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成纤维细胞生长因子 21 对非酒精性脂肪性肝炎的作用及机制的研究*

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摘要 目的:探索成纤维细胞生长因子 21(FGF-21)对非酒精性脂肪性肝炎(NASH)的作用及其机制。**方法:**用浓度为 500 $\mu\text{mol/L}$ 的油酸和棕榈酸混合物(摩尔比=2:1)诱导 HepG2 细胞建立 NASH 细胞模型,实验分为 5 组:正常对照组(Control)、模型组(Model)、低剂量 FGF-21 组(LFGF-21, 0.5 $\mu\text{mol/L}$)、中剂量 FGF-21 组(MFGF-21, 1.0 $\mu\text{mol/L}$)和高剂量 FGF-21 组(HFGF-21, 2.0 $\mu\text{mol/L}$)。油红 O 染色法观察细胞内脂滴,全自动生化分析仪检测细胞内 ALT、AST、TC、TG 的水平,Real-time PCR 和 Western blot 分别检测细胞内核因子 E2 相关因子-2(Nrf-2)、核苷酸结合寡聚化结构域样受体 3(NLRP3)的 mRNA 和蛋白水平,ELISA 检测 IL-1 β 、TNF- α 水平。**结果:**NASH 细胞造模成功,油红 O 染色结果显示对照组细胞无明显脂滴蓄积,模型组细胞内可见大量橘红色脂滴,并出现融合现象。不同浓度 FGF-21 治疗组的细胞内红色脂滴明显减少,并呈剂量依赖性。模型组 ALT、AST、TC、TG、IL-1 β 、TNF- α 和 NLRP3 的水平均高于对照组($P<0.05$),FGF-21 治疗组其水平低于模型组($P<0.05$)。模型组 Nrf2 的水平低于对照组($P<0.05$),FGF-21 治疗组 Nrf2 的水平高于模型组($P<0.05$)。**结论:**FGF-21 通过促进 Nrf-2、抑制 NLRP3 减少非酒精性脂肪性肝炎细胞的脂质沉积,减轻炎症反应,对 NASH 有保护作用。

关键词:成纤维细胞生长因子 21;非酒精性脂肪性肝炎;核因子 E2 相关因子-2;核苷酸结合寡聚化结构域样受体 3

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Effect of Fibroblast Growth Factor 21 on Non-alcoholic Steatohepatitis and Its Mechanism*

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ABSTRACT Objective: To investigate the effect of fibroblast growth factor 21 (FGF-21) on non-alcoholic steatohepatitis(NASH) and the mechanism of its action. **Methods:** Culturing HepG2 cells with DMEM medium supplemented with 10% fetal bovine serum. HepG2 cells were randomly divided into five groups: control group, model group (500 $\mu\text{mol/L}$ FFA), low dose FGF-21 (LFGF-21, 0.5 $\mu\text{mol/L}$), middle dose FGF-21 (MFGF-21, 1.0 $\mu\text{mol/L}$) and high dose FGF-21 (HFGF-21, 2.0 $\mu\text{mol/L}$). Observing intracellular lipid droplets by oil red O staining, the levels of AST, ALT, TC and TG were measured by automatic chemistry analyzer. The mRNA contents and protein levels of Nrf-2 and NLRP3 were determined by Real-time PCR and Western blot. The protein levels of IL-1 β and TNF- α were measured by ELISA kit. **Results:** The NASH cell model was established. The oil red O staining showed that no lipid droplets were found in the control group, and there were mass lipid droplets in the model group, and some were fused, and those in the treatment groups decreased significantly compared with the model group on dose-dependent. The levels of AST, ALT, TC, TG, IL-1 β , TNF- α and NLRP3 in the model group were significantly higher than those in the control group ($P<0.05$), and those in the treatment group decreased significantly compared with the model group ($P<0.05$). The levels of Nrf-2 in the model group were significantly lower than those in the control group ($P<0.05$), and that in the treatment group increased significantly compared with the model group ($P<0.05$). **Conclusion:** FGF-21 can reduce lipid deposition and inhibit inflammation through activating Nrf-2 and inhibiting NLRP3 to attenuate steatohepatitis.

Key words: Fibroblast growth factor 21; Non-alcoholic steatohepatitis; Nrf-2; NLRP3

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前言

非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)是一种肝脏慢性炎症性疾病,排除酒精、感染、药物、代谢等因

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素,主要病理特征为肝细胞脂肪变性、弥散性肝小叶轻度炎症和/或肝中央静脉、肝窦周围胶原沉积等^[1]。NASH是可逆的病理过程,亦可进展为肝纤维化、肝硬化,甚至肝癌,是病情发展的关键转折点^[2,3]。目前临床尚缺乏治疗NASH的有效药物,故探索新型药物意义重大。

成纤维细胞生长因子21 (fibroblast growth factor 21, FGF-21)是成纤维细胞生长因子家族的成员之一,主要由肝脏分泌,并具有多种生物学功能。FGF-21作为一种分泌性蛋白,可通过内分泌途径作用于全身靶器官,其中肝脏是其作用的主要靶器官^[4]。研究表明,FGF-21可以抑制D-半乳糖诱导的肝脏炎症反应和氧化应激,减轻肝细胞的损伤,可保护肝脏功能及逆转肝脏脂肪变性^[5-7],但其分子机制尚未完全明确。本实验以油酸和棕榈酸诱导HepG2细胞建立的NASH细胞模型为研究对象,探索FGF-21对NASH的作用及其可能的作用机制。

1 材料与方法

1.1 材料

FGF-21成熟蛋白及HepG2细胞:由东北农业大学生命科学学院实验室馈赠,FGF-21成熟蛋白制备及提纯的方法同参考文献^[8];DMEM培养基、胎牛血清购自GIBICO公司;Nrf-2抗体、NLRP3抗体购于Abcam公司;Western细胞蛋白裂解液购自碧云天公司;TNF- α 、IL-1 β ELISA试剂盒购自R&D公司。

1.2 方法

1.2.1 细胞的培养与处理 HepG2细胞于含有10%胎牛血清、10万U/L青链霉素的DMEM培养基、37℃、5%CO₂、饱和湿度孵育箱内培养。分为正常对照组(Control)、模型组(Model)、低剂量FGF-21组(LFGF-21, 0.5 μ mol/L)、中剂量FGF-21组(MFGF-21, 1.0 μ mol/L)和高剂量FGF-21组(HFGF-21, 2.0 μ mol/L)。当细胞贴壁生长至60%-70%后,正常组换用新鲜DMEM培养液,而模型组改为含有游离脂肪酸(油酸和棕榈酸=2:1)浓度为500 μ mol/L的DMEM培养基诱导培养24h。低、中、高剂量FGF-21组给予游离脂肪酸的同时给予FGF-21(浓度分别为0.5 μ mol/L, 1.0 μ mol/L, 2.0 μ mol/L)。实验重复3次。

1.2.2 油红O染色法观察细胞内脂滴 PBS洗涤细胞3次,每次5min,4%多聚甲醛固定10min,PBS洗涤细胞2次,60%异丙醇漂洗1min,室温下油红O染色10min,蒸馏水终止染色,显微镜下观察,拍照。

1.2.3 检测细胞内ALT、AST、TC和TG的水平 细胞裂解后,收集上清液用全自动生化分析仪检测。

1.2.4 Real-time PCR检测细胞内Nrf-2和NLRP3的mRNA水平 应用Trizol提取总RNA,Real-time PCR系统进行扩增,以 β -actin为内参照,通过2^{- $\Delta\Delta$ CT}方法计算目的基因的相对表达量。

相关引物序列为:

Nrf-2:F5' -CCAGCACATCCAGACAGACAC-3' ,

R5' -GATATCCAGGGCAAGCGACTC-3' ;

NLRP3:F5' -CCCCGTGAGTCCCATT-3' ,

R5' -GACGCCAGTCCAACAT-3' ;

β -actin:F5' -ACATCTGCTGGAAGGTGGAC-3' ,

R5' -GGTACCACCATGTACCCAGG-3' 。

1.2.5 ELISA检测IL-1 β 、TNF- α 的水平 细胞裂解后,用

ELISA试剂盒分别检测IL-1 β 、TNF- α 的水平。

1.2.6 Western blot检测Nrf-2、NLRP3的蛋白水平 细胞裂解后,蛋白定量;调节电压为110V,SDS-PAGE电泳约2h;调节恒流为350mA湿转膜约1h;BSA封闭1h;一抗人抗鼠抗体4℃摇床过夜孵育,二抗山羊抗兔抗体,37℃孵育1h;曝光、显影后,软件分析光密度值,以目的基因/ β -actin带的密度比值表示目的基因蛋白表达水平。

1.3 统计学方法

以SPSS17.0统计软件录入数据及进行统计学分析,计量资料采用均数 $\pm$ 标准差($\bar{x}\pm s$)表示,以Graphpad prism 5制图软件进行作图。组间差异比较采用单因素方差分析(ANOVA),两两比较采用LSD-t检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 油红O染色结果显示

对照组细胞体积较小,细胞边缘清晰,细胞无明显橘红色脂滴蓄积。模型组细胞明显肿大,细胞膜轮廓模糊,细胞内可见大量橘红色脂滴,并出现脂滴融合现象,部分脂滴甚至融合成链状或环状。不同浓度FGF-21治疗组,可见细胞内红色脂滴明显减少,并呈剂量依赖性,高剂量FGF-21组细胞内仅有少量橘红色脂滴,颜色较淡。见图1。

2.2 细胞内ALT、AST、TC、TG检测结果

模型组ALT、AST、TC、TG的水平均高于对照组($P<0.05$),FGF-21治疗组ALT、AST、TC、TG的水平较模型组下降($P<0.05$),见表1。

2.3 IL-1 β 、TNF- α ELISA结果

模型组IL-1 β 、TNF- α 的水平高于对照组($P<0.05$),低、中、高剂量FGF-21治疗组IL-1 β 、TNF- α 的水平均低于模型组($P<0.05$),见图2。

2.4 FGF-21对各组HepG2细胞NLRP3、Nrf2表达的影响

模型组NLRP3的水平较对照组升高($P<0.05$),而低、中、高剂量FGF-21治疗组NLRP3的水平均低于模型组($P<0.01$),模型组Nrf2的水平低于对照组($P<0.05$),中、高剂量FGF-21治疗组Nrf2的水平均高于模型组($P<0.01$),低剂量FGF-21治疗组Nrf2的平均水平虽高于模型组,但无统计学意义,见图3。

3 讨论

NASH已成为全球慢性肝病的重要病因,其主要发病机制为“二次打击”学说,初次打击为胰岛素抵抗致肝细胞脂肪变,表现为单纯性脂肪肝,二次打击为细胞因子等炎症介质激活致肝细胞损伤,进而导致单纯性脂肪肝进展为NASH^[9],但其具体分子机制仍不完全明确。研究表明,慢性炎症在NASH进程中发挥重要作用^[10,11],炎症因子的过表达是导致单纯性脂肪肝向NASH转变的重要原因^[12],IL-1 β 、TNF- α 等促炎因子是促进NASH发生发展的关键炎症因子,可导致肝细胞损伤,加重肝脏炎症,并且IL-1 β 可通过自分泌形式促进炎症反应的进一步放大^[13-15]。

核因子E2相关因子2(nuclear factor-erythroid 2-related factor-2,Nrf2)是一种具有碱性亮氨酸拉链结构的转录因子,可抵抗氧化应激和炎症反应,可抑制脂肪在肝脏中的堆积,对肝

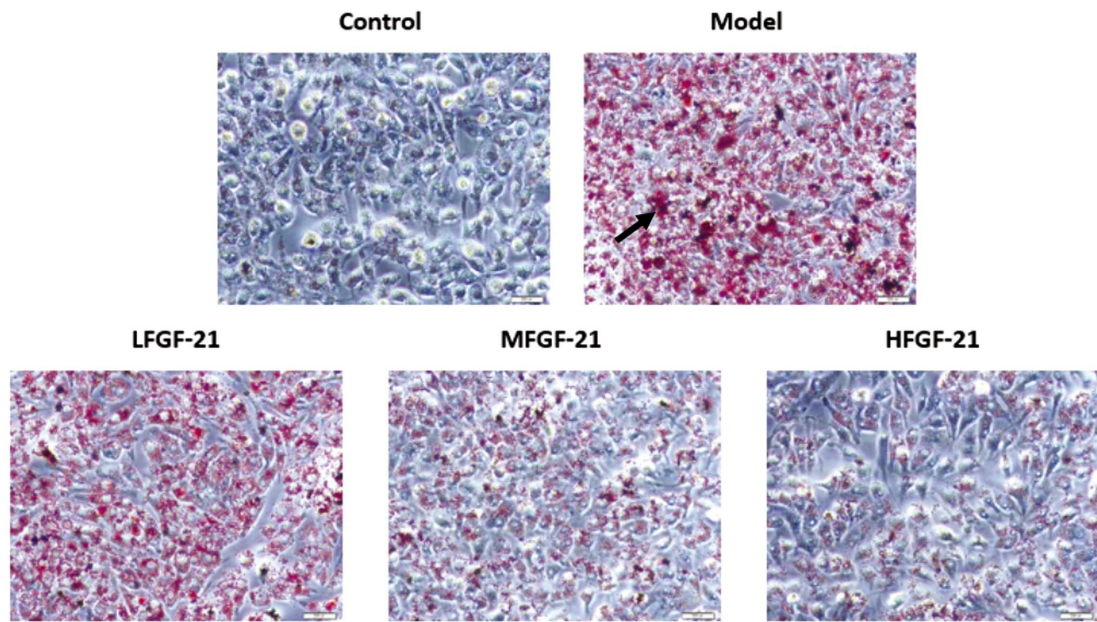


图 1 油红 O 染色观察各组细胞的脂质沉积情况(× 200)

Fig.1 Oil red O method for lipofuscin to observe lipid deposition(× 200)

Note: the arrow point to lipid droplets.

表 1 各组细胞内 ALT、AST、TC、TG 的水平

Table 1 The levels of ALT, AST, TC and TG in five groups

Groups	ALT(U/L)	AST(U/L)	TC(mmol/L)	TG(mmol/L)
Control group	8.80± 2.36	130.73± 26.70	0.036± 0.005	0.027± 0.006
Model group	79.23± 5.49**	450.73± 23.79**	0.057± 0.006**	0.060± 0.017**
LFGF-21 group	65.67± 2.30 [#]	313.90± 7.46 [#]	0.043± 0.006 [#]	0.057± 0.006
MFGF-21 group	29.06± 1.10 [#]	267.77± 15.58 [#]	0.037± 0.005 [#]	0.063± 0.015
HFGF-21 group	13.23± 1.21 [#]	156.00± 4.62 [#]	0.033± 0.005 [#]	0.033± 0.006 [#]

Note: ** $P<0.05$, compared with control group; [#] $P<0.05$, compared with model group.

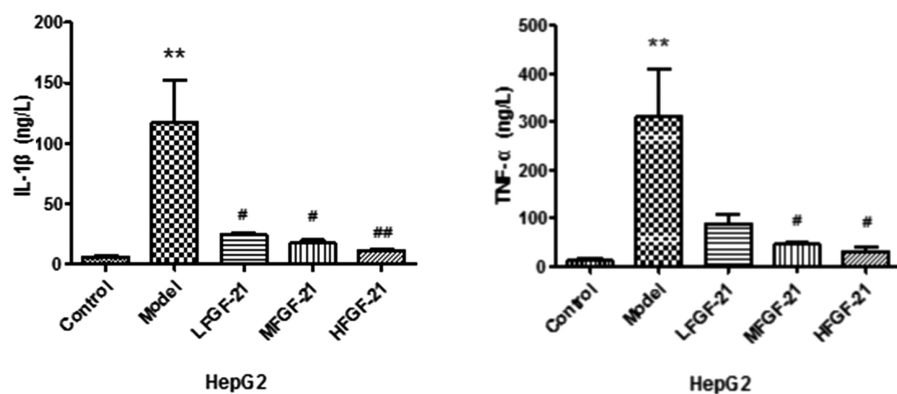


图 2 各组细胞 IL-1β、TNF-α 的蛋白水平

Fig.2 The protein levels of IL-1β、TNF-α in five groups.

Note: ** $P<0.05$, compared with control group; [#] $P<0.01$, compared with model group; [#] $P<0.05$, compared with model group;

脏起到保护作用^[16]。核苷酸结合寡聚化结构域样受体 3 (nucleotide binding oligomerization domain like receptor 3, NLRP3)炎症小体是人体固有免疫系统的重要组成部分,可识别多种病原体及内源性危险信号,如细菌、胆固醇、脂蛋白等^[17,18],并可调控 IL-1β、IL-18 等炎症因子的成熟和分泌^[19],与 NASH 的发生发展密切相关。研究证实,Nrf2 对 NLRP3 炎症小体的活

化具有抑制作用^[20],Nrf2 可以抑制急性肝损伤、狼疮肾炎和脓毒症 NLRP3 炎症小体的活化,进而减轻炎症反应^[21-23],但 Nrf2 是否通过抑制 NLRP3 炎症小体在 NASH 中发挥肝脏保护作用尚不明确。

本实验通过建立 HepG2 NASH 细胞模型,初步探索了 FGF-21 对 NASH 的作用及其可能的作用机制。本实验结果显

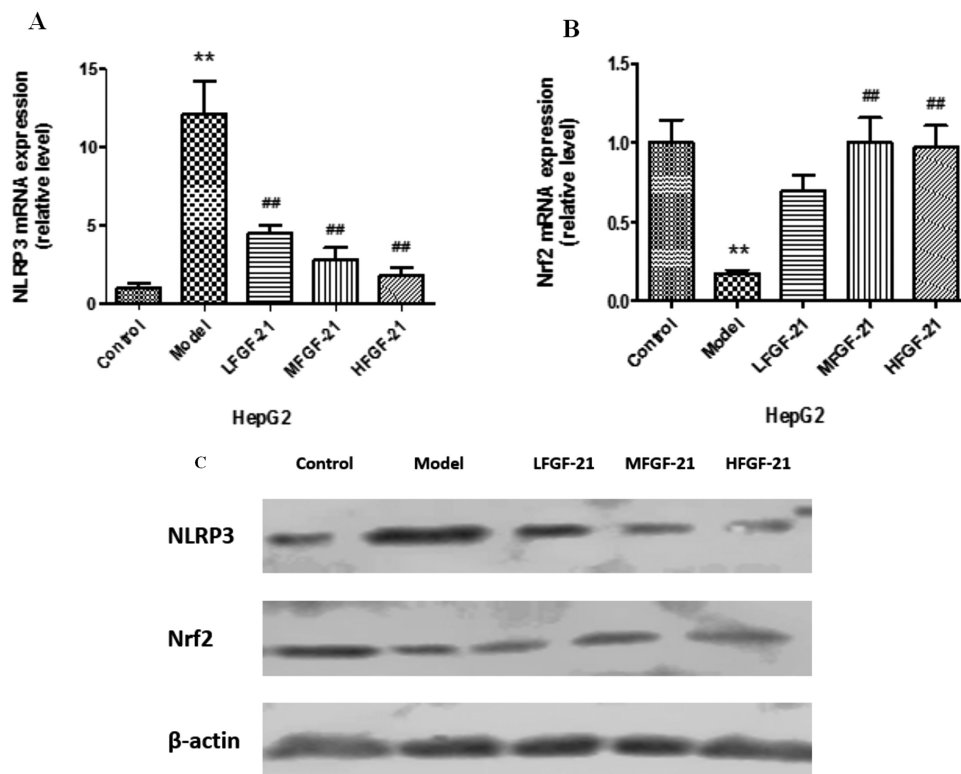


图3 各组 HepG2 细胞 NLRP3、Nrf2 的水平

Fig. 3 The levels of NLRP3 and Nrf2 in five groups

A. The transcription level of NLRP3 in five groups. B. The transcription level of Nrf2 in five groups. C. The western blot of NLRP3 and Nrf2 in five groups.

Note: ** $P < 0.05$, compared with control group; ## $P < 0.01$, compared with model group.

示模型组 HepG2 细胞内脂质沉积明显, 细胞内可见大量橘红色脂滴, 并出现脂滴融合现象, 同时模型组 ALT、AST、TC、TG 的水平均高于对照组, 说明 NASH 细胞造模成功。不同浓度 FGF-21 治疗组的细胞内橘红色脂滴明显减少, 颜色较淡, 并呈剂量依赖性, FGF-21 治疗组 ALT、AST、TC、TG 的水平较模型组明显下降。这说明 FGF-21 可以减少非酒精性脂肪性肝炎细胞的脂质沉积, 减轻肝细胞的损伤。模型组 IL-1 β 、TNF- α 的水平明显高于对照组, 而 FGF-21 治疗组较模型组明显下降, 这说明 FGF-21 可以抑制非酒精性脂肪性肝炎的促炎因子的表达, 可以减轻 NASH 的炎症反应, 对 NASH 有改善作用。

为进一步探索 FGF-21 改善 NASH 的作用机制, 本实验检测了 Nrf2 和 NLRP3 的水平, 结果显示模型组 NLRP3 的水平明显高于对照组, 而 FGF-21 治疗组较模型组明显下降; 模型组 Nrf2 的水平明显低于对照组, 而 FGF-21 治疗组较模型组明显升高。这说明 FGF-21 可以促进 Nrf2、抑制 NLRP3 的表达, 从而抑制炎症反应, 减少脂质沉积, 改善 NASH。

本实验初步探索了 FGF-21 改善 NASH 的作用及其可能的作用机制, 由于实验时间较短, 仅进行了细胞实验, 尚有许多不足之处。但本实验为治疗 NASH 提供了新的方向, Nrf2、NLRP3 可能成为 NASH 治疗的新靶点。

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