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髓系细胞触发受体-1在脂多糖急性肺损伤大鼠肺组织中的表达及其与内质网应激和炎性反应的关系

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摘要 目的:研究髓系细胞触发受体-1(TREM-1)在脂多糖急性肺损伤(ALI)大鼠肺组织中的表达及其与内质网应激和炎性反应的关系。**方法:**选择成年雄性SD大鼠100只作为研究对象,将其分成ALI组(n=60)、对照1组(n=15)、观察组(n=20)和对照2组(n=5)。对比ALI组和对照1组TREM-1、内质网应激表达及肿瘤坏死因子-α(TNF-α)水平、Smith评分,对比观察组和对照2组的CHOP mRNA、GRP mRNA表达情况,并分析TREM-1与内质网应激、炎性反应和Smith评分的相关性。**结果:**ALI组6h、12h、1d及2d时间点的TREM-1 mRNA、CHOP mRNA、GRP78 mRNA、TREM-1、TNF-α水平及Smith评分均高于对照1组,且ALI组随着时间的推移,TREM-1 mRNA、CHOP mRNA、GRP78 mRNA、TREM-1、TNF-α水平及Smith评分均呈升高的趋势,在1d时达到最高,然后呈下降趋势(P<0.05)。观察组6h、12h、1d及2d时间点的CHOP mRNA、GRP mRNA表达高于对照2组,且观察组随着时间的推移CHOP mRNA、GRP mRNA表达均呈升高的趋势,在1d时达到最高,然后呈下降趋势(P<0.05)。根据Spearman法分析相关性发现,TREM-1 mRNA及TREM-1水平均与CHOP mRNA、GRP78 mRNA及Smith评分呈正相关,且TREM-1水平与TNF-α呈正相关(P<0.05)。**结论:**TREM-1在脂多糖ALT大鼠肺组织中的表达较高,且参与ALT肺部炎性反应,激活TREM-1可增强巨噬细胞内质网应激。

关键词:髓系细胞触发受体-1;脂多糖;急性;肺损伤;大鼠;表达;内质网应激;炎性反应;关系

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Expression of Triggering Receptor Expressed on Myeloid Cells-1 in Lung Tissue of Rats with Acute Lung Injury Induced by Lipopolysaccharide and Its Relationship with Endoplasmic Reticulum Stress and Inflammatory Response

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ABSTRACT Objective: To investigate the expression of triggering receptor expressed on myeloid cells-1 (TREM-1) in lung tissue of rats with acute lung injury (ALI) induced by lipopolysaccharide and its relationship with endoplasmic reticulum stress and inflammatory response. **Methods:** 100 adult male SD rats were selected as research subjects, and they were divided into ALI group (n=60), control 1 groups (n=15), observation group (n=20) and control 2 group (n=5). The expression of TREM-1 and endoplasmic reticulum stress, the level of tumor necrosis factor-α (TNF-α) and the score of Smith were compared between the ALI group and control 1 group. The expression of CHOP mRNA and GRP mRNA in the observation group and the control 2 groups were compared. The correlation between TREM-1 and endoplasmic reticulum stress, inflammatory response and Smith score was analyzed. **Results:** The levels of TREM-1 mRNA, CHOP mRNA, GRP78 mRNA, TREM-1,TNF-α and Smith scores in the ALI group at 6 h, 12 h, 1 d, 2 d were significantly higher than those in the control 1 group (P<0.05), and TREM-1 mRNA, CHOP mRNA, GRP78 mRNA,TREM-1,TNF-α and Smith scores in the ALI group were increased with the time, which were reached the highest level at 1 d, then there had a downward trend (P<0.05). The expression of CHOP mRNA and GRPmRNA in the observation group at 6 h, 12 h, 1 d and 2 d was higher than that of the control 2 group, the expression of CHOP mRNA and GRP mRNA in the observation group increased with the time, which were reached the highest level at 1 d, then there had a downward trend (P<0.05). According to the correlation analysis of Spearman method showed that TREM-1 mRNA and TREM-1 levels were positively correlated with CHOP mRNA, GRP78 mRNA and Smith score, and TREM-1 level was positively correlated with TNF-α (P<0.05). **Conclusion:** The expression of TREM-1 is higher in the lung tissue of rats with ALI induced by lipopolysaccharide, and it is involved in the inflammatory response of the ALT lung. Activation of TREM-1 can enhance the endoplasmic reticulum stress of macrophages.

Key words: Triggering receptor expressed on myeloid cells-1; Lipopolysaccharide; Acute; Lung injury; Rat; Expression;

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Endoplasmic reticulum stress; Inflammatory reaction; Relationship

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前言

急性肺损伤(acute lung injury, ALI)在临床上较为常见,可由创伤、感染以及急性胰腺炎等因素引发[1,2]。ALI 患者的临床症状通常较重,当前仍缺乏十分有效的治疗手段,因其导致的死亡率高达 34%-46%,严重危害着患者的生存预后[3]。近年来的研究发现,肺内炎症的失控属于 ALI 的基础病理改变,并与 ALI 的病情产生及进展有一定联系[4]。而髓样细胞表达触发受体 -1(triggering receptor expressed on myeloid cells-1,TREM-1)作为免疫球蛋白有关超家族的一种细胞表面受体,其可介导细胞的吞噬、分泌及炎症反应等[5]。有报道称,TREM-1 经脂多糖诱导的机体炎症反应中可同接头蛋白 DAP12 发生作用而激活相应的免疫细胞,最终加重炎症反应[6]。内质网应激主要是指机体的细胞在受到多类损伤时,内质网内的未折叠蛋白质明显增多且超出了内质网的处理能力,从而激发的一种未折叠蛋白性反应[7]。转录因子 CHOP 及 GRP78 均为内质网应激的重要标志蛋白,二者的表达上升通常预示着内质网应激反应的形成[8]。本研究通过分析 TREM-1 在脂多糖 ALI 大鼠肺组织中的表达及其与内质网应激和炎性反应的关系,旨在提供科学的数据支持,现报道如下。

1 材料与方法

1.1 实验动物与分组

选择上海实验动物中心的成年雄性 SD 大鼠 100 只作为研究对象,将所有大鼠分成 ALI 组(n=60)、对照 1 组(n=15)、观察组(n=20)和对照 2 组(n=5)。ALI 组大鼠周龄为 28-31 周,平均(30.45± 0.39)周;体重 321-353 g,平均(336.03± 2.11)g。对照 1 组大鼠周龄为 27-32 周,平均(29.55± 0.43)周;体重 325-349 g,平均(335.79± 2.05)g。观察组大鼠周龄为 28-33 周,平均(30.89± 0.41)周;体重 320-347g,平均(334.98± 2.58)g。对照 2 组大鼠周龄为 26-30 周,平均(28.93± 0.48)周;体重 319-351 g,平均(335.77± 2.65)g。各组大鼠的周龄和体重比较差异无统计学意义(P>0.05),均衡可比。此次实验已经获得我院的动物实验伦理委员会评审通过。

1.2 模型制备与干预方法

1.2.1 ALI 模型制备及指标检测 ALI 组和对照 1 组给予 10%的水合氯醛麻醉,ALI 组大鼠实施气管注射脂多糖(美国 Sigma 公司)5 mg/kg 制成 ALI 模型,在造模之后的 6 h、12 h、1 d、2 d 各时间点分别取 15 只大鼠,麻醉后取出肺组织。对照 1 组大鼠注射等量的生理盐水,6 h 后取出肺组织,均通过液氮速冻之后放入 -80℃的冰箱中保存待测。提取 4-6 μm 厚的肺组织,经石蜡包埋后进行 HE 染色,在光学显微镜辅助下实施肺病理组织的 Smith 评分,对肺损伤情况进行半定量评估,评分项目包括肺水肿、出血、肺不张、炎性细胞浸润等,分值越高说明肺损伤越严重。TREM-1 和肿瘤坏死因子 -α(Tumor necrosis factor-α,TNF-α)水平的检测选用购自美国 R&D 公司生产的试剂盒进行操作,通过美国 AWARENESS 型酶标仪依次在波长为 450 nm 及 492 nm 区域检测光密度(optical density,OD)值,并按照标准品的浓度曲线算出实际水平。

1.2.2 TREM-1 激活后 CHOP 及 GRPmRNA 等指标的检测 观察组和对照 2 组从腹腔注射 3mL 3%的 TGA 4d 后通过颈椎脱臼法将大鼠处死,给予酒精消毒之后以 10mL 预冷后采用 RIPM1640 型培养基(美国 Hyclone 公司)对腹腔实施冲洗,而后依次进行重悬及离心,清除未贴壁细胞,得到高纯度的巨噬细胞标本。其中观察组给予 MAB1187 激活抗体使 TREM-1 激活,分别在激活后的 6 h、12 h、1 d、2 d 各时间点分别取 5 只大鼠收集细胞并提取 RNA。对照 2 组不激活 TREM-1,仅在 6h 后收集细胞并提取 RNA。

1.2.3 RNA 提取及基因表达的检测 将肺组织样本经液氮研磨成粉,添加 1 mL 的 TRIzol 使其充分裂解,而后对肺组织及细胞样本通过酚氯仿法将总 RNA 提取出,分别取 OD260/OD280 于 1.8-2.0 间并且电泳条带较为清晰的 RNA 样本实施检测。选择 1 μg 的总 RNA 通过逆转录试剂盒(日本 TaKaRa 公司)合成 cDNA,并用荧光定量聚合酶链式反应(polymerase chain reaction,PCR)仪(美国 Bio-rad 公司)实施 PCR 测定,将 β-actin 作为内参,通过 $2^{-\Delta\Delta Ct}$ 法算出基因相对表达量。其中 TREM-1 的上游引物为 5'- GACTGCTGTGCGTGTTCTTTG -3',下游引物为 5'- GCCAAGCCTTCTGGCTGTT -3',产物大小为 144kb。CHOP 的上游引物为 5'- TTGCCCTCTTATTGGTCCAGC -3',下游引物为 5'- TAGCGACTGTTCTGTTCCCAC -3',产物大小为 101kb。GRP78 的上游引物为 5'- GCATCACGCCGTCGTATGT -3',下游引物为 5'- ATTCCAAGTGCGTCCGATGAG -3',产物大小为 134kb。β-actin 的上游引物为 5'- GGCTGTATTCCCCTCCATCG -3',下游引物为 5'- CCAGTTGGTAACAATGCCATGT -3',产物大小为 154 kb。

1.3 观察指标

对比 ALI 组和对照 1 组 TREM-1、内质网应激表达及 TNF-α 水平、Smith 评分,对比观察组和对照 2 组的 CHOP mRNA、GRP mRNA 表达情况,并分析 TREM-1 与内质网应激、炎性反应和 Smith 评分的相关性。

1.4 统计学方法

选用 SPSS21.0 统计软件处理统计数据,计量资料用($\bar{x}$± s)表示,实施 t 检验,计数资料以[n(%)]表示,实施 x^2 检验,通过 Spearman 法对指标间的相关性实施分析,P<0.05 为差异有统计学意义。

2 结果

2.1 ALI 组和对照 1 组 TREM-1、内质网应激表达及 TNF-α 水平、Smith 评分对比

ALI 组 6 h、12 h、1 d 及 2 d 时间点的 TREM-1 mRNA、CHOP mRNA、GRP78 mRNA、TREM-1、TNF-α 水平及 Smith

评分均高于对照 1 组，且 ALI 组随着时间的推移，TREM-1 mRNA、CHOP mRNA、GRP78 mRNA、TREM-1、TNF-α 水平及 Smith 评分均呈升高的趋势，在 1d 时达到最高，然后呈下降趋势（P<0.05）。见表 1。

表 1 ALI 组和对照 1 组 TREM-1、内质网应激表达及 TNF-α 水平、Smith 评分对比（$\bar{x}\pm s$）

Table 1 Comparison of the expression of TREM-1, endoplasmic reticulum stress, and TNF-α level and Smith score in ALI group and control 1 group($\bar{x}\pm s$)

Groups	n	Time	TREM-1 mRNA (%)	CHOP mRNA (%)	GRP78 mRNA (%)	TREM-1level (pg/mL)	TNF-α(pg/mL)	Smith score (scores)
Control 1 group	15	6 h	1.00± 0.01	1.05± 0.03	1.04± 0.04	276.32± 51.30	229.17± 31.04	0.31± 0.25
ALI group	15	6 h	6.58± 0.06*	2.98± 0.08*	3.95± 0.23*	789.24± 103.97*	301.28± 25.44*	7.82± 0.85*
	15	12 h	34.67± 0.80*#	3.24± 0.10*#	7.87± 0.49*#	1153.82± 43.19*#	369.74± 95.30*#	8.49± 0.89*#
	15	1 d	60.98± 13.55*#△	6.32± 0.11*#△	16.57± 1.32*#△	1508.92± 104.47*#△	487.26± 25.43*#△	9.28± 0.85*#△
	15	2 d	55.79± 7.94*¥	5.18± 0.79*¥	12.78± 2.68*¥	463.95± 87.21*¥	281.03± 50.52*¥	7.46± 0.73*¥

Note: compared with control group, *P<0.05; compared with 6h, #P<0.05; compared with 12 h, △ P<0.05; compared with 1 d, ¥P<0.05.

2.2 观察组和对照 2 组的 CHOP mRNA、GRP mRNA 表达情况对比

观察组 6 h、12 h、1 d 及 2 d 时间点的 CHOP mRNA、GRPmRNA 表达高于对照 2 组，且观察组随着时间的推移 CHOP mRNA、GRPmRNA 表达均呈升高的趋势，在 1 d 时达到最高，然后呈下降趋势（P<0.05）。见表 2。

表 2 观察组和对照 2 组的 CHOP mRNA、GRP mRNA 表达情况对比（$\bar{x}\pm s$）

Table 2 Comparison of the expression condition of CHOP mRNA and GRP mRNA in observation group and control 2 group($\bar{x}\pm s$)

Groups	n	Time	CHOP mRNA(%)	GRP78 mRNA(%)
Control 2 group	5	6 h	1.04± 0.05	1.03± 0.02
Observation group	5	6 h	2.84± 0.06*	3.97± 0.21*
	5	12 h	3.13± 0.12*#	7.85± 0.43*#
	5	1 d	6.38± 0.11*#△	16.59± 1.37*#△
	5	2 d	5.10± 0.74*¥	12.77± 2.64*¥

Note: compared with control group, *P<0.05; compared with 6h, #P<0.05; compared with 12 h, △ P<0.05;compared with 1 d, ¥P<0.05.

2.3 TREM-1 与内质网应激、炎性反应、Smith 评分的相关性分析

根据 Spearman 法分析相关性发现，TREM-1 mRNA 及 TREM-1 水平均与 CHOP mRNA、GRP78 mRNA 及 Smith 评分呈正相关，且 TREM-1 水平与 TNF-α 呈正相关（P<0.05）。见表 3。

表 3 TREM-1 与内质网应激、炎性反应、Smith 评分的相关性分析（r，P）

Table 3 Correlation analysis between TREM-1 and endoplasmic reticulum stress, inflammatory response and Smith score(r, P)

Objects	CHOP mRNA	GRP78 mRNA	TNF-α	Smith score
TREM-1 mRNA	(0.582, 0.001)	(0.701, 0.000)	(0.404, 0.051)	(0.665, 0.000)
TREM-1level	(0.634, 0.000)	(0.650, 0.000)	(0.629, 0.000)	(0.521, 0.002)

3 讨论

临床上，ALI 属于是一种十分常见的急危重症，此病的发病率较高，预后较差，对患者的生存造成了较大程度的威胁[9]。在人体中，肺泡巨噬细胞作为肺组织中重要的一类居留型吞噬细胞，是防御呼吸道有关致病原的首道防线，对于侵入气道内的感染型和致敏型颗粒物的清除具有重要作用[10,11]。有报道证实，巨噬细胞在被激活之后可分泌出炎性因子、趋化因子、损伤介质及抗炎因子等，在 ALI 疾病的形成和进展中产生调节作用[12,13]。而 ALI 患者机体内发生失控型炎症反应过程中 TREM 有关成员可能扮演较为重要的角色，TREM-1 是最早发现的 TREM 成员之一，其在粒细胞、单核细胞以及巨噬细胞的表面可大量表达，与机体的免疫炎症反应具有一定的关联，但具体关系尚需进一步研究[14]。国外报道表明，内质网应激与机体内的多类免疫疾病及炎症疾病有关，且当前已发现内质网应激对于缺血再灌注所诱导的 ALI 是一个重要性致病因素[15,16]。为了更加明确地分析 ALI 疾病的内在细胞生物学联系，研究 TREM-1 在 ALI 肺组织中的表达及其与内质网应激和炎性反

应的关系显得尤为必要。

本研究结果显示,ALI 大鼠肺组织的 TREM-1 mRNA、CHOP mRNA、GRP78 mRNA 表达明显上升，且 TREM-1、TNF-α 水平及 Smith 评分也明显升高,并均在 1 d 后达到峰值。分析原因,主要可能与 ALI 大鼠机体的炎症反应进程的变化等因素有关。TREM-1 是在 2000 年研究发现的一种可表达在髓样细胞中的重要炎症放大性受体，其可对 Toll 样受体及 Nod 样受体产生协同作用而介导机体内的炎症失控状态[17]。在 ALI 大鼠机体中,中性粒细胞和巨噬细胞等有关髓系细胞不断发生大量的聚集活化,致使 TREM-1 mRNA 持续性地强化表达。同时,TREM-1 能够上调处于下游位置的 TNF-α 等炎性因子的表达,并启动了炎性反应的级联放大链,进而加重了肺损伤。而 Smith 评分是对肺损伤进行评估的一个有效方式，肺损伤的进行性加重使其水平也随之产生适应性的变化 [18]。CHOP 及 GRP78 参与了内质网蛋白质的折叠、转运和糖基化修饰等,当机体存在慢性心肺疾病或神经性疾病等时,CHOP 及 GRP78 表达迅速升高;而当内质网应激时间超过一定时间时,内质网功能失代偿,导致转录因子 CHOP 及 GRP78 迅速下降[19-21]。而内质网应激则可参与炎症性疾病，发生 ALT 的大鼠 CHOP mRNA、GRP78 mRNA 表达明显上升，充分说明了 CHOP mRNA、GRP78 mRNA 可能参与了 ALT 的发病进程[22,23]。随着时间的延长,ALI 大鼠机体的自我修复功能及免疫炎症调节机制产生的作用使得 TREM-1、TNF-α 及 CHOP mRNA、GRP78 mRNA 等有关指标的水平有所下降,但较正常大鼠仍处在偏高水平。同时，本研究还发现,TREM-1 激活能够明显提升 CHOPmRNA 及 GRPmRNA 的表达,并且二者的表达在激活后 1d 时达到峰值。分析原因,主要可能是因为 TREM-1 在激活之后能够由机体内的 Ca^{2+} 依赖型方式逐渐活化了细胞内的信号转导通路,而此种通路可能属于诱导巨噬细胞有关内质网应激的重要机制[24,25]。最后,本研究根据 Spearman 法分析相关性发现,TREM-1 mRNA 及 TREM-1 水平均与 CHOP mRNA、GRP78 mRNA 及 Smith 评分呈正相关，且 TREM-1 水平与 TNF-α 呈正相关，说明肺内 TREM-1 的激活诱导了内质网应激,同时 TREM-1 又参与了 ALT 的肺部炎症反应,因此上述指标表现出了较强的相关性。

综上所述,TREM-1 在 ALI 大鼠肺组织中的表达明显升高，且其与内质网应激和炎性反应之间存在一定程度的正相关，其可能是通过调节 CHOP mRNA、GRP78mRNA 等的表达影响大鼠内质网应激和炎性反应。

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