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论著

PKC/Raf-1/NF-κB信号通路在低氧诱导大鼠单核细胞表达TNF-α中的作用

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摘要 目的：研究PKC/Raf-1/NF-κB信号通路在低氧诱导大鼠外周血单核细胞（PBMCs）肿瘤坏死因子α（TNF-α）表达中的作用，探讨低氧与全身炎症反应综合征(SIRS)的关系，为进一步研究老年多器官功能障碍综合征(MODSE)的肺启动机制奠定基础。方法:采用明胶法分离大鼠外周血单核细胞，分为chelerythrine+低氧组、forskolin+低氧组和单纯低氧组。Chelerythrine+低氧组和forskolin+低氧组细胞在低氧前分别予10 μmol/L chelerythrine和50 μmol/L forskolin预处理。然后各组均于低氧条件下（3 % O 2, 5 % CO 2, 92 % N 2）培养0、1、3、6、9、12、24 h后，收集细胞及培养液上清，分别采用PKC、Raf活性检测试剂盒、电泳迁移分析法（EMSA）、逆转录PCR（RT-PCR）和酶联免疫吸附试验（ELISA）检测PKC、Raf-1、NF-κB活性及TNF-α表达量。结果:低氧1-9 h，PKC、Raf-1活性、NF-κB结合活性及TNF-α表达量显著高于正常对照组（P<0.01）。低氧后1-24 h，PKC、Raf-1活性、NF-κB结合活性与TNF-α mRNA和蛋白表达水平间呈显著正相关（P<0.01，P<0.05）。10 μmol/L chelerythrine可显著抑制低氧诱导的PKC、Raf-1、NF-κB活性升高和TNF-α表达。50 μmol/L forskolin可显著抑制低氧诱导的Raf-1、NF-κB活性升高及TNF-α表达。结论:低氧可显著增强大鼠外周血单核细胞的PKC、Raf-1活性及NF-κB结合活性,并可诱导其产生大量的促炎症因子TNF-α，这些变化可能与急性呼吸窘迫综合征（ARDS）时血浆中大量促炎症因子持续存在密切相关。

关键词 低氧 NF-κB； 肿瘤坏死因子； PKC/Raf-1/NF-κB信号通路

分类号 R364.4； R392.12； R392.13

Role of PKC/Raf-1/NF-kappa B signal cascade in expression of TNF-alpha in rat monocytes exposed to hypoxia

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Abstract

<FONT face=Verdana>AIM: To investigate the role of PKC/Raf-1/NF-κB signal cascade in the expression of TNF-α in rat peripheral blood mononuclear cells (PBMCs) exposed to hypoxia, and to explore the relationship between hypoxia and system inflammation response syndrome(SIRS) for the further study of the primordial role of lung in the pathogenesis of the multiple organ dysfunction syndrome in the elderly (MODSE). METHODS: Purified rat PBMCs were divided randomly into three groups: chelerythrine + hypoxia group, forskolin + hypoxia group and hypoxia group. The chelerythrine + hypoxia group and forskolin + hypoxia group were pretreated with 10 μmol/L chelerythrine and 50 μmol/L forskolin respectively before being exposed to hypoxia. Then three groups were exposed to hypoxia (3%O2, 5%CO2, 92%N2) for 0, 1, 3, 6, 9, 12, 24 h. The PKC and Raf-1 activity were assayed by PKC kit and Raf-1 kit, respectively. The NF-κB binding activity was detected by electrophoretic mobility shift assay (EMSA). The expression of TNF-α was detected by reverse transcriptase PCR(RT-PCR) and enzyme linked immunosorbent assay(ELISA). RESULTS: The activities of PKC, Raf-1 and NF-κB and the expression of TNF-α increased significantly during 1-9 h of hypoxic exposure (P<0.01). There were significant positive correlations between the activities of PKC, Raf-1 and NF-κB and the expression of TNF-α (P<0.01,P< 0.05).
 Chelerythrine at concentration of 10 μmol/L suppressed the hypoxia-

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induced PKC, Raf-1 and NF-κB activation and the expression of TNF-α. Forskolin at concentration of 50 μmol/L suppressed the hypoxia-induced Raf-1 and NF-κB activation and the expression of TNF-α. CONCLUSION: Hypoxia enhances the activities of PKC, Raf-1 and NF-κB in rat PBMCs, and up-regulates the expression of TNF-α in mRNA and protein levels subsequently, leading to the existance of massive pro-inflammatory factors persistently in the blood plasma of acute respiratory distress syndrome (ARDS) patients.</FONT>

Key words Hypoxia NF-kappa B Tumor necrosis factor PKC/Raf-1/NF-κB signal pathway

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