·论著·

右美托咪定通过上调Nur77抑制脂多糖诱导的巨噬细胞糖酵解和炎症反应

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摘要 目的 探讨右美托咪定(Dex)是否通过Nur77调控脓毒症巨噬细胞糖酵解和炎症反应。**方法** 利用基因表达综合(GEO)数据库分析Nur77与糖酵解、炎症相关基因的相关性。将小鼠白血病单核巨噬细胞系RAW264.7分为对照组、脂多糖(LPS)组、Dex+LPS组、Nur77抑制剂(DIM)+LPS组、Dex+DIM+LPS组。用Western blotting检测Nur77蛋白表达;用实时定量PCR及ELISA检测炎症因子白细胞介素(*IL*)-1β、*IL-10*、*TNF-α*的mRNA及蛋白表达水平;检测细胞上清液乳酸含量及NAD^+/NADH比值,评估糖酵解水平。**结果** 生物信息学分析显示,LPS刺激后,糖酵解基因表达在2 h达峰值,炎症反应在6 h达峰值,且糖酵解通路评分与炎症反应评分呈显著正相关($r = 0.77$,$P = 0.034$),提示糖酵解激活先于并促进炎症反应。Nur77与糖酵解关键酶GAPDH、PDK1呈显著负相关,*Nur77*基因敲除可上调糖酵解和炎症相关基因表达。与LPS组比较,Dex+LPS组Nur77表达显著上调,促炎性细胞因子*IL-1β*、*TNF-α* mRNA和蛋白表达水平显著降低,抗炎细胞因子*IL-10* mRNA和蛋白表达水平显著升高,乳酸含量显著减少,NAD^+/NADH比值显著升高。Nur77抑制剂DIM可部分逆转Dex的上述作用。**结论** 脓毒症时糖酵解激活和炎症反应相关。Dex通过上调Nur77表达抑制LPS诱导的巨噬细胞糖酵解和炎症反应。

关键词 右美托咪定;脓毒症;巨噬细胞;Nur77;糖酵解;炎症反应
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Dexmedetomidine inhibits LPS-induced inflammatory response and glycolysis in macrophages by upregulating Nur77

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Abstract Objective To investigate whether dexmedetomidine (Dex) regulates glycolysis and inflammatory responses in septic macrophages through Nur77. **Methods** The Gene Expression Omnibus database was used to analyze the correlation of Nur77 with glycolysis-related and inflamation-related genes. The murine leukimia monocyte/macrophage RAW264.7 cells were divided into control, lipopolysaccharide (LPS), dexmedetomidine treatment (Dex+LPS), Nur77 inhibitor (DIM) +LPS, Dex+DIM+LPS groups. Western blotting was performed to detect Nur77 protein expression. Real-time quantitative polymerase chain reaction and enzyme-linked immunosorbent assay were used to measure the mRNA and protein levels of the inflammatory cytokines *IL-1β*, *IL-10*, and *TNF-α*. Lactate content and the NAD^+/NADH ratio were measured to assess glycolysis levels. **Results** Bioinformatics analysis revealed that glycolytic gene expression peaked 2 hours after LPS stimulation, while the inflammatory response peaked at 6 hours, with a significant positive correlation between the glycolysis pathway score and inflammation score ($r = 0.77$, $P = 0.034$), suggesting that glycolysis activation precedes and promotes inflammatory response. In cell experiments, compared with the LPS group, the Dex+LPS group exhibited significantly higher Nur77 expression, lower levels of pro-inflammatory cytokines *IL-1β* and *TNF-α*, higher levels of the anti-inflammatory cytokine *IL-10*, reduced lactate content, and an elevated NAD^+/NADH ratio. The Nur77 inhibitor, DIM, partially reversed the effects of Dex. Furthermore, Nur77 expression had a significant negative correlation with the glycolytic enzymes GAPDH and PDK1, while *Nur77* knockout increased the expression of glycolysis- and inflammation-related genes. **Conclusion** Glycolysis activation is associated with the inflammatory response during sepsis, and Dex inhibits LPS-induced macrophage glycolysis and inflammatory responses by upregulating Nur77 expression, thereby exerting protective effects in sepsis.

Keywords dexmedetomidine; sepsis; macrophage; Nur77; glycolysis; inflammatory response

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脓毒症是机体对感染反应失调引起的危及生命的器官功能障碍[1]，其发病机制复杂，死亡率高，是重症监护室患者死亡的一个重要原因[2]。巨噬细胞在脓毒症时发生代谢重编程，表现为糖酵解增强，促炎性细胞因子大量释放，加重脓毒症的器官损伤[3]。右美托咪定（dexmedetomidine，Dex）是α_2肾上腺素受体激动剂，临床上主要用于镇静、镇痛。近年来研究[4-6]表明，Dex具有抗炎作用，可降低脓毒症死亡率，但其具体机制尚未阐明。

Nur77是孤儿核受体家族成员之一，在细胞增殖、分化、凋亡、自噬、炎症以及代谢等生命活动过程中发挥重要作用[7]。Nur77在巨噬细胞中高表达，可通过转录调控与线粒体相关途径调节巨噬细胞的炎症反应和代谢重编程[8-9]，还可抑制某些炎症模型中促炎性细胞因子的产生，并调控细胞代谢[10]。然而，Dex与Nur77及巨噬细胞糖酵解和炎症反应的关系目前尚不清楚。因此，本研究拟探讨Dex调控Nur77对脓毒症巨噬细胞糖酵解和炎症反应的影响。

1　材料与方法

1.1　材料

1.1.1　细胞：小鼠白血病单核巨噬细胞系RAW264.7对脂多糖（lipopolysaccharide，LPS）反应模式、糖酵解代谢特征及炎症因子分泌谱与原代巨噬细胞高度相似[11-12]，故采用该细胞系作为研究对象。用专用培养基（DMEM-H+10%胎牛血清+1%谷氨酰胺+1%丙酮酸钠，苏州海星生物科技有限公司），在37 ℃、5%CO_2培养箱中培养RAW264.7细胞（上海富衡生物科技有限公司），每2 d更换1次培养基，取对数生长期细胞进行实验。

1.1.2　试剂：LPS（美国Sigma-Aldrich公司），Dex（江苏恒瑞医药股份有限公司），Nur77抑制剂DIM-C-pPhOH（以下简称DIM，美国Med Chem Express公司），RIPA裂解液（北京索莱宝科技有限公司），GAPDH一抗（杭州华安生物技术有限公司），Nur77一抗（美国abcam公司）。NAD^+/NADH比值分析试剂盒（美国Amplite公司），酶联免疫吸附试验（enzyme-linked immunosorbent assay，ELISA）试剂盒（美国Novus公司），L-乳酸检测试剂盒（苏州格锐思生物科技有限公司），RNA提取试剂盒（上海奕杉生物科技有限公司），cDNA反转录试剂盒（北京天根生化科技有限公司），Talent荧光定量试剂盒（北京天根生化科技有限公司）。

1.2　方法

1.2.1　细胞分组及处理[13]：将RAW264.7细胞按照1×10^6/mL移至6孔板，培养12 h。将细胞分为对照（Control）组、LPS组、LPS+Dex组、LPS+Nur77抑制剂（DIM）组、LPS+Dex+DIM组。LPS组RAW264.7细胞用500 ng/mL LPS诱导3 h；LPS+Dex组在LPS诱导前采用10 μmol/L Dex预处理30 min；LPS+DIM组在LPS诱导前使用30 μmol/L DIM-C-pPhOH预处理30 min；LPS+Dex+DIM组使用DIM-C-pPhOH预处理30 min后，加入Dex处理30 min，随后加入LPS孵育3 h。为确保结果的可靠性，每个处理条件独立重复3次，每组设3个复孔。

1.2.2　Western blotting：用RIPA裂解液充分裂解各组细胞，收集上清并测定蛋白浓度。取30 μg蛋白上样，10% SDS-PAGE凝胶电泳后转至PVDF膜。5%脱脂牛奶室温封闭1 h，加入Nur77（1 ∶ 2 000）、GAPDH（1 ∶ 5 000）一抗，4 ℃孵育过夜。TBST洗膜，加入HRP标记二抗，室温孵育1 h，化学发光显影。使用ImageJ软件分析蛋白表达灰度值。

1.2.3　实时定量PCR：提取各组细胞总RNA，反转录合成cDNA。按照Talent荧光定量试剂盒说明书操作，进行实时定量PCR。PCR引物序列如下：白细胞介素（interlukin，*IL*）*-10*，正向5'-CAGGACTTTAAGGGTTACTTGG-3'，反向5'-GGCCTTGTAGACACCTTGGTC-3'；*IL-1β*，正向5'-GCAACTGTTCCTGAACTCAACT-3'，反向5'-ATCTTTTGGGGTCCGTCAACT-3'；肿瘤坏死因子α（tumor necrosis factor-α，*TNF-α*），正向5'-CTCACACTCAGATCATCTTCT-3'，反向5'-GCTACGACGTGGGCTACAG-3'；*GAPDH*，正向5'-GGTTGTCTCCTGCGACTTCA-3'，反向5'-TGGTCCAGGGTTTCTTACTCC-3'。以*GAPDH*为内参基因（对各组*GAPDH*的Ct值进行稳定性评估，各组间Ct值差异均在可接受范围内，提示本实验条件下*GAPDH*表达相对稳定，符合内参使用标准）。采用$2^{-\Delta\Delta Ct}$法计算mRNA相对表达量。每组每个基因设3个复孔检测，重复3批样本。

1.2.4　ELISA：各组细胞处理结束后，取培养液至无菌离心管，4 ℃、300 *g*离心5 min，收集上清，按照ELISA试剂盒说明书进行操作，检测450 nm处吸光

度值，计算IL-1β、IL-10、TNF-α的浓度。每组设3个复孔。

1.2.5　细胞上清液乳酸含量测定：收集各组细胞培养液，12 000 r/min离心10 min，取20 μL上清加入96孔板，每组设3个复孔。按照乳酸检测试剂盒说明书进行操作，检测450 nm处吸光度值，计算乳酸含量。

1.2.6　NAD^+/NADH比值测定：按照试剂盒说明书，用裂解缓冲液37 ℃孵育裂解各组细胞15 min，12 000 r/min离心5 min，取25 μL上清至96孔板，分别加入NADH标准品和工作液混匀，37 ℃孵育15 min，检测460 nm处吸光度值，计算NAD^+、NADH、NAD含量及NAD^+/NADH比值。

1.2.7　生物信息学分析：从基因表达综合（gene expression omnibus，GEO）数据库（https://www.ncbi.nlm.nih.gov/geo/）获取相关基因表达数据集，使用基因集变异分析（gene set variation analysis，GSVA）方法计算糖酵解通路和炎症反应通路的富集评分。分析LPS刺激后不同时间点信号通路活性变化，并采用Pearson相关分析评估糖酵解与炎症反应的关系。

1.2.8　Nur77与糖酵解关键酶的相关性分析：从GEO数据库下载数据集GSE154346，提取Nur77及糖酵解过程相关酶（包括HK2、PFKFB3、GAPDH、PKM、LDHA、SLC2A1、PDK1、HIF1A）的表达数据。采用Pearson相关分析Nur77与各糖酵解关键酶之间的相关性，并绘制相关性柱状图和散点图进行可视化展示。

1.2.9　*Nur77*敲除对炎症和糖酵解相关基因表达的影响分析：从GEO数据库下载数据集GSE68167，该数据集包含*Nur77*敲除（knockout，KO）和野生型（wild-type，WT）小鼠骨髓源性巨噬细胞在对照、IL-4刺激和LPS刺激条件下的基因表达数据。提取糖酵解相关基因和炎症相关基因的表达数据，比较WT组与KO组在各处理条件下的差异。进行全基因组水平的相关性分析，以验证数据质量，并绘制特定基因的表达对比图。

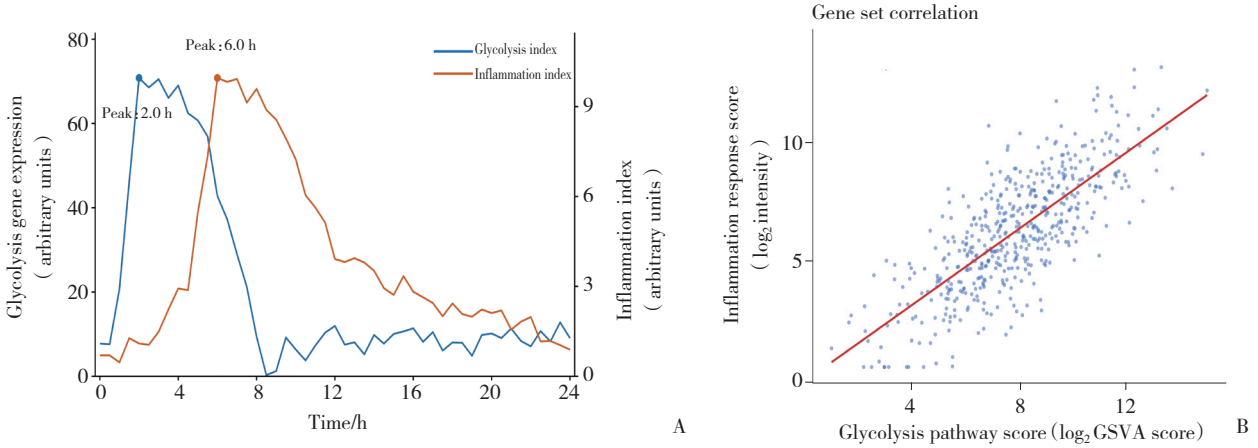
1.3　统计学分析

采用GraphPad Prism 10.0软件进行统计分析。计量资料用$\bar{x} \pm s$表示，2组比较采用独立样本t检验。多组间比较采用单因素方差分析后Tukey多重比较检验。$P<0.05$为差异有统计学意义。

2　结果

2.1　生物信息学分析糖酵解与炎症反应的相关性

GEO数据库分析结果显示，糖酵解基因表达在LPS刺激后2 h达到峰值，而炎症反应在6 h达到峰值，提示糖酵解的激活先于炎症反应。进一步的基因集相关性分析显示，糖酵解通路评分与炎症反应评分呈正相关（$r=0.77$，$P=0.034$），提示二者可能存在关联，但仍需进一步通过代谢干预实验验证。见图1。



A，temporal changes in glycolysis and inflammatory response following LPS stimulation. The blue line represents the glycolysis gene expression index (glycolysis index), while the orange line represents the inflammation response index (inflammation index); B, correlation analysis between the glycolysis pathway and inflammation response gene sets. The X-axis represents the glycolysis pathway score (log_2 GSVA score), and the Y-axis represents the inflammation response score (log_2 intensity).

图1　糖酵解与炎症反应的相关性分析

Fig.1　Correlation analysis between glycolysis and inflammation response

2.2　生物信息学分析验证Nur77与糖酵解的负调控关系

为进一步探讨Nur77与糖酵解的关系，利用GEO数据库进行相关分析。基于GSE154346数据集（n = 18）的Pearson相关分析显示，Nur77的表达水平与糖酵解关键酶GAPDH（r = −0.625，P < 0.01）和PDK1（r = −0.469，P < 0.05）呈负相关，见图2A、2B。进一步对GSE68167数据集中*Nur77* KO小鼠与WT小鼠的转录组数据进行分析，结果显示，在LPS刺激条件下，与WT组相比，*Nur77* KO组小鼠糖酵解相关基因（*GAPDH*、*HIF1A*、*LDHA*、*PKM2*）和炎症相关基因（*IL-1B*、*TNF-α*）表达显著上调，而抗炎性细胞因子*IL-10*表达显著下调，见图2C。从独立数据集角度验证了Nur77对糖酵解和炎症反应的负调控作用。

2.3　Dex对巨噬细胞中Nur77蛋白表达的影响

Western blotting结果显示，与Control组相比，LPS组Nur77蛋白表达水平升高；而LPS+Dex组Nur77蛋白较LPS组进一步升高（P < 0.05）；与LPS组相比，LPS+DIM组Nur77蛋白表达水平显著下降（P < 0.05）；与LPS+DIM组相比，LPS+Dex+DIM组Nur77蛋白表达水平进一步降低（P < 0.05）。见图3。

2.4　Dex通过上调Nur77抑制LPS诱导的RAW264.7细胞糖酵解

乳酸含量和NAD^+/NADH比值检测结果显示，LPS组乳酸含量和NAD^+/NADH比值较Control组显著升高；与LPS组比较，LPS+Dex组乳酸含量显著降低，NAD^+/NADH比值显著升高；与LPS组比较，LPS+DIM组乳酸含量显著升高，NAD^+/NADH比值降低；LPS+Dex+DIM组乳酸含量高于LPS+Dex组，但低于LPS+DIM组，NAD^+/NADH比值显著低于LPS+Dex组，但高于LPS+DIM组，差异均有统计学意义（均P < 0.05）。表明Dex可抑制LPS诱导的糖酵解，Nur77抑制剂可部分逆转Dex对糖酵解的抑制作用。见表1。

2.5　Dex通过上调Nur77抑制LPS诱导的RAW264.7细胞炎症反应

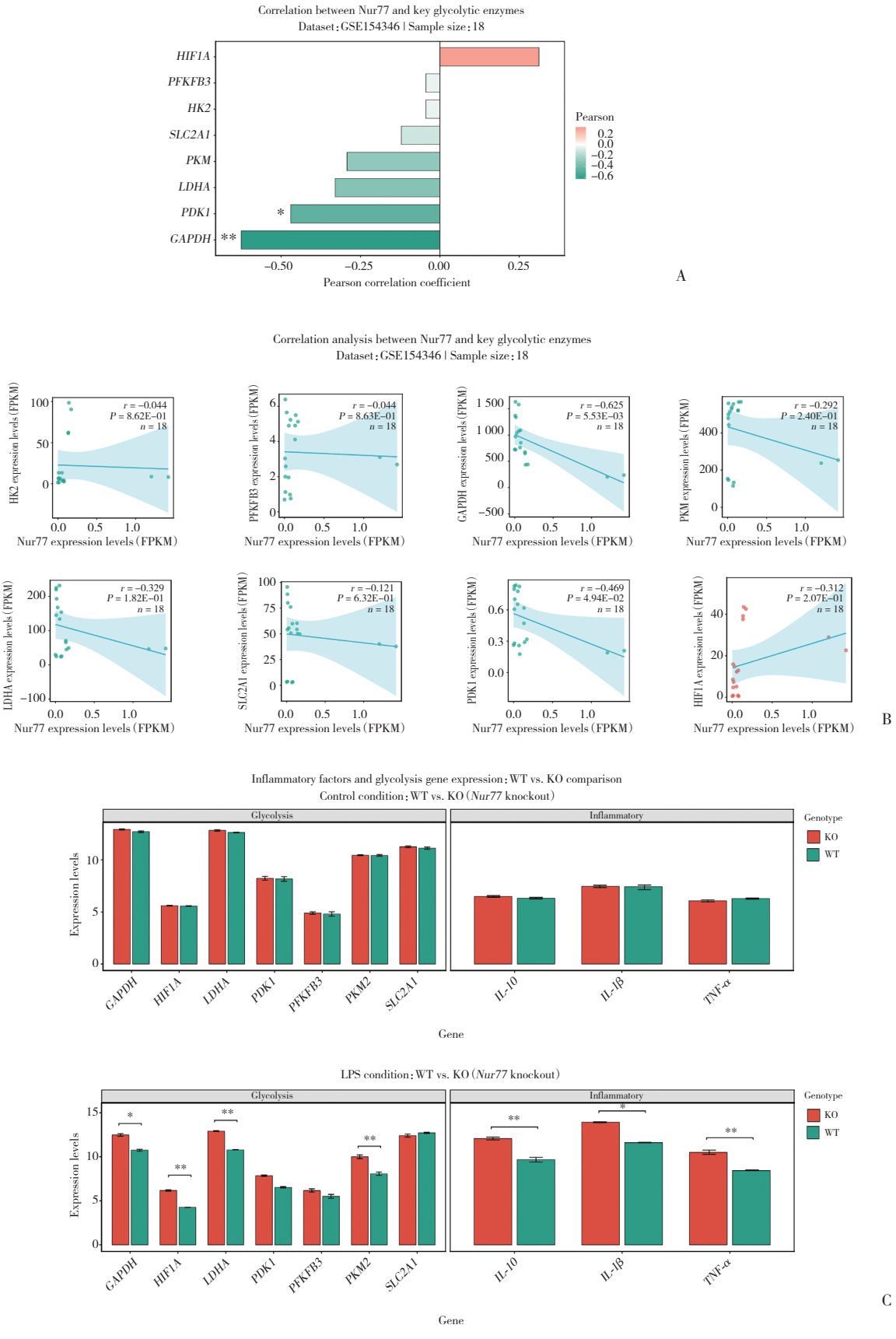
实时定量PCR和ELISA结果显示，与LPS组相比，LPS+Dex组*IL-10* mRNA及蛋白表达水平显著升高，*IL-1β*、*TNF-α* mRNA及蛋白表达水平显著降低（P < 0.05）；与LPS组相比，LPS+DIM组*IL-10* mRNA及蛋白表达水平降低，而*IL-1β*、*TNF-α* mRNA及蛋白表达水平升高（P < 0.05），提示Nur77抑制剂DIM可削弱抗炎细胞因子表达并加剧LPS诱导的促炎反应；与LPS+Dex组相比，LPS+Dex+DIM组*IL-10* mRNA及蛋白表达水平均降低，而*IL-1β*、*TNF-α* mRNA及蛋白表达水平均升高（P < 0.05），提示Nur77抑制剂DIM可部分逆转Dex的抗炎作用。见表2。

3　讨论

炎症反应过度激活是脓毒症多器官功能障碍发生的关键因素[14]。巨噬细胞作为天然免疫的重要效应细胞，在脓毒症早期大量释放促炎性细胞因子，加剧组织损伤[15]。Dex可通过激活α_2肾上腺素受体发挥抗炎作用[16]，但其下游分子机制尚未完全阐明。本研究证实了Dex通过上调Nur77抑制LPS诱导的巨噬细胞糖酵解和炎症反应。

糖酵解与炎症反应之间存在密切的双向调控关系：炎症信号可通过激活HIF-1α等转录因子上调糖酵解关键酶表达；糖酵解代谢产物，如乳酸，可作为信号分子进一步放大炎症反应[17]。本研究通过生物信息学分析发现，糖酵解激活先于炎症反应，并与后者呈正相关，提示糖酵解可能是炎症反应的上游事件。既往研究[18-19]证实，糖酵解抑制剂2-DG通过抑制LPS激活的糖酵解代谢显著降低巨噬细胞中TNF-α和IL-1β的分泌。本研究结果显示，Dex在抑制糖酵解的同时，还可减轻炎症反应，且该效应依赖于Nur77，提示Dex可能通过Nur77介导的糖酵解抑制发挥抗炎作用。

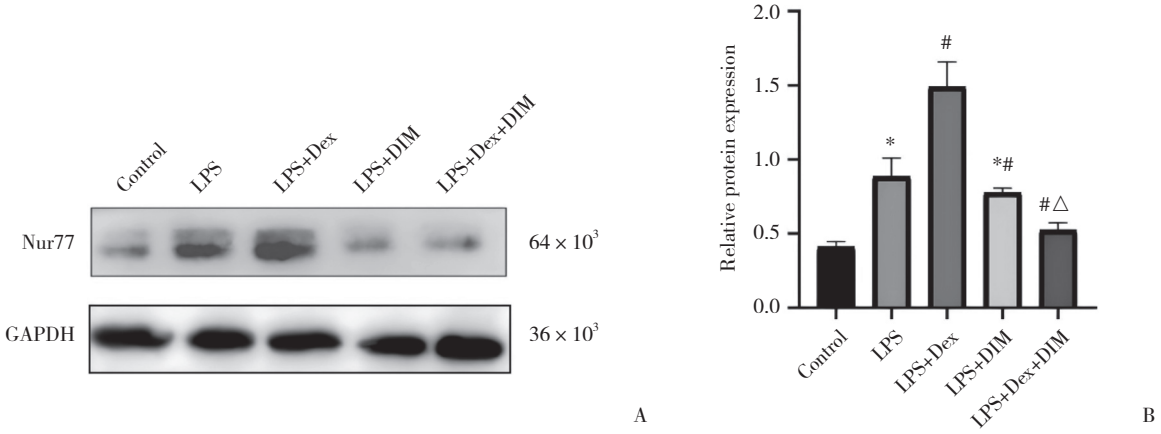
本研究还发现，LPS刺激导致乳酸生成增加的同时，NAD^+/NADH比值亦升高。多项研究[20-22]亦报道了LPS刺激巨噬细胞后NAD^+/NADH比值升高的现象。这反映了脓毒症巨噬细胞糖酵解代谢重编程的复杂性。在糖酵解过程中，甘油醛−3−磷酸脱氢酶催化的底物氧化步骤将NAD^+还原为NADH，而乳酸脱氢酶在将丙酮酸还原为乳酸的过程中将NADH氧化再生为NAD^+，这种NAD^+再循环机制维持了糖酵解所需的NAD^+供应，同时稳定细胞内NAD^+/NADH氧化还原平衡[23]。NAD^+/NADH比值升高可能与NAD^+补救合成通路的增强有关。LPS刺激可通过核因子κB（nuclear factor-κB，NF-κB）信号通路上调烟酰胺磷酸核糖转移酶表达，增强NAD^+的从头合成，从而提升细胞内NAD^+水平，这是巨噬细胞应对炎症应激和高能量需求的重要代偿机制[24-26]。



A, Pearson correlation heatmap between Nur77 and key glycolytic enzymes (data source GSE154346, $n = 18$); B, scatter plots depicting correlations between Nur77 and enzymes involved in the glycolytic process; C, comparison of inflammatory cytokine and glycolysis-related gene expression in *Nur77* knockout (KO) versus wild-type (WT) mice under LPS stimulation (data source GSE68167, $n = 10$). $^{*}P < 0.05$, $^{**}P < 0.01$.

图2　生物信息学分析验证Nur77与糖酵解及炎症的关系

Fig.2　Bioinformatics analysis validating the association between Nur77 and glycolysis and inflammation



A, Western blotting analysis of Nur77 protein expression levels in each group; B, densitometric analysis of Nur77 protein bands across groups. *$P < 0.05$ vs. Control group; #$P < 0.05$ vs. LPS group; △$P < 0.05$ vs. LPS+DIM group. LPS, lipopolysaccharide; Dex, dexmedetomidine; DIM, DIM-C-pPhOH.

图3　各组RAW264.7细胞的Nur77蛋白表达水平比较

Fig.3　Comparison of Nur77 protein expression levels among different groups of RAW264.7 cells

表1　各组RAW264.7细胞中糖酵解指标比较

Tab.1　Comparison of glycolytic indicators among different groups of RAW264.7 cells

Item	Control group	LPS group	LPS+Dex group	LPS+DIM group	LPS+Dex+DIM group
LAC (mmol/L)	1.15 ± 0.10	1.60 ± 0.05[1)]	1.45 ± 0.09[2)]	2.20 ± 0.08[2)]	1.85 ± 0.12[3),4)]
NAD^+/NADH	1.90 ± 0.22	4.00 ± 0.40[1)]	5.80 ± 0.15[2)]	2.20 ± 0.44[2)]	4.72 ± 0.30[3),4)]

1) $P < 0.05$ vs. Control group; 2) $P < 0.05$ vs. LPS group; 3) $P < 0.05$ vs. LPS+Dex group; 4) $P < 0.05$ vs. LPS+DIM group. LAC, lactate; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide.

表2　各组Raw264.7细胞中IL-10、IL-1β及TNF-α表达水平比较

Tab.2　Comparison of IL-10, IL-1β and TNF-α expression levels in RAW264.7 cells among different groups

Group	IL-10		IL-1β		TNF-α	
	mRNA	Protein (pg/mL)	mRNA	Protein (pg/mL)	mRNA	Protein (pg/mL)
Control	10.2 ± 1.8	96.4 ± 7.1	2.4 ± 0.6	5.1 ± 1.0	8.2 ± 0.4	22.3 ± 2.8
LPS	189.5 ± 10.3	121.6 ± 6.4	181.4 ± 13.8	40.2 ± 3.1	46.1 ± 3.8	75.8 ± 4.5
LPS+Dex	349.8 ± 38.4[1)]	150.3 ± 5.5[1)]	149.2 ± 14.5[1)]	27.1 ± 2.8[1)]	36.4 ± 4.5[1)]	63.7 ± 6.8[1)]
LPS+DIM	104.6 ± 19.2[1)]	106.8 ± 6.4[1)]	209.7 ± 9.3[1)]	51.8 ± 3.4[1)]	58.2 ± 3.6[1)]	90.5 ± 4.7[1)]
LPS+Dex+DIM	72.3 ± 9.5[2)]	135.4 ± 6.3[2)]	227.6 ± 6.3[2)]	30.4 ± 2.5[2)]	62.1 ± 3.8[2)]	74.9 ± 5.9[2)]

1) $P < 0.05$ vs. LPS group; 2) $P < 0.05$ vs. LPS+Dex group. IL-10, interleukin-10; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α.

本研究检测的细胞总NAD^+/NADH比值反映细胞质和线粒体的综合状态。LPS诱导的线粒体代谢重编程可能导致不同亚细胞区室间NAD^+/NADH分布改变，从而影响全细胞水平结果[27]。Dex在LPS基础上进一步升高NAD^+/NADH比值，同时减少乳酸生成，提示Dex可能通过以下机制发挥作用：通过上调Nur77抑制糖酵解通量，减少底物氧化步骤NAD^+消耗；改善线粒体电子传递链功能，促进NADH向NAD^+的氧化再生。Nur77可调控线粒体稳态相关过程，并在部分疾病或应激情境下通过改善线粒体功能发挥保护作用[28-29]，而Dex在多种脓毒症/内毒素相关损伤模型中被报道可改善线粒体结构与功能，调节线粒体动力学与质量控制（如促进自噬/线粒体自噬、降低氧化应激与凋亡），从而发挥器官保护作用[30-31]。提高NAD^+水平可降低脓毒症小鼠血清乳酸水平、氧化应激和炎症反应，保护多脏器功能[32]。

本研究存在以下局限性：仅采用RAW264.7细胞进行体外实验，未在人源THP-1细胞或原代巨噬细胞中验证，影响结论的普适性；未检测细胞外酸化率、糖酵解关键酶活性等相关指标，无法全面反映代谢重编程的动态变化；所测总细胞NAD^+/NADH比值无法区分细胞质和线粒体2个区室的独立变化[33-34]；生物信息学分析采用的GEO数据集实验条件与本研究存在差异，相关性分析未排除混杂因素，但这些分析结果主要作为假设生成和趋势验证的参考依据。未来研究将在动物模型和人源细胞中进一步验证本研究结果，并结合Seahorse代谢分析仪实时监测、亚细胞NAD^+/NADH分别测定等技术，深入论证“Dex-Nur77-糖酵解-炎症”这一信号通路。

综上所述，本研究证实了Dex可通过上调Nur77表达抑制LPS诱导的巨噬细胞糖酵解和炎症反应，揭示了糖酵解激活先于炎症反应，并明确了Nur77与糖酵解关键酶的负调控关系，为探索脓毒症免疫代谢调控策略提供了新的依据。

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