虫草素通过Nrf2/HO-1通路抑制铁死亡延缓AKI向CKD转化的作用机制研究Δ

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中图分类号 R965；R285 **文献标志码** A **文章编号** 1001-0408（2026）11-1428-06
DOI 10.6039/j.issn.1001-0408.2026.11.08

摘 要 目的 研究虫草素延缓急性肾损伤（AKI）向慢性肾脏病（CKD）（以下简称“AKI-CKD”）转化的作用机制。**方法** 采用网络药理学和生物信息学分析并预测虫草素延缓AKI-CKD的信号通路及其与铁死亡途径的关系。采用细胞实验对预测结果进行验证：将人肾小管上皮细胞HK-2分为空白组、虫草素组、模型组、H_2O_2+虫草素组，除空白组和虫草素组外，其余各组加入150 μmol/L H_2O_2处理72 h以诱导细胞持续性氧化应激损伤；虫草素（40 μmol/L）干预72 h后，检测细胞中谷胱甘肽过氧化物酶4（GPX4）、长链脂酰辅酶A合成酶4（ACSL4）、核转录因子红系2相关因子2（Nrf2）、血红素加氧酶1（HO-1）蛋白和mRNA表达水平。另在H_2O_2+虫草素的基础上引入Nrf2抑制剂ML385以验证Nrf2/HO-1通路的作用。**结果** 网络药理学及生物信息学分析结果显示，虫草素与AKI-CKD及铁死亡相关的交集基因有42个，其中38个被注释为铁死亡相关基因；HO-1与Nrf2可能是虫草素抑制铁死亡的重要靶点，虫草素与Nrf2、HO-1蛋白的结合能分别为－8.5、－6.7 kcal/mol。细胞实验结果显示，与模型组比较，H_2O_2+虫草素组细胞中GPX4、Nrf2、HO-1蛋白和mRNA表达水平均显著升高（$P<0.05$），ACSL4蛋白和mRNA表达水平均显著降低（$P<0.05$）；加入Nrf2抑制剂ML385后，虫草素对上述蛋白和mRNA的作用被显著逆转（$P<0.05$）。**结论** 虫草素可通过激活Nrf2/HO-1通路抑制铁死亡，减轻肾小管上皮细胞持续性氧化应激损伤，延缓AKI-CKD进展。

关键词 虫草素；急性肾损伤；慢性肾脏病；Nrf2/HO-1通路；铁死亡；网络药理学；生物信息学

Study on the mechanism of cordycepin inhibiting ferroptosis via the Nrf2/HO-1 pathway to delay the transformation from AKI to CKD

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ABSTRACT OBJECTIVE To investigate the mechanism of cordycepin in delaying the transformation from acute kidney injury (AKI) to chronic kidney disease (CKD) (short for "AKI-CKD"). **METHODS** Network pharmacology and bioinformatics were used to analyze and predict the signaling pathways of cordycepin in delaying AKI-CKD progression and its relationship with the ferroptosis pathway. Cell experiments were performed to verify the predicted results. Human renal tubular epithelial HK-2 cells were divided into blank group, cordycepin group, model group, and H_2O_2+cordycepin group. Except for the blank group and cordycepin group, all other groups were treated with 150 μmol/L H_2O_2 for 72 h to induce persistent oxidative stress injury in cells. After 72 h of cordycepin (40 μmol/L) intervention, the protein and mRNA expression levels of glutathione peroxidase 4 (GPX4), long-chain acyl-CoA synthetase 4 (ACSL4), nuclear factor-erythroid 2-related factor 2 (Nrf2), and heme oxygenase-1 (HO-1) in cells were detected. Furthermore, the Nrf2 inhibitor ML385 was added on the basis of H_2O_2+cordycepin to verify the role of the Nrf2/HO-1 pathway. **RESULTS** Network pharmacology and bioinformatics analysis showed that there were 42 overlapping genes related to AKI-CKD and ferroptosis that interact with cordycepin ferroptosis, among which 38 were annotated as ferroptosis-related genes. HO-1 and Nrf2 might be important targets for cordycepin to inhibit ferroptosis. The binding

Δ **基金项目** 国家自然科学基金项目（No.82300846）；中央引导地方科技发展资金项目（No.YDZJSX2025B007）

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