国内最早进行了自体骨髓干细胞治疗严重下肢缺血^[3],但得到改善的病人其长期疗效并不令人满意。这说明需要优化干细胞(包

括内皮祖细胞)移植治疗肢体缺血的策略,来提高其疗效。

1997年,内皮祖细胞(Endothelial progenitor cells, EPC)被成功的从外周血分离并证明其能够整合进血管新生的"活跃点"^[4],并且在动脉硬化等导致的血管老化修复方面以及药物和创新疗法干预治疗缺血性疾病方面均起着非常重要的作用^[5-8]。当前干细胞体外研究大多采用21%氧浓度(即自然界大气氧浓度)环境,这个氧浓度对于长期生存在较低氧浓度的干细

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胞来说并非最适合环境^[9],有研究报道低氧对 EPC 产生一定的影响,Dai 等^[10]发现低氧通过激活 PI3K/Akt 信号途径从而增加 CXCR4 的表达,进而增强 EPC 的迁移功能;Zhang 等^[11]报道低氧能够诱导 EPC 的增殖功能。本研究设计体外诱导分化、扩增骨髓来源的 EPC,观察不同氧浓度对 EPC 分泌血管内皮生长因子(Vascular endothelial growth factor, VEGF)、基质细胞衍生因子-1 α (Stromal-derived factor-1 α , SDF-1 α)、胰岛素样生长因子 I(Insulin-like growth factor-I, IGF-I)等这些与血管新生相关的生长因子的影响,为提高应用于干细胞移植治疗慢性严重肢体缺血临床疗效提供一定的理论研究基础。

1 材料和方法

1.1 骨髓源 EPC 的获取、体外诱导和培养扩增

SD 大鼠(15 只,雄性,体重 200~250 g,北京维通利华实验动物有限公司提供);腹腔内注射 10%水合氯醛(0.5 mL/100g)深度麻醉后断头处死,75%乙醇浸泡 15 min,剪取股骨和胫骨;离断两端骨髓,预冷至 4℃的 PBS 溶液 5~10 mL 冲洗骨髓腔直至骨变白,冲洗液清亮。应用密度梯度离心法分离骨髓单个核细胞,接种于预先用纤维连接蛋白铺底的 25 cm² 培养瓶,培养瓶加入 EBM-2 完全培养基,置于 37℃细胞培养箱中培养,48 h 后轻轻换液,弃去未贴壁细胞,以后每隔 2 天更换培养液。每天于倒置相差显微镜下观察细胞生长情况^[12]。

1.2 骨髓源 EPC 的鉴定

分离后培养第 7 天,采用功能鉴定方法,用乙酰化的低密度脂蛋白(DiI-Ac-LDL)和异硫氰酸荧光素-荆豆凝集素-I(FITC-UEA-I)进行双阳性鉴定。在荧光显微镜下观察细胞,用

510 nm 激发光激发 DiI,用 488 nm 激发光激发 FITC。荧光染色双阳性细胞被认为是正在分化中的 EPC。

1.3 不同氧浓度对 EPC 分泌促血管新生相关生长因子的影响

分离后培养第 8 天,将 EPC 计数分组,并分别置入不同氧浓度(1%,5%,21%)的培养箱中继续培养和观察。按照 Quantikine ELISA Rat VEGF Immunoassay Kit (R&D Systems, Inc. 美国)、Rat SDF-1 α ELISA Kit (CUSABIO BIOTECH CO., LTD. 日本)、Quantikine ELISA Mouse/Rat IGF-I Immunoassay Kit (R&D Systems, Inc. 美国)各试剂盒操作说明,应用 ELISA 方法对不同氧浓度下各组细胞外培养基中促血管新生的生长因子(VEGF, SDF-1 α , IGF-I)含量进行分析。

1.4 统计方法

连续变量统计指标表达为平均值 $\pm$ 标准差($\bar{x} \pm s$),对各组资料进行正态性检验和方差齐性检验,满足正态分布和方差齐性,各组之间相互比较采用多个样本均数之间多重比较的方差分析方法(SNK-q 检验); $P < 0.05$ 认为具有显著统计学差异。所有统计分析采用 SPSS 统计分析软件(16.0 版本,美国)。

2 结果

2.1 骨髓源 EPC 体外诱导和培养扩增

新分离的大鼠骨髓单个核细胞呈圆形,大小不一。细胞培养 72 h 后,可见细胞开始贴壁,由圆形逐渐伸展开,呈长梭形、三角形、纺锤形或不规则形,并呈集落样生长(图 1,箭头示集落)。此后细胞进入对数生长期,生长旺盛。至培养第 7 到 8 天,细胞逐渐成铺路石样单层排列,约 80%铺满(图 2)。

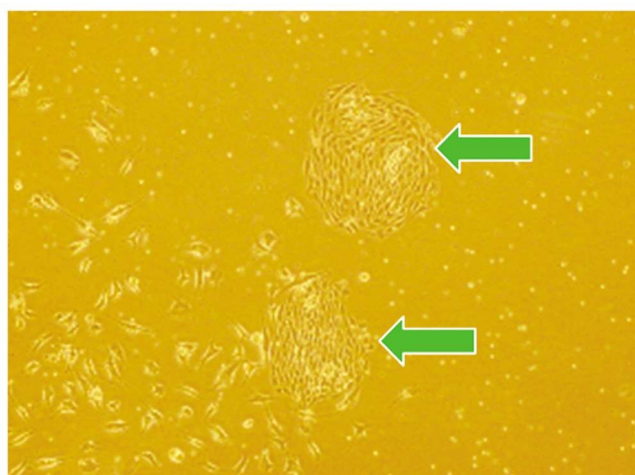


图 1 培养第 3 天,呈长梭形、三角形(箭头示细胞集落)($\times 100$)

Fig.1 On day 3, cells show fusiform and triangle (arrow directs to cell colony)

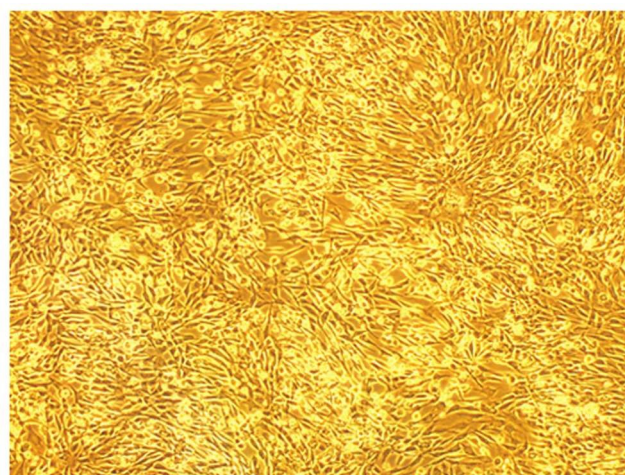


图 2 细胞培养至第 7 天,见细胞呈铺路卵石样单层排列,约 80%铺满($\times 100$)

Fig.2 On day 7, cells show cobblestone arrange about 80% of view

2.2 骨髓源 EPC 的鉴定

在培养至第 7 天,用乙酰化的低密度脂蛋白(DiI-Ac-LDL)和异硫氰酸荧光素-荆豆凝集素-I(FITC-UEA-I)进行双阳性鉴定。我们的实验显示荧光染色双阳性细胞约占细胞总数的 98%以上(图 3-图 5)。

2.3 不同氧浓度对 EPC 分泌促血管新生相关的生长因子的影响

3 讨论

重度肢体缺血(Critical limb ischemia, CLI)表现为肢体静息痛、溃疡、肢体坏疽和组织缺失;代表着外周血管缺血性疾病已进展到终末期,明显影响病人生活质量,且预后差,致残率和死亡率高^[13,14],截肢常常是这些患者不得不面对的残酷现实。干细胞(包括 EPC)移植为这些患者提供了一个治疗机会,通过血管

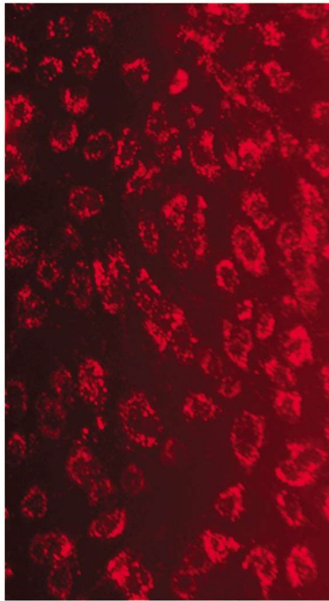


图3 Dil-Ac-LDL 摄取实验($\times 200$)

Fig.3 Dil-Ac-LDL absorption assay

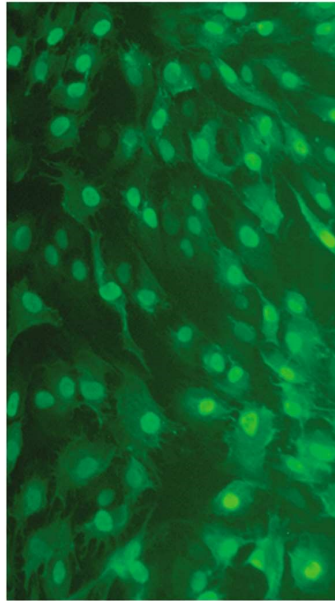


图4 FITC-UEA 结合实验($\times 200$)

Fig.4 FITC-UEA combination assay

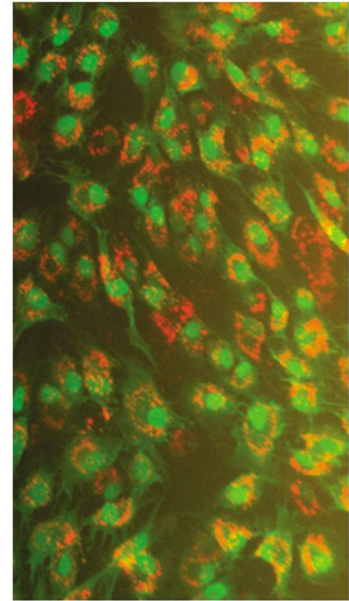


图5 双荧光染色阳性的细胞($\times 200$)

Fig.5 Double fluorescence staining positive cells

表 1 不同氧浓度环境下培养基中 VEGF 浓度($\times 10^3$ pg/mL)

Table 1 VEGF concentration in different oxygen concentration condition($\times 10^3$ pg/mL)

	1 % oxygen concentration($\bar{x} \pm s$)	5 % oxygen concentration($\bar{x} \pm s$)	21 % oxygen concentration($\bar{x} \pm s$)
On day 3	1.72 $\pm$ 0.11	1.68 $\pm$ 0.15	1.70 $\pm$ 0.22
On day 7	7.33 $\pm$ 1.22	12.56 $\pm$ 1.65	3.67 $\pm$ 1.09
On day 10	6.17 $\pm$ 2.28	10.92 $\pm$ 1.94	2.43 $\pm$ 1.06

Note: On day 3, ($C_{1\%}$ VS $C_{5\%}$, $P=0.663$; $C_{1\%}$ VS $C_{21\%}$, $P=0.869$; $C_{5\%}$ VS $C_{21\%}$, $P=0.712$); On day 7 and 10, ($C_{1\%}$ VS $C_{5\%}$, $P<0.001$; $C_{1\%}$ VS $C_{21\%}$, $P<0.001$; $C_{5\%}$ VS $C_{21\%}$, $P<0.001$).

表 2 不同氧浓度环境下培养基中 SDF-1 α 浓度($\times 10^3$ pg/mL)

Table 2 SDF-1 α concentration in different oxygen concentration condition($\times 10^3$ pg/mL)

	1 % oxygen concentration($\bar{x} \pm s$)	5 % oxygen concentration($\bar{x} \pm s$)	21 % oxygen concentration($\bar{x} \pm s$)
On day 3	0.38 $\pm$ 0.07	0.39 $\pm$ 0.11	0.36 $\pm$ 0.05
On day 7	0.62 $\pm$ 0.12	0.99 $\pm$ 0.18	0.33 $\pm$ 0.13
On day 10	0.59 $\pm$ 0.11	0.82 $\pm$ 0.17	0.27 $\pm$ 0.13

Note: On day 3, ($C_{1\%}$ VS $C_{5\%}$, $P=0.745$; $C_{1\%}$ VS $C_{21\%}$, $P=0.687$; $C_{5\%}$ VS $C_{21\%}$, $P=0.334$); On day 7 and 10, ($C_{1\%}$ VS $C_{5\%}$, $P<0.001$; $C_{1\%}$ VS $C_{21\%}$, $P<0.001$; $C_{5\%}$ VS $C_{21\%}$, $P<0.001$).

表 3 不同氧浓度环境下培养基中 IGF-I 浓度($\times 10^3$ pg/mL)

Table 3 IGF-I concentration in different oxygen concentration condition($\times 10^3$ pg/mL)

	1 % oxygen concentration($\bar{x} \pm s$)	5 % oxygen concentration($\bar{x} \pm s$)	21 % oxygen concentration($\bar{x} \pm s$)
On day 3	4.98 $\pm$ 0.38	4.79 $\pm$ 0.31	4.84 $\pm$ 0.44
On day 7	5.02 $\pm$ 0.52	4.86 $\pm$ 0.45	4.91 $\pm$ 0.39
On day 10	4.96 $\pm$ 0.28	4.55 $\pm$ 0.62	4.89 $\pm$ 0.51

Note: On day 3, ($C_{1\%}$ VS $C_{5\%}$, $P=0.653$; $C_{1\%}$ VS $C_{21\%}$, $P=0.817$; $C_{5\%}$ VS $C_{21\%}$, $P=0.771$); On day 7, ($C_{1\%}$ VS $C_{5\%}$, $P=0.418$; $C_{1\%}$ VS $C_{21\%}$, $P=0.736$; $C_{5\%}$ VS $C_{21\%}$, $P=0.493$); On day 10, ($C_{1\%}$ VS $C_{5\%}$, $P=0.577$; $C_{1\%}$ VS $C_{21\%}$, $P=0.831$; $C_{5\%}$ VS $C_{21\%}$, $P=0.562$).

新生改善 CLI 患者缺血组织的血供从而达到改善或缓解临床症状、促进溃疡愈合(或者缩小溃疡面积)、甚至避免截肢(或者降低截肢平面)等目的。

大量的动物实验和初步临床试验显示了干细胞移植治疗的有效性和安全性^[2,15-17]。我们单位在国内较早开展应用骨髓源或者外周血干细胞移植治疗 " 无治疗选择 " 的 CLI 患者或者

接受外科旁路移植和或腔内治疗后失败的 CLI 患者^[3,18,19], 至今已有 10 余年的临床经验, 结果显示虽然部分病例显示出短期良好结果, 但远期疗效并不理想, 部分患者仍然避免不了截肢的命运。有研究显示: 高血糖、高血脂以及严重肢体缺血等会导致 EPC 功能障碍和数量减少^[20-23], 所以, 研究各种方法来增强移植前的干细胞(包括 EPC)促血管新生功能是提高其临床疗

效的有效途径。

在干细胞(包括 EPC)移植前,对其培养环境中的氧浓度进行调整或者进行适当的干预,有可能进一步优化它们的治疗潜能。最近已经有学者报道了低氧对 EPC 相关生物学特性的影响,Dai 等^[10]发现低氧通过激活 PI3K/Akt 信号途径从而增加 CXCR4 的表达,进而增强 EPC 的迁移功能;Zhang 等^[11]报道低氧通过上调 Apelin/APLNR/MAPK 信号通路从而诱导 EPC 的增殖功能。Kütscher 等^[24]发现 EPC 高表达低氧诱导因子-1 α 后能够改善其血管新生相关的功能。

我们的研究显示:适当时间(7 到 10 天)的低氧环境(1%和 5%氧浓度)培养能够显著刺激 EPC 分泌 VEGF 和 SDF-1 α ,但是低氧环境培养对 EPC 分泌 IGF-I 影响不大。大量研究显示:VEGF 是被证实了的能够显著促进血管新生的因子,它几乎参与了血管新生的每一个步骤,不仅刺激干细胞(包括 EPC)从骨髓通过粘附、迁移等向外周血动员和缺血组织归巢,还参与新生血管的形成。基质细胞衍生因子 SDF-1 α (又叫趋附因子 CXCL12)是另外一个在干细胞(包括 EPC)归巢中起着重要作用的细胞因子,它和它的受体 CXCR4 对表达有 CXCR4 的细胞具有强烈的化学趋附作用,另外 SDF-1 α (CXCL12)还具有抗缺血的保护效应^[25,26]。另外一项研究证实:VEGF 和 SDF-1 的协同作用可以增大的增殖与迁移能力,从而促进血管的新生与修复^[27]。

我们的研究也为当前血管组织工程构建研究提供了一个重要的提示:EPC 在血管组织工程构建中扮演者非常重要的角色,不仅应该在三维环境中构建血管组织工程^[28],也应注意其微环境的氧浓度,因为调整氧浓度对于干细胞(包括 EPC)迁移能力、增殖能力和分泌血管生长因子等生物学特性将产生一定的影响,进而构建更加优化的组织工程血管。

本研究为当前干细胞培养环境的优化提供了一个参考,也提示我们在应用干细胞(包括 EPC)移植治疗缺血性血管疾病时,移植前进行适当的低氧培养(比如置入 1%到 5%氧浓度环境),可以增强其促进血管新生的能力;但是,由于研究经费所限,最佳的氧浓度和低氧培养时间仍需要进一步的研究来验证,从而优化当前临床应用干细胞(包括 EPC)移植的临床疗效。

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