·基础研究·

红系前体细胞在阿尔茨海默病中作用及机制研究

李娜 刘晓莉 朱爱琴 艾林

【摘要】 **目的** 探讨红系前体细胞(EPC)及其亚型在阿尔茨海默病中的作用及其机制。**方法** 对2018年10月至2019年10月在青海省人民医院首次诊断与治疗的30例阿尔茨海默病患者(AD组)予以奥氮平联合多奈哌齐治疗,同时选取相匹配的30例正常对照者(对照组),均采用流式细胞术检测外周血红系前体细胞及其亚型CD45$^+$EPC和CD45$^-$EPC比例;进一步培养原代皮质神经元并构建阿尔茨海默病细胞模型,采用流式细胞术检测对照组、AD模型组、CD45$^+$EPC组、CD45$^-$EPC组、Artemin阻断组神经元凋亡比例。**结果** AD组与对照组、AD组治疗前后外周血红系前体细胞比例差异均无统计学意义(均$P>0.05$);但AD组治疗前CD45$^+$EPC比例($t=7.277$,$P=0.000$)和活性氧含量($t=10.817$,$P=0.000$)高于对照组、CD45$^-$EPC比例($t=7.277$,$P=0.000$)和Artemin含量($t=6.547$,$P=0.000$)低于对照组,而治疗前后CD45$^+$EPC和CD45$^-$EPC比例、活性氧和Artemin含量差异均无统计学意义(均$P>0.05$)。神经元凋亡实验显示,不同处理组神经元凋亡比例差异有统计学意义($F=25.662$,$P=0.000$),AD模型组($t=9.330$,$P=0.000$)、CD45$^+$EPC组($t=14.362$,$P=0.000$)、CD45$^-$EPC组($t=2.423$,$P=0.036$)和Artemin阻断组($t=9.970$,$P=0.000$)神经元凋亡比例均高于对照组,AD模型组($t=4.548$,$P=0.001$)、CD45$^+$EPC组($t=8.759$,$P=0.000$)和Artemin阻断组($t=5.387$,$P=0.000$)均高于CD45$^-$EPC组,CD45$^+$EPC组亦高于AD模型组($t=5.091$,$P=0.000$)和Artemin阻断组($t=3.175$,$P=0.004$)。**结论** 阿尔茨海默病患者外周血CD45$^+$EPC比例显著增加,CD45$^-$EPC比例显著减少。CD45$^-$EPC可以通过分泌Artemin减少阿尔茨海默病引起的神经元凋亡。

【关键词】 阿尔茨海默病; 红系前体细胞; 抗原,CD; 细胞凋亡

The role and mechanism of erythroid precursor cells in Alzheimer´s disease

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【**Abstract**】 **Objective** To investigate the role and mechanism of erythroid precursor cells (EPC) and its subtypes in Alzheimer's disease (AD). **Methods** The patients with AD (AD group) firstly diagnosed and treated in Qinghai Provincial People's Hospital from October 2018 to October 2019 were included, and olanzapine combined with donepezil were used for treatment; while 30 healthy volunteers were selected as the control group. The proportion of EPC, CD45$^+$EPC and CD45$^-$EPC in peripheral blood in control group and AD group before and after treatment was detected and sorted by flow cytometry. Primary cortical neurons were used to construct AD cells model, flow cytometry was used to detect the apoptosis of neurons in control group, AD model group, CD45$^+$EPC group, CD45$^-$EPC group and Artemin block group. **Results** There was no significant difference in the proportion of EPC in peripheral blood between AD group and control group, or between AD group before and after treatment ($P>0.05$, for all). However, the proportion of CD45$^+$EPC subtype ($t=7.277$, $P=0.000$) and ROS content ($t=10.817$, $P=0.000$)

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in AD group before treatment were higher than those in control group. The proportion of $CD45^-$EPC subtype (t = 7.277, P = 0.000) and Artemin content (t = 6.547, P = 0.000) were lower than those in control group, but there were no significant differences in proportion of $CD45^+$EPC and $CD45^-$EPC subtypes, ROS and Artemin contents before and after treatment in AD group (P > 0.05, for all). Neuronal apoptosis experiment showed the proportion of neuronal apoptosis in different treatment groups was significantly different (F = 25.662, P = 0.000). The proportion of neuronal apoptosis in AD model group (t = 9.330, P = 0.000), $CD45^+$EPC group (t = 14.362, P = 0.000), $CD45^-$EPC group (t = 2.423, P = 0.036) and Artemin block group (t = 9.970, P = 0.000) were higher than those in control group. AD model group (t = 4.548, P = 0.001), $CD45^+$EPC group (t = 8.759, P = 0.000), Artemin block group (t = 5.387, P = 0.000) were higher than those in $CD45^-$EPC group. $CD45^+$EPC group was also higher than that in AD model group (t = 5.091, P = 0.000) and Artemin block group (t = 3.175, P = 0.004). **Conclusions** The proportion of $CD45^+$EPC subtype in peripheral blood of AD patients was significantly increased and the proportion of $CD45^-$EPC subtype was decreased. $CD45^-$EPC subtype can reduce the neuronal apoptosis induced by AD by secreting Artemin.

【Key words】 Alzheimer disease; Erythroid precursor cells; Antigens, CD; apoptosis

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Conflicts of interest: none declared

阿尔茨海默病(AD)是好发于老年人群的进展性神经系统变性疾病,主要表现为记忆、视空间能力和执行功能障碍,给社会和家庭带来沉重疾病负担[1]。目前尚缺乏有效治疗或逆转疾病进程的药物,因此探寻新的治疗靶点具有十分重要的意义[2]。流行病学调查显示,贫血人群罹患阿尔茨海默病的风险较普通人群高40%[3-4],提示贫血可诱发阿尔茨海默病,虽然其作用机制尚不清楚,但引起研究者对红系前体细胞(EPC)的关注。红系前体细胞可增殖分化为成熟红细胞,在维持红系稳态中发挥关键作用[5]。CD45又称白细胞共同抗原(LCA),$CD45^+$EPC可使阿尔茨海默病患者活性氧(ROS)水平升高[6-7];而$CD45^-$EPC分泌ROS的能力较弱,但具有较强的Artemin分泌能力。Artemin系神经营养因子,具有促进神经修复和营养神经之功效[8-9]。本文拟就红系前体细胞不同亚型在阿尔茨海默病进展中的作用及其减少神经元凋亡的机制进行研究,以为阿尔茨海默病的预防与治疗提供新的靶点。

对象与方法

一、观察对象

1.阿尔茨海默病组(AD组) 收集2018年10月至2019年10月在青海省人民医院老年医学科首次住院治疗的阿尔茨海默病患者共30例。阿尔茨海默病的诊断参照《2018中国痴呆与认知障碍诊治指南(二):阿尔茨海默病诊治指南》[10]且年龄>18岁;排除合并恶性肿瘤、严重心脏或肺部疾病、糖尿病、自身免疫性疾病、血液系统疾病、获得性免疫缺陷综合征(AIDS)或乙型肝炎患者。男性18例,女性12例;年龄51~63岁,平均(56.83±3.67)岁;体重53.26~75.64 kg,平均(63.16±3.66)kg;病程1~5年,平均(3.23±1.64)年;红细胞计数(4.32~4.90)×10^{12}/L,平均(4.88±0.19)×10^{12}/L;血红蛋白(Hb)132~150 g/L,平均(137.27±4.05)g/L。

2.正常对照组(对照组) 选择同期在我院进行体格检查的30名健康志愿者作为对照,男性16例,女性14例;年龄50~62岁,平均(56.17±2.36)岁;体重52.61~75.32 kg,平均(64.33±5.14)kg;红细胞计数(4.30~4.84)×10^{12}/L,平均(4.62±0.21)×10^{12}/L;血红蛋白133~155 g/L,平均(134.71±4.05)g/L。

两组受试者性别、年龄、体重、红细胞计数和血红蛋白比较,差异无统计学意义(均P>0.05,表1),均衡可比。

二、研究方法

1.试剂与仪器 (1)药品与试剂:奥氮平(国药准字H20010799)由江苏豪森药业集团有限公司提供,盐酸多奈哌齐(国药准字H20050978)为卫材药业有限公司产品;淋巴细胞分离液(规格100 ml)、胎牛血清(FBS,规格500 ml)和RPMI1640培养基(规格500 ml)购自美国Hyclone公司,细胞凋亡检测试剂盒(规格100 T)、TER-119-异硫氰酸荧光素(FITC,规格0.50 mg)、$CD71^-$藻红蛋白(PE,规格0.50 mg)和$CD45^-$藻蓝蛋白(APC,规格0.50 mg)购自美国BD公司,多聚赖氨酸(规格50 ml)、β-淀粉样

表1 AD组与对照组受试者一般资料的比较

Table 1. Comparison of general data between AD group and control group

观察指标	对照组(n=30)	AD组(n=30)	χ^2或t值	P值
性别[例(%)]			0.271	0.602
男性	16(53.33)	18(60.00)		
女性	14(46.67)	12(40.00)		
年龄($\bar{x}\pm s$,岁)	56.17±2.36	56.83±3.67	0.153	0.882
体重($\bar{x}\pm s$,kg)	64.33±5.14	63.16±3.66	0.185	0.857
红细胞计数($\bar{x}\pm s$,$\times10^{12}$/L)	4.62±0.21	4.88±0.19	0.891	0.394
血红蛋白($\bar{x}\pm s$,g/L)	134.71±4.05	137.27±4.05	0.411	0.690

χ^2 test for comparison of sex, and two-independent-sample t test for comparison of others,性别的比较采用χ^2检验,其余指标的比较采用两独立样本的t检验。AD,Alzheimer's disease,阿尔茨海默病

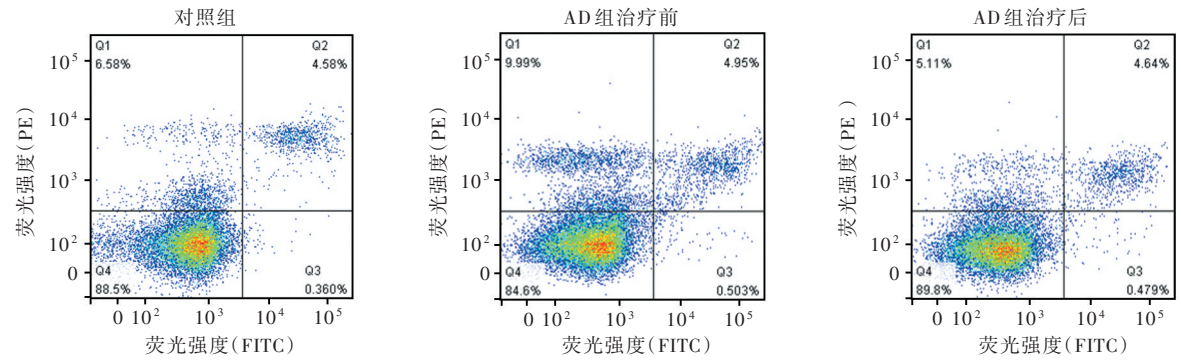
蛋白42($A\beta_{42}$,规格250 μg)和ROS检测试剂盒购自美国Sigma公司,Artemin中和抗体(规格100 μl)购自英国Abcam公司,酶联免疫吸附试验(ELISA)试剂盒(规格96 T)购自北京欣博盛生物科技有限公司,细胞培养添加剂B27(规格10 ml)和NeuroCult培养基(规格500 ml)购自北京诺为生物科技有限公司。(2)设备与仪器:Transwell共培养小室购自美国Corning公司,FACSCalibur流式细胞仪购自美国BD公司,ELx808酶标仪购自美国Biotek公司。

2.流式细胞术检测外周血红系前体细胞比例以及ROS和Artemin含量 阿尔茨海默病患者予奥氮平(初始剂量2.50 mg/晚,1个月后增至12.50 mg/晚)联合多奈哌齐(初始剂量为5 mg/晚,1个月后增至10 mg/晚)口服,持续3个月。(1)外周血红系前体细胞比例:采集AD组治疗前后以及对照组体检时外周血各5 ml,淋巴细胞分离液分离出外周血单个核细胞(PBMC);磷酸盐缓冲液洗涤3次,分别加入150 μl含有$CD71^-$PE、$CD45^-$APC和TER-119-FITC的磷酸盐缓冲液,37 ℃避光孵育15 min;磷酸盐缓冲液洗涤3次,在流式细胞仪上通过Flowjo软件(https://www.flowjo.com/)自动计算淋巴细胞中红系前体细胞($CD71^+$TER-119^+细胞)比例,以及红系前体细胞中$CD45^+$EPC(即$CD71^+$TER-119^+CD45^+细胞)和$CD45^-$EPC(即$CD71^+$TER-119^+CD45^-细胞)比例。(2)ROS和Artemin含量:在流式细胞仪上分选出红系前体细胞后,将ROS检测试剂盒中DCFH-DA试剂加入部分分选细胞中,37 ℃孵育20 min,磷酸盐缓冲液洗涤3次,在流式细胞仪上通过Flowjo软件自动计算红系前体细胞平均荧光强度,代表ROS含量。另一部分红系前体细胞置于含10%胎牛血清的RPMI1640培养基中,37 ℃培养48 h,收集细胞培养上清液,ELISA法检测Artemin含量,严格按照试剂盒说明书进行操作,在酶标仪上检测450 nm处光密度值(OD值),代表Artemin含量。

3.阿尔茨海默病细胞模型构建 为进一步明确红系前体细胞在阿尔茨海默病中的作用机制,构建阿尔茨海默病细胞模型。分离胚胎期2周的无特定病原体(SPF)C57BL/6胎鼠购自北京维通利华实验动物技术有限公司[许可证号:SCXK(京)2021-0006],断头切取脑组织并分离大脑皮质,去除血管和周围结缔组织,以0.25%胰蛋白酶消化和分离神经细胞,将分离出的细胞置于含B27的NeuroCult培养基中培养,培养板预包被多聚赖氨酸,贴壁且呈梭形的细胞即为皮质神经元。参照文献[11-13]的方法构建阿尔茨海默病细胞模型,即原代皮质神经元培养1周后,加入终浓度为1 μmol/L的凝聚态$A\beta_{42}$共培养1 h,用于本实验。

4.实验分组及流式细胞术检测神经元凋亡比例 将红系前体细胞和原代皮质神经元以Transwell小室共培养,上室为红系前体细胞,下室为原代皮质神经元。共分为5组,即对照组(未予处理的神经元)、AD模型组(阿尔茨海默病细胞)、$CD45^+$EPC组(上室加入50×10^3个$CD45^+$EPC,构建阿尔茨海默病细胞模型)、$CD45^-$EPC组(上室加入50×10^3个$CD45^-$EPC,构建阿尔茨海默病细胞模型)、Artemin阻断组(上室加入50×10^3个$CD45^-$EPC的同时加入Artemin中和抗体,构建阿尔茨海默病细胞模型),每组1×10^6个细胞。共培养48 h后,收集下室神经元,磷酸盐缓冲液洗涤3次,加入细胞凋亡检测试剂盒中FITC标记的Annexin V和碘化丙啶(PI),避光结合15 min,在流式细胞仪上通过Flowjo软件自动计算神经元凋亡比例,即流式细胞图右上象限和右下象限数值之和。神经元凋亡实验共重复6次,取平均值。

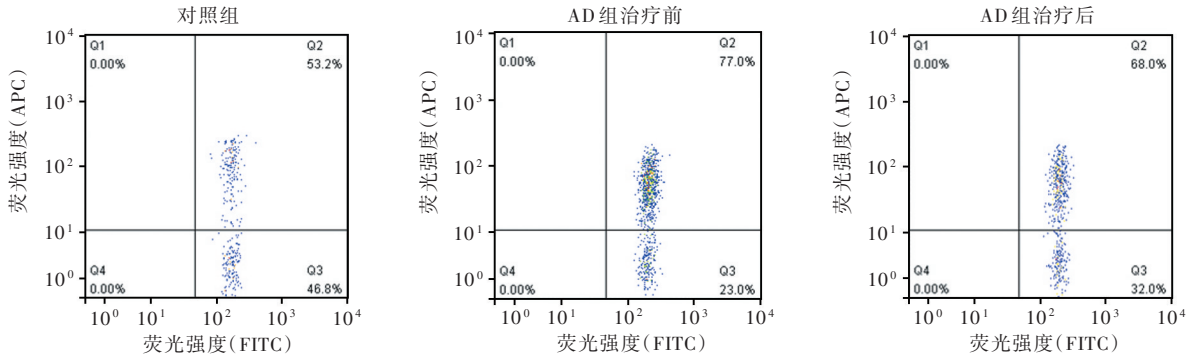
5.统计分析方法 采用GraphPad 5.0软件进行数据处理与分析。Kolmogorov-Smirnov检验进行正态性检验,呈正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示,组内比较采用配对t检验;两组间比较采用两独立样本的t检验;多组间比较采用单因素方差分析,两两比较行LSD-t检验。以$P\leqslant0.05$为差异具有统计学意义。



AD,阿尔茨海默病;FITC,异硫氰酸荧光素;PE,藻红蛋白

图1 流式细胞术显示,对照组与AD组治疗前、AD组治疗前后外周血红系前体细胞比例均无显著差异

Figure 1 Flow cytometry showed there was no significant difference in the proportion of EPC in peripheral blood between the control group and the AD group before and after treatment.



AD,阿尔茨海默病;FITC,异硫氰酸荧光素;APC,藻蓝蛋白

图2 流式细胞术显示,与对照组相比,AD组治疗前外周血$CD45^+EPC$比例较高、$CD45^-EPC$比例较低;而AD组治疗前后$CD45^+EPC$和$CD45^-EPC$比例无明显差异

Figure 2 Flow cytometry showed compared with the control group, the proportion of $CD45^+EPC$ in peripheral blood was higher and the proportion of $CD45^-EPC$ was lower in AD group before treatment. There was no significant difference in the proportion of $CD45^+EPC$ and $CD45^-EPC$ before and after treatment in AD group.

结　果

对照组外周血红系前体细胞比例为3.26%～5.65%、平均为(4.52±0.35)%,AD组治疗前为4.12%～5.46%、平均为(4.93±0.20)%,两组之间差异无统计学意义($t=1.039$,$P=0.323$),提示阿尔茨海默病对红系前体细胞并无影响;AD组治疗后外周血红系前体细胞比例为3.96%～5.55%、平均为(4.73±0.25)%,治疗前后差异亦无统计学意义($t=2.262$,$P=0.073$),提示药物治疗对阿尔茨海默病红系前体细胞亦无影响(图1)。

对照组外周血$CD45^+EPC$比例为46.12%～59.44%、平均为(52.37±1.93)%,AD组治疗前为65.58%～82.33%、平均为(75.50±2.53)%,两组之间差异具有统计学意义($t=7.277$,$P=0.000$),提示阿尔茨海默病可使$CD45^+EPC$比例增加;AD组治疗后外周血$CD45^+EPC$比例为64.48%～77.95%、平均为(70.17±2.24)%,治疗前后差异无统计学意义($t=2.034$,$P=0.098$),提示药物治疗对阿尔茨海默病$CD45^+EPC$比例并无影响(图2)。

对照组外周血$CD45^-EPC$比例为40.56%～53.88%、平均为(47.63±1.93)%,AD组治疗前为17.67%～34.42%、平均为(24.50±2.53)%,两组之间差异具有统计学意义($t=7.277$,$P=0.000$),提示阿尔茨海默病可使$CD45^-EPC$比例减少;AD组治疗后外周血$CD45^-EPC$比例为22.05%～35.52%、平均为(29.83±2.24)%,治疗前后差异无统计学意义($t=2.034$,$P=0.098$),提示药物治疗对阿尔茨海默病$CD45^-EPC$比例并无影响(图2)。

对照组外周血红系前体细胞ROS荧光强度为

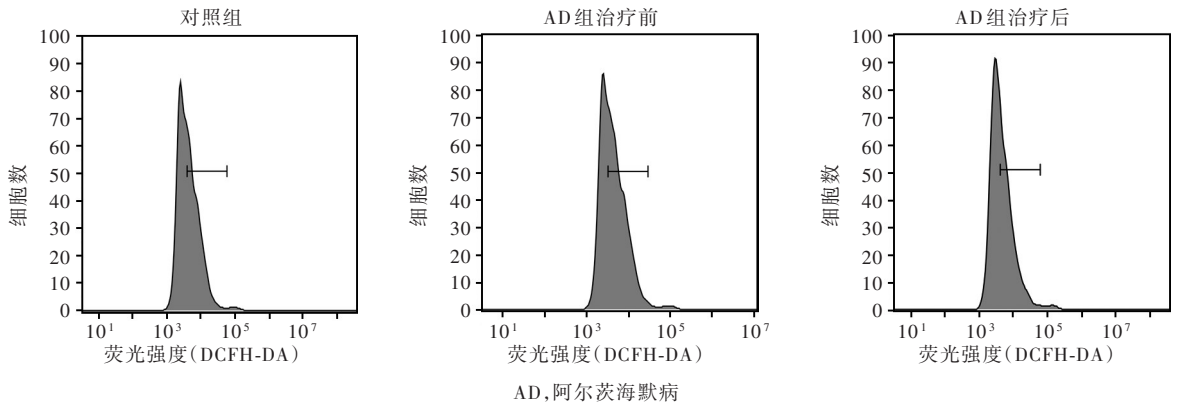


图3 流式细胞术显示,AD组治疗前红系前体细胞ROS平均荧光强度高于对照组,而AD组治疗后ROS平均荧光强度较治疗前无明显差异

Figure 3 Flow cytometry showed the average fluorescence intensity of ROS in AD group before treatment was higher than that in the control group. There was no significant difference in the average fluorescence intensity of ROS before and after treatment in AD group.

181~254、平均为225.33±12.92,AD组治疗前为388~472、平均为424.81±13.17,两组之间差异具有统计学意义(t=10.817,P=0.000),提示阿尔茨海默病可使红系前体细胞ROS含量升高;AD组治疗后外周血红系前体细胞ROS荧光强度为336~445、平均为388.75±16.77,治疗前后差异无统计学意义(t=1.230,P=0.273),提示药物治疗对阿尔茨海默病红系前体细胞ROS含量并无影响(图3)。

对照组外周血红系前体细胞上清中Artemin含量为35.11~75.63 ng/ml、平均(52.77±5.43) ng/ml,AD组治疗前为9.66~21.58 ng/ml、平均为(15.33±1.80) ng/ml,两组之间差异具有统计学意义(t=6.547,P=0.000),提示阿尔茨海默病可使红系前体细胞Artemin含量降低;AD组治疗后外周血红系前体细胞上清中Artemin含量为14.46~32.16 ng/ml、平均为(21.83±2.87) ng/ml,治疗前后差异无统计学意义(t=1.852,P=0.123),提示药物治疗对阿尔茨海默病红系前体细胞Artemin含量并无影响。

神经元凋亡实验显示,不同处理组神经元凋亡比例差异有统计学意义(P=0.000,表2),进一步两两比较,AD模型组(P=0.000)、$CD45^+$EPC组(P=0.000)、$CD45^-$EPC组(P=0.036)、Artemin阻断组(P=0.000)神经元凋亡比例均高于对照组;$CD45^+$EPC组神经元凋亡比例高于AD模型组(P=0.000)和Artemin阻断组(P=0.004),AD模型组(P=0.001)、$CD45^+$EPC组(P=0.000)、Artemin阻断组(P=0.000)均高于$CD45^-$EPC组(表3,图4)。

讨 论

CD45亦称为白细胞共同抗原(LCA),表达于所有白系细胞中,在淋巴细胞发育成熟、功能调控和免疫信号传导中发挥重要作用[14-15],主要通过流式细胞术和免疫组化染色等方法用于疾病的辅助诊断[16-17]。慢性炎症反应是阿尔茨海默病发生发展的重要机制,目前绝大多数研究集中于白系细胞领域,较少涉及红系细胞领域。2018年,Zhao等[6]首次报告$CD45^+$EPC比例在恶性肿瘤晚期合并贫血患者中显著升高,且此类患者预后更差,因此认为$CD45^+$EPC是肿瘤合并贫血患者病情恶化的危险因素,进一步行基因检测发现,$CD45^+$EPC通过分泌ROS抑制$CD8^+$T细胞功能,进而抑制抗肿瘤免疫反应。ROS含量升高是阿尔茨海默病早期主要的病理生理学特征之一,可引起神经元凋亡,上调细胞内Aβ水平,进而导致认知功能障碍[18-19]。$CD45^+$EPC自身可产生大量ROS[6-7],而$CD45^-$EPC的ROS生成能力相对较弱,提示$CD45^+$EPC可促进阿尔茨海默病进展,故$CD45^+$EPC比例增加可能是阿尔茨海默病发生发展的重要危险因素,可以作为阿尔茨海默病监测和治疗的有效生物学标志物。本研究结果显示,阿尔茨海默病患者与正常对照者以及阿尔茨海默病患者奥氮平联合多奈哌齐治疗前后外周血红系前体细胞比例均无明显差异;但阿尔茨海默病患者治疗前$CD45^+$EPC比例和ROS含量均高于正常对照者,$CD45^-$EPC比例低于正常对照者,

表2 不同处理组神经元凋亡比例的比较($\bar{x}\pm s$,%)

Table 2. Comparison of neuronal apoptosis in different groups ($\bar{x}\pm s$, %)

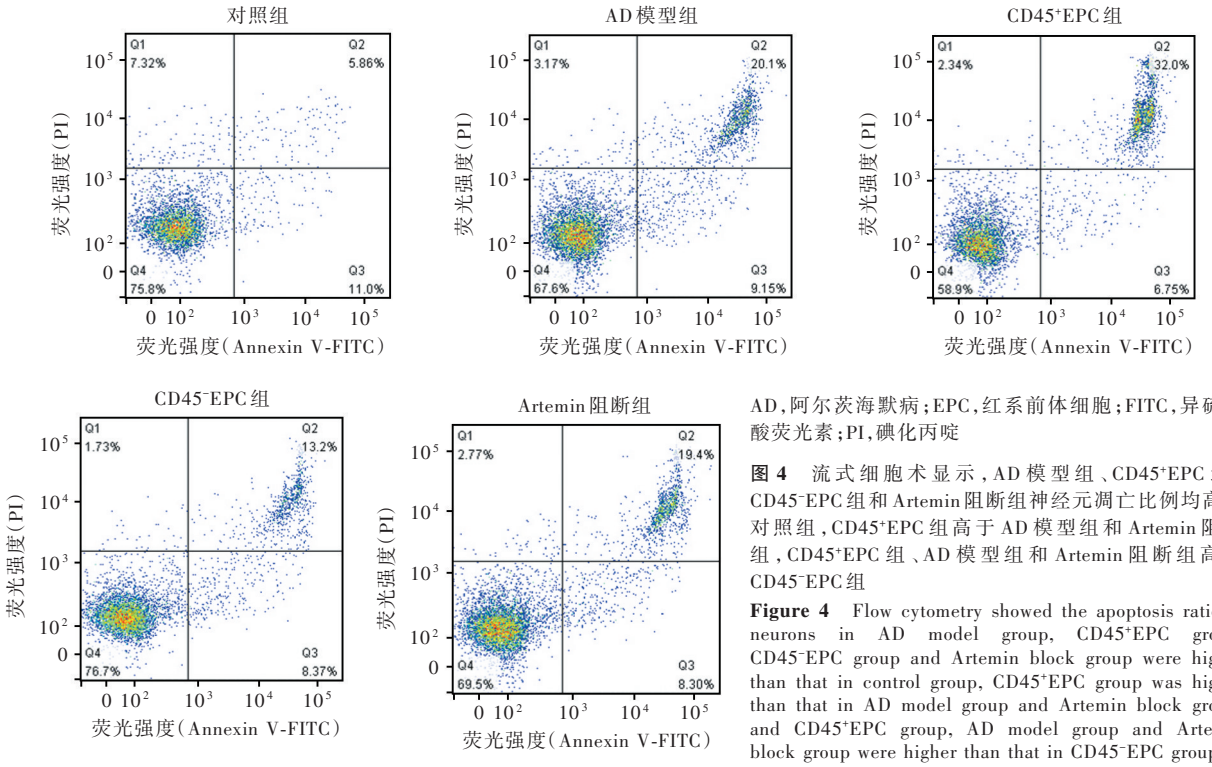
组别	细胞数	神经元凋亡比例	F值	P值
对照组(1)	1×10^6	15.08±0.81		
AD模型组(2)	1×10^6	29.39±1.30		
$CD45^+EPC$组(3)	1×10^6	39.47±1.49	25.662	0.000
$CD45^-EPC$组(4)	1×10^6	19.65±1.70		
Artemin阻断组(5)	1×10^6	31.72±1.46		

AD, Alzheimer's disease, 阿尔茨海默病; EPC, erythroid precursor cells, 红系前体细胞

表3 不同处理组神经元凋亡比例的两两比较

Table 3. Pairwise comparison of neuronal apoptosis among different groups

组间两两比	t值	P值	组间两两比	t值	P值
(1):(2)	9.330	0.000	(2):(4)	4.548	0.001
(1):(3)	14.362	0.000	(2):(5)	1.192	0.261
(1):(4)	2.423	0.036	(3):(4)	8.759	0.000
(1):(5)	9.970	0.000	(3):(5)	3.715	0.004
(2):(3)	5.091	0.000	(4):(5)	5.387	0.000



AD, 阿尔茨海默病; EPC, 红系前体细胞; FITC, 异硫氰酸荧光素; PI, 碘化丙啶

图4 流式细胞术显示, AD模型组、$CD45^+EPC$组、$CD45^-EPC$组和Artemin阻断组神经元凋亡比例均高于对照组, $CD45^+EPC$组高于AD模型组和Artemin阻断组, $CD45^+EPC$组、AD模型组和Artemin阻断组高于$CD45^-EPC$组

Figure 4 Flow cytometry showed the apoptosis ratio of neurons in AD model group, $CD45^+EPC$ group, $CD45^-EPC$ group and Artemin block group were higher than that in control group, $CD45^+EPC$ group was higher than that in AD model group and Artemin block group, and $CD45^+EPC$ group, AD model group and Artemin block group were higher than that in $CD45^-EPC$ group.

而阿尔茨海默病患者药物治疗前后$CD45^+EPC$和$CD45^-EPC$比例、ROS含量无显著差异,提示红系前体细胞亚型失衡可能是阿尔茨海默病发生的重要原因,而奥氮平联合多奈哌齐等药物对红系前体细胞亚型和ROS含量并无影响,这是否是上述药物无法根治阿尔茨海默病的根本原因,尚待后续研究。

Artemin属于胶质细胞源性神经营养因子(GDNF)家族配体,是一种重要神经营养因子,广泛表达于人体内[20-21],可介导神经元生长、分化、存活和轴突生成,保护神经元抵御外界损伤[21-23]。Artemin在多种常见肿瘤如肺癌、前列腺癌和胰腺癌中均呈高表达[24-26],其表达变化与$CD45^-EPC$比例呈正相关,$CD45^-EPC$通过分泌Artemin促进恶性肿瘤生长和转移[9],但鲜见Artemin与阿尔茨海默病相关性的报道。本研究结果显示,阿尔茨海默病患者药物治疗前$CD45^-EPC$比例和Artemin含量均低于正常对照者,而治疗前后$CD45^-EPC$比例和Artemin含量无显著差异;此外,神经元凋亡实验显示,$CD45^-EPC$组神经元凋亡比例低于AD模型组、$CD45^+EPC$组和Artemin阻断组,提示Artemin可能是$CD45^-EPC$发挥生物学功能的重要机制,而奥氮平和多奈哌齐等药物对阿尔茨海默病患者Artemin水平无明显影响可能与这些药物无法平衡红系前体细胞亚型有关。

综上所述,阿尔茨海默病患者外周血$CD45^+EPC$比例增加、$CD45^-EPC$比例减少。

CD45⁻EPC通过分泌Artemin减少阿尔茨海默病引起的神经元凋亡，为阿尔茨海默病的预防与治疗提供了新的靶点。

利益冲突 无

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