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论著

对乙酰氨基酚诱导的急性肝损伤大鼠血浆miR-122表达的变化

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摘要 目的 探讨血浆微RNA(miR)-122在药物性肝损伤中的变化及其在肝毒理临床前评价中的作用。方法 SD雄性大鼠单次ig给予对乙酰氨基酚0，625和1250 mg·kg^{-1}，并于给药后1.5，3，6，12，24，36及96 h采集血样。以乙酰氨基酚诱导急性肝损伤大鼠血浆中稳定表达的miR-103为校正基因，实时定量逆转录PCR(RT-qPCR)法检测不同时间点大鼠血浆miR-122的表达。测定血浆中不同时间点谷丙转氨酶(GPT)和谷草转氨酶(GOT)和肝组织病理学检查。结果 组织病理学观察结果显示，与正常对照组相比，大鼠分别ig给予对乙酰氨基酚625 mg·kg^{-1} 1.5和3 h后，肝组织病理无明显变化，给药后6和12 h，肝腺泡III带出现明显的空泡样变性和肝窦充血，给药后24 h肝腺泡III带有明显的细胞坏死；而36 h时基本恢复正常；而对乙酰氨基酚1250 mg·kg^{-1}组给药后24和36 h时肝腺泡III带有明显的细胞坏死。与正常对照组相比，大鼠分别ig给予对乙酰氨基酚625和1250 mg·kg^{-1}后12和24 h，血清GPT和GOT均有显著性升高(P<0.05)，且对乙酰氨基酚1250 mg·kg^{-1}组大鼠血清GPT活性均是对照组2倍以上。与正常对照组相比，血浆miR-122在大鼠给予对乙酰氨基酚1250 mg·kg^{-1} 1.5 h即升高3.6倍(P<0.05)，并且持续升高，12 h达峰值后开始下降，96 h 恢复正常水平；大鼠给予625 mg·kg^{-1}对乙酰氨基酚给药后6 h，血浆miR-122升高5.2倍，12 h达峰值后开始下降，36 h恢复正常水平。肝损伤大鼠血浆miR-122不同时间点的表达水平与肝损伤GPT和GOT变化相似。结论 循环miR-122可能成为药物性肝损伤临床前和临床早期检测的理想的血液学分子标志物。

关键词 对乙酰氨基酚 肝损伤 miR-122 动力学

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Changes in miR-122 expression in plasma of rats with acute liver injury induced by acetaminophen

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Abstract

OBJECTIVE To explore the changes and role of plasma microRNA(miR-122) in non-clinical evaluation of drug-induced liver injury. **METHODS** Male SD rats were ig given acetaminophen(APAP) 0(control), 625 and 1250 mg·kg^{-1}. At 1.5, 3, 6, 12, 24, 36 and 96 h after administration, blood samples were collected. miR-103, as a suitable endogenous reference gene for plasma microRNAs quantification in rats with acetaminophen-induced hepatotoxicity, was employed to detect the expression of miR-122 in plasma samples with real-time quantitative reverse transcription PCR (RT-qPCR). The blood levels of glutamic pyruric transminase (GPT) and glutamic oxaloacetic trnasminase (GOT) were detected and pathological changes in liver tissue were observed. **RESULTS** Histopathological examination showed that, compared with normal control group, there was no significant difference at 1.5 and 3 h after rats were ig given APAP 625 and 1250 mg·kg^{-1}. Vacuolated hepatocytes and congestion in sinusoids were observed in zone III at 6 and 12 h after administration, while at 24 h centrilobular necrosis was prominent in APAP 625 and 1250 mg·kg^{-1} groups. Compared with normal control group, GPT and GOT in serum significantly increased at 12 and 24 h in APAP 625 and 1250 mg·kg^{-1} groups, and GPT activity more than doubled in APAP 1250 mg·kg^{-1} group. Compared with normal control group, plasma miR-122 increased by 5.2-fold at 6 h after administration in APAP 625 mg·kg^{-1} and 3.6-fold at 1.5 h after administration in APAP 1250 mg·kg^{-1}. The level of plasma miR-122 continued to elevate but returned to normal at 36 h in APAP 625 mg·kg^{-1} group and at 96 h in APAP 1250 mg·kg^{-1} group, respectively. The course of plasma miR-122 levels displayed similar kinetics to GPT and GOT. **CONCLUSION** miR-122 Expression in plasma may become an ideal hematologic molecular marker for early detection of drug-induced liver injury in pre-clinical and clinical evaluation.

Key words acetaminophen liver injury miR-122 kinetics

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