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LKB1 协同二甲双胍影响宫颈癌HeLa细胞的增殖与凋亡及其可能的机制

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摘要：

目的： 探索肝脏激酶B1 (liver kinase B1, LKB1 或serine-threonine kinase 11, S TK11)基因协同二甲双胍对人宫颈癌HeLa细胞增殖与凋亡的影响及其可能的机制。 方法： 构建含有 LKB1 基因的重组质粒LKB1-pEGFP-n1并转染HeLa细胞，MTT检测 LKB1 基因对经二甲双胍处理的HeLa细胞增殖的影响，流式细胞术检测对细胞周期和凋亡的影响，Western blotting检测对LKB1-AMPK信号通路相关蛋白AMPK、ACC和Rb磷酸化水平的影响。 结果： LKB1-pEGFP-n1和空载体pEGFP-n1成功转染HeLa细胞，LKB1-pEGFP-n1转染细胞内稳定表达LKB1。二甲双胍处理LKB1-pEGFP-n1转染细胞的IC 50显著低于pEGFP-n1转染细胞\[(2.9±0.4) vs (7.8±1.3) mmol/L; t =-6.9921, P =0.002 2\]及野生型HeLa细胞\[(2.9±0.4) vs (9.6±1.5) mmol/L; t =-7.527 1, P =0.001 7\]。经二甲双胍处理后，LKB1-pEGFP-n1转染细胞周期阻滞于G 1期，而pEGFP-n1转染和野生型细胞周期无显著变化。二甲双胍作用剂量为15 mmol/L时，LKB1-pEGFP-n1转染细胞凋亡率较pEGFP-n1转染及野生型HeLa细胞显著增多\[（28.6±2.3）% vs （9.6±1.6）%、（17.8±1.9）%，均 P <0.05\]。LKB1-pEGFP-n1转染细胞内AMPKα和ACC的磷酸化水平较pEGFP-n1转染和野生型细胞升高，Rb磷酸化水平降低。 结论： LKB1 能够协同二甲双胍影响HeLa细胞的增殖与凋亡，其可能通过LKB1-AMPK信号通路发挥作用。

关键词：宫颈癌 HeLa细胞 肝脏激酶B1基因 二甲双胍 凋亡

Synergistic effects and underlying mechanisms of liver kinase B1 and metformin on proliferation and apoptosis of cervical cancer cells and its spossible mechanism

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Abstract:

Objective : To explore synergistic effects and the underlying mechanisms of liver kinase B1 (LKB1) or serine-threonine kinase 11 (STK11) and metformin on proliferation and apoptosis of human cervical cancer cells using the HeLa cell line as a model. Methods: A recombinant plasmid LKB1-pEGFP-n1 was constructed. HeLa cells were transfected with this construct and the mock-vehicle pEGFP-n1 respectively. Transfectants were then treated with metformin. Cell viability was assessed by MTT assays, apoptosis and cycle progression by flow cytometry, and phosphorylation of AMRK, ACC and Rb (key players in the LKB1-AMPK signaling pathway) by Western blotting, 24 h after metformin treatment. Results: Both LKB1-pEGFP-n1 and the mock-vehicle pEGFP-n1 were successfully transfected into HeLa cells. After metformin treatment, IC 50 was significantly lower in cells transfected with LKB1-pEGFP-n1(2.9±0.4) mmol/L than those transfected with pEGFP-n1 (7.8±1.3) mmol/L and wild type HeLa cells (9.6±1.5) mmol/L (P <0.01), indicating a significant cell growth-inhibiting effect for LKB1. LKB1-pEGFP-n1 group showed a G 1 phase arrest after treatment with metformin. In contrast, no cell cycle arrest was evident in wild type Hela cells or HeLa cells transfected with pEGFP-n1. After treatment with 15 mmol/L metformin, apoptosis rate was significantly higher in cells transfected with LKB1-pEGFP-n1 (28.6±2.3)% than that in cells transfected with pEGFP-n1 (9.6±1.6)% and wild type cells (17.8±1.9)% (P <0.05). Phosphorylation of AMPKα and ACC was increased but phosphorylation of Rb was decreased in cells transfected with LKB1-pEGFP-n1 as compared with untransfected cells and cells transfected with pEGFP-n1. Conclusion: LKB1 and metformin may affect the proliferation and apoptosis of cervical cancer cells in a coordinated manner, possibly involving the LKB1-AMPK signaling pathway.

Keywords:cervical cancer HeLa cell liver kinase B1 gene metformin apoptosis

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