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PI3K/Akt 信号通路参与 LPS 诱导大鼠肺微血管内皮细胞表达 RACK1 及 rac1

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摘要 **目的** 探讨磷脂酰肌醇 3-激酶(PI3K)/丝氨酸-苏氨酸蛋白激酶(Akt)信号通路对脂多糖(LPS)诱导大鼠肺微血管内皮细胞(PMVEC)表达活化的蛋白激酶 C 受体 1(RACK1)和 ras 相关 C3 肉毒菌毒物底物 1(rac1)的影响。**方法** 体外培养大鼠 PMVEC:① LPS 量效组:0、1、5、10 mg/L LPS 与大鼠 PMVEC 孵育 12 h;② LPS 时效组:10 mg/L LPS 与 PMVEC 孵育 0、3、6、8、12、24 h;③ IGF-1 时效组:100 ng/ml IGF-1 与 PMVEC 孵育 0、3、6、8、12、24 h;④ LPS+LY294002 组:100 ng/ml LY294002 预孵育 PMVEC 1 h 后加入 10 mg/L LPS 继续孵育 12 h,设空白组、LPS 组和 LY294002 组为对照。所有干预结束后 Western blot 法检测 RACK1、rac1 及 p-Akt 蛋白表达。**结果** ① LPS 量效组:RACK1、rac1 及 p-Akt 蛋白表达量均呈浓度依赖性增加,各蛋白组组内比较差异均有统计学意义:(F=120.455,P<0.001)、(F=165.813,P<0.001)及(F=309.346,P<0.001)。② LPS 时效组:RACK1 和 rac1 蛋白表达呈时间依赖性增加,LPS 刺激 24 h 后达最高,各蛋白组组内比较差异均有统计学意义:(F=454.034,P<0.001)和(F=423.630,P<0.001);p-Akt 表达自 3 h(0.460±0.089)上调,12 h 达最高(2.022±0.244),24 h(1.264±0.074)仍高于 0 h(0.237±0.063),组间比较差异有统计学意义(F=137.726,P<0.001)。③ IGF-1 时效组:IGF-1 诱导 PMVEC 表达 RACK1、rac1 及 p-Akt 呈时间依赖性增加,各组组间比较差异有统计学意义(F=188.293,P<0.001)、(F=115.071,P<0.001)及(F=60.175,P<0.001)。④ LY294002 干预组:LPS+LY294002 作用 PMVEC 后:RACK1 蛋白表达量较 LPS 组下调[(0.732±0.137) *vs* (1.498±0.167),P<0.001];rac1 蛋白表达量较 LPS 组下调[(0.758±0.084) *vs* (1.384±0.170),P<0.001];p-Akt 蛋白表达量较 LPS 组下调[(0.492±0.148) *vs* (1.106±0.219),P<0.001]。**结论** PI3K/Akt 信号通路通过干预 RACK1 和 rac1 表达,参与 LPS 致 PMVEC 损伤。

关键词 肺微血管内皮细胞;活化的蛋白激酶 C 受体 1;ras 相关 C3 肉毒菌毒物底物 1;磷脂酰肌醇 3-激酶/丝氨酸-苏氨酸蛋白激酶;急性呼吸窘迫综合征
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肺微血管内皮细胞(pulmonary microvascular endothelial cells,PMVEC)损伤致弥漫性肺间质及肺泡水肿是急性呼吸窘迫综合征(acute respiratory distress syndrome,ARDS)病理学特征,多种信号通路参与调控[1]。磷脂酰肌醇 3-激酶(phosphatidylinositol 3-kinase,PI3K)/丝氨酸-苏氨酸蛋白激酶(protein kinase B,Akt)信号通路通过调控炎症细胞活化和炎症介质释放参与脂多糖(lipopolysaccharide,LPS)介导的细胞损伤过程,但机制尚不明确[2];活化的蛋白激酶 C 受体 1(receptor for activated C kinase 1,RACK1)是细胞支架蛋白,与多种蛋白结合,整合来自不同信号途径的信息[3];ras 相关 C3 肉毒菌毒物底物 1(ras-related C3 botulinum toxin substrate 1,rac1)作为小 G 蛋白成员参与内皮细胞屏障功能调控[4]。研究[5]发现 Akt 调控 rac1 活化,而 RACK1 与 rac1 活化关系密切,因此,推测 PI3K/Akt 信号通路可能通过调控 RACK1/rac1 参与 LPS 致 PMVEC 损伤。

1 材料与方法

1.1 试剂与仪器 DMEM 培养基(美国,Hyclone 公司),胎牛血清(澳大利亚,Gibco 公司),p-Akt 单克隆抗体、RACK1 单克隆抗体及 rac1 单克隆抗体(英国,Abcom 公司)、辣根过氧化物酶标记的羊抗兔 IgG(北京,中杉金桥),LY294002(PI3K/Akt 信号通路特异抑制剂,美国,Selleck 公司),IGF-1(PI3K/Akt 信号通路特异激动剂,美国,CST 公司),其余实验试剂均为国产分析纯,SD 大鼠购自安徽医科大学动物实验中心[SPF 级,合格证号:SCXK(皖)2011-002]。

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1.2　方法

1.2.1　大鼠PMVEC分离培养及鉴定　按照本实验室建立的方法及参考文献进行[2]。

1.2.2　Western blot检测RACK1、rac1及p-Akt蛋白表达　裂解3代大鼠PMVEC 30 min后收集蛋白。选择10%分离胶和5%浓缩胶进行电泳,蛋白转移至PVDF膜上,封闭液中室温封闭2 h后,TBS-T溶液洗膜,与RACK1、rac1或p-Akt单克隆抗体(1∶1 000)4 ℃过夜,辣根过氧化物酶标记的山羊抗兔IgG溶液(1∶20 000)室温90 min孵育,底物化学发光法显影,扫描仪扫描存盘,Quantity One软件分析、测定各组目的蛋白与同一样本中的内参β-actin(武汉博士德生物工程有限公司)积分光密度,比值衡量蛋白表达量的相对变化。

1.2.3　实验分组和处理　(1)量效实验:分别以0、1、5、10 mg/L LPS与PMVEC孵育12 h;(2)时效实验:以10 mg/L LPS或100 ng/ml IGF-1分别与PMVEC孵育0、3、6、8、12、24 h;(3)LPS+LY294002干预组:以100 ng/ml LY294002孵育1 h后继续加入10 mg/L LPS预孵育12 h,设空白组、LPS组和LY294002组为对照。干预结束后均检测RACK1、rac1及p-Akt蛋白表达。

1.3　统计学处理

采用SPSS 17.0软件进行统计学分析,数据以$\bar{x} \pm s$表示,两组变量间比较采用t检验,多组变量间比较采用单因素方差分析,$P<0.05$为差异有统计学意义。

2　结果

2.1　不同浓度LPS诱导大鼠PMVEC表达RACK1、rac1及p-Akt　PMVEC低表达RACK1和rac1,0、1、5、10 mg/L LPS刺激上调rac1表达($F=165.813$,$P<0.001$);0、1、5、10 mg/L LPS刺激后,RACK1表达上调,各组间比较差异有统计学意义($F=120.455$,$P<0.001$)。LPS未刺激时,PMVEC低表达p-Akt,0、1、5、10 mg/L LPS诱导p-Akt表达增加,各组间比较差异有统计学意义($F=309.346$,$P<0.001$)。见图1、表1。

2.2　LPS刺激不同时间诱导大鼠PMVEC表达rac1、RACK1及p-Akt　10 mg/L LPS刺激3 h后rac1表达增加,24 h达最高,组间差异有统计学意义($F=423.630$,$P<0.001$);10 mg/L LPS刺激3 h后,RACK1表达上调,组间差异有统计学意义($F=454.034$,$P<0.001$);10 mg/L LPS刺激3 h后,p-Akt表达上调,12 h达最高,24 h开始降低,组间差异有统计学意义($F=137.726$,$P<0.001$)。见图2、表2。

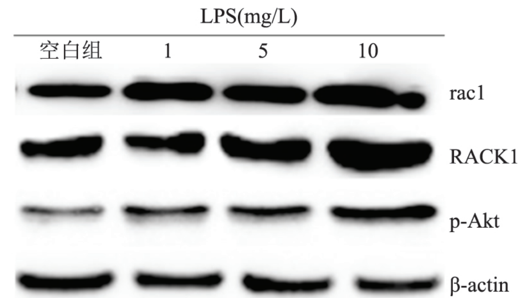

图1　不同浓度LPS诱导PMVEC表达RACK1、rac1及p-Akt

表1　不同浓度LPS与PMVEC孵育后rac1、RACK1及p-Akt的相对表达量($n=5$,$\bar{x} \pm s$)

孵育浓度(mg/L)	rac1	RACK1	p-Akt
0	0.883±0.151	2.007±0.202	0.135±0.032
1	2.129±0.166[a]	2.489±0.225[a]	0.378±0.041[a]
5	2.550±0.191[ab]	3.695±0.252[ab]	0.700±0.115[ab]
10	3.160±0.158[abc]	4.278±0.169[abc]	1.958±0.163[abc]
F值	165.813	120.455	309.346
P值	<0.001	<0.001	<0.001

与0 mg/L组比较:[a]$P<0.05$;与1 mg/L组比较:[b]$P<0.05$;与5 mg/L组比较:[c]$P<0.05$

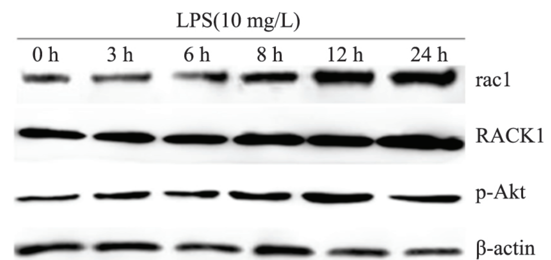

图2　LPS刺激不同时间诱导PMVEC表达RACK1、rac1及p-Akt

表2　LPS与PMVEC孵育不同时间后rac1、RACK1及p-Akt的相对表达量($n=5$,$\bar{x} \pm s$)

孵育时间(h)	rac1	RACK1	p-Akt
0	0.364±0.056	0.983±0.133	0.237±0.063
3	0.848±0.103[a]	1.252±0.107[a]	0.460±0.089[a]
6	1.089±0.102[ab]	1.504±0.070[ab]	0.622±0.084[ab]
8	1.330±0.443[abc]	2.293±0.179[abc]	0.886±0.087[abc]
12	3.487±0.265[abcd]	2.585±0.278[abcd]	2.022±0.244[abcd]
24	4.070±0.224[abcde]	4.489±0.236[abcde]	1.264±0.074[abcde]
F值	423.630	454.034	137.726
P值	<0.001	<0.001	<0.001

与0 h组比较:[a]$P<0.05$;与3 h组比较:[b]$P<0.05$;与6 h组比较:[c]$P<0.05$;与8 h组比较:[d]$P<0.05$;与12 h组比较:[e]$P<0.05$

2.3 IGF-1 刺激不同时间诱导大鼠 PMVEC 表达 rac1、RACK1 及 p-Akt 100 ng/ml IGF-1 刺激 3 h 后 rac1 表达上调，组间比较差异有统计学意义（$F=115.071$，$P<0.001$）；100 ng/ml IGF-1 刺激 3 h 后 RACK1 表达上调，组间比较差异有统计学意义（$F=188.293$，$P<0.001$）；100 ng/ml IGF-1 刺激后，p-Akt 表达自 3 h 开始上调，组间比较差异有统计学意义（$F=60.175$，$P<0.001$）。见图 3、表 3。

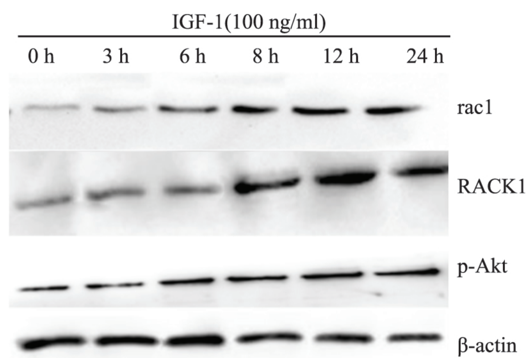

图 3 IGF-1 刺激不同时间诱导 PMVEC 表达 RACK1、rac1 及 p-Akt

表 3 IGF-1 与 PMVEC 孵育不同时间后 rac1、RACK1 及 p-Akt 的相对表达量（$n=5$，$\bar{x}\pm s$）

孵育时间(h)	rac1	RACK1	p-Akt
0	0.133±0.033	0.129±0.024	0.149±0.119
3	0.285±0.087[a]	0.255±0.049[a]	0.258±0.034[a]
6	0.503±0.050[ab]	0.401±0.078[ab]	0.349±0.037[ab]
8	0.927±0.144[abc]	0.809±0.084[abc]	0.450±0.089[abc]
12	1.339±0.155[abcd]	1.360±0.157[abcd]	0.657±0.109[abc]
24	1.450±0.154[abcd]	1.425±0.098[abcd]	0.760±0.070[abcde]
F 值	115.071	188.293	60.175
P 值	<0.001	<0.001	<0.001

与 0 h 组比较：[a]$P<0.05$；与 3 h 组比较：[b]$P<0.05$；与 6 h 组比较：[c]$P<0.05$；与 8 h 组比较：[d]$P<0.05$；与 12 h 组比较：[e]$P<0.05$

2.4 LY294002 对 LPS 诱导大鼠 PMVEC 表达 RACK1、rac1 及 p-Akt 的影响 与 LPS 组比较，LPS+LY294002 组 PMVEC 表达 RACK1、rac1 及 p-Akt 均显著下调，差异有统计学意义（$P<0.001$）；LY294002 单独刺激 PMVEC 后，RACK1、rac1 和 p-Akt 表达较空白组下调，差异有统计学意义（$P<0.001$）。见图 4、表 4。

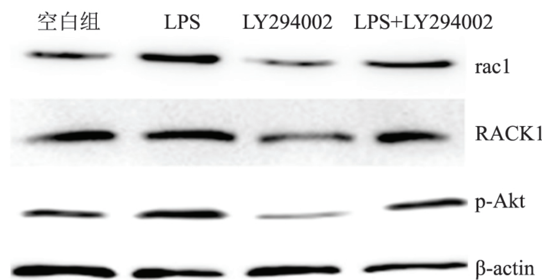

图 4 LY294002 对 LPS 诱导 PMVEC 表达 RACK1、rac1 及 p-Akt 干预作用

表 4 LY294002 影响 LPS 诱导 PMVEC 的 rac1、RACK1 及 p-Akt 相对表达量（$n=5$，$\bar{x}\pm s$）

组别	rac1	RACK1	p-Akt
空白组	0.638±0.076	0.736±0.150	0.430±0.097
LPS	1.384±0.170[a]	1.498±0.167[a]	1.106±0.219[a]
LY294002	0.495±0.054[ab]	0.663±0.126[ab]	0.256±0.056[b]
LPS+LY294002	0.758±0.084[bc]	0.732±0.137[bc]	0.492±0.148[bc]
F 值	68.566	36.668	33.315
P 值	<0.001	<0.001	<0.001

与空白组比较：[a]$P<0.05$；与 LPS 组比较：[b]$P<0.05$；与 LY294002 组比较：[c]$P<0.05$

3 讨论

研究发现激活的 PI3K 磷酸化 Akt，p-Akt 移动到胞质及胞核，再结合 NF-κB、Bcl-2 和 mTOR 等，调控炎症细胞活化和炎症介质释放，故 p-Akt 可作为 PI3K/Akt 信号通路活化的标志物[2,7-8]；另外，研究证实 p-Akt 作为 LPS 下游信号通路，上调 IL-1、IL-6 和 TNF-α 等参与 LPS 损伤过程[2,8]。本研究显示在 LPS 刺激 PMVEC 过程中，p-Akt 表达水平呈时间及浓度依赖性增加，因此，PI3K/Akt 信号通路参与 LPS 致 PMVEC 损伤过程，但其下游信号传导机制尚不明确。

具有 7 个 WD40 位点的 RACK1 是 G 蛋白 β 亚基的同族体，可结合蛋白激酶 C、Src 等[9]，维持细胞活化状态，引导活化蛋白前往特定区域，介导多种信号通路，参与炎症反应[3,9-10]。研究证实 PI3K/Akt 信号通路激活与 RACK1 密切相关：在食管鳞状细胞癌株中过表达 RACK1 增加 p-Akt，激活 PI3K/Akt 信号通路[3]。本研究表明在 LPS 损伤 PMVEC 过程中，RACK1 表达水平与 p-Akt 一致，呈时间和浓度依赖性增加，提示 PI3K/Akt 信号通路与 RACK1 相互促进；进一步研究发现 PI3K/Akt 特异性激动剂诱导 PMVEC 的 RACK1 表达量呈时间依赖性增加，而抑制 PI3K/Akt 信号通路后，RACK1 表达量呈时间依赖性下降，推测 RACK1 可能为 PI3K/Akt 信号通路效应因子。

rac1 是小 G 蛋白家族成员，调控细胞形态、黏附、骨架及内皮细胞迁移等[5,11-12]；rac1 参与 RACK1 活性调控[5]，如在上皮细胞中，rac1 解除 Src 与 RACK1 的绑定，进而与 RACK1 形成复合物，促进细胞周期进程及细胞生长[13-14]；此外，rac1 也作为 PI3K/Akt 信号通路的下游靶点[11-12]。本研究表明在 LPS 诱导 PMVEC 过程中，rac1 表达水平与 RACK1 一致，提示 rac1 和 RACK1 同步参与 LPS 致 PMVEC 损伤。实验进一步证实应用信号通路特异性激动剂激活 PI3K/Akt 后，rac1 表达水平呈时间依赖性增加，而应用信号通路特异性抑制剂抑制 PI3K/Akt 后，rac1 表达水平下降，且其趋势与 RACK1 一致，故推测 PI3K/Akt 信号通路可能通过调控 RACK1-rac1 复合物参与 LPS 致 PMVEC 损伤过程。

综上所述，本研究证实 LPS 损伤 PMVEC 过程中，PI3K/Akt 信号通路被激活；LPS 诱导大鼠 PMVEC 表达 RACK1 及 rac1 增加；PI3K/Akt 信号通路通过调控 RACK1 及 rac1 表达参与 LPS 损伤 PMVEC，从而为 ARDS 的发病和诊治提供思路，但在 PMVEC 中，RACK1 与 rac1 是否通过复合物形式参与 PI3K/Akt 信号通路调控有待进一步探讨。

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The PI3K/Akt signaling pathway involved in the expression of RACK1 and rac1 in the rat pulmonary microvascular endothelial cells induced by lipopolysaccharide

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Abstract ***Objective*** To explore the effects of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signaling pathway on the expression of receptor for activated C kinase 1 (RACK1) and ras-related C3 botulinum toxin substrate 1 (rac1) in rat pulmonary microvascular endothelial cells (PMVEC) induced by lipopolysaccharide

(LPS). Methods Cultured rat PMVEC in vitro were divided into different groups of LPS dose-dependent group, LPS time-dependent group, IGF-1 time-dependent group and LPS + LY294002 group. ① For LPS dose-dependent group, PMVEC were cultured with 0, 1, 5, 10 mg/L LPS for 12 h. ② For LPS time-dependent group, PMVEC were cultured with 10 mg/L LPS for 0, 3, 6, 8, 12, 24 h. ③ For IGF-1 time-dependent group, PMVEC were cultured with IGF-1 for 0, 3, 6, 8, 12, 24 h. ④ For LPS + LY294002 group, PMVEC were cultured with 100 ng/ml LY294002 for 1 h before the treatment of 10 mg/L LPS for an additional 12 h. In addition, blank, LPS and LY294002 groups were set as references. After intervention, the levels of RACK1, rac1 and p-Akt were detected with Western blot. ***Results*** ① In LPS dose-dependent group, the relative expression levels of RACK1, rac1 and p-Akt increased in a dose-dependent manner, and there were significant differences among the groups of RACK1 (F = 120.455, P < 0.001), among the groups of rac1 (F = 165.813, P < 0.001) and among the groups of p-Akt (F = 309.346, P < 0.05), respectively. ② In LPS time-dependent group, the relative expression levels of RACK1 and rac1 increased in a time-dependent manner, and there were significant differences among the groups of RACK1 (F = 454.034, P < 0.001) and among the groups of rac1 (F = 423.630, P < 0.001), respectively. The relative expression level of p-Akt raised at 3 h (0.460 ± 0.089), peaked at 12 h (2.022 ± 0.244), and it was still higher at 24 h (1.264 ± 0.074) than 0 h (0.237 ± 0.063). There were significant differences (F = 137.726, P < 0.001) among the groups of p-Akt expression. ③In IGF-1 time-dependent group, the relative expression levels of RACK1, rac1 and p-Akt increased in a time-dependent manner, and there were significant differences among the groups of RACK1 (F = 188.293, P < 0.001), rac1 (F = 115.071, P < 0.001) and p-Akt (F = 60.175, P < 0.001). ④ In LPS + LY294002 intervention group, the expression of RACK1 was lower than that of the LPS group [(0.732 ± 0.137) *vs* (1.498 ± 0.167), P < 0.001], the expression of rac1 was lower than that of the LPS group [(0.758 ± 0.084) *vs* (1.384 ± 0.170), P < 0.001], the expression of p-Akt was lower than that of the LPS group [(0.492 ± 0.148) *vs* (1.106 ± 0.219), P < 0.001]. ***Conclusions*** PI3K/Akt signaling pathway participates in LPS-induced PMVEC injury by interfering with RACK1 and rac1 expression.

Key words pulmonary microvascular endothelial cells; activation of protein kinase C receptor 1; ras-related C3 botulinum toxin substrate 1; PI3K/Akt signaling pathway; acute respiratory distress syndrome

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Effect of TET1 overexpression on the proliferation of cervical cancer cells

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Abstract ***Objective*** To investigate the effect of TET1 gene on the proliferation and migration of HeLa cells. ***Methods*** The overexpression plasmid of TET1 was constructed by transcription activator-like effectors (TALE)-vp64 system and transfected into cervical cancer HeLa cells. The proliferation of HeLa cells was monitored by thiazolyl blue tetrazolium bromide (MTT), the migration ability of HeLa cells was detected by scratch test, and the invasion ability of HeLa cells was detected by Transwell. ***Results*** MTT assay showed that the proliferation ability of TET1overexpressed cells was significantly lower than that of wild-types (P < 0.05). The numbers of HeLa cells passed through the matrigel were (Clone 1, 21 ± 5) and (Clone 2, 22 ± 6) in TET1 overexpresed cells, and (38 ± 7) in wild-type HeLa group, the difference between the two group was statistically significant (P < 0.05). The migration rates of HeLa cell in TET1 overexpressed (Clone 1, Clone 2) and the wild-type group at 24 h and 48 h were detected by scratch test, the latter was significantly higher than the former (P < 0.01). TET1 overexpression could restrain the ability of proliferation, invasion and migration of HeLa cells. ***Conclusion*** Overexpression of TET1 gene can inhibit the biological behavior of cervical cancer cells.

Key words TET1; cervical cancer; invision; proliferation