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论文

辛伐他汀通过内质网应激途径诱导K562细胞凋亡

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摘要：

探讨内质网应激在辛伐他汀诱导K562细胞凋亡中的作用。采用荧光显微镜观察凋亡细胞的形态变化，AnnexinV-FITC/PI双染法检测细胞凋亡率，激光扫描共聚焦显微镜检测细胞内Ca^{2+}浓度，RT-PCR检测葡萄糖调节蛋白78 (glucose regulated protein 78，GRP78)、钙蛋白酶(calpain)基因mRNA表达水平，Western blotting检测GRP78、 calpain、 caspase-3， -6， -7， -9， -12蛋白水平。结果显示，10、 20、 30 μmol·L^{-1}辛伐他汀(simvastatin，Sim)作用K562细胞72 h后，细胞出现典型的凋亡形态，凋亡率分别为12.41%、 19.08%和23.41%；细胞内Ca^{2+}浓度增加，荧光强度分别为43、54和64；GRP78、calpain基因mRNA表达上调；calpain、 caspase-3， -6， -7， -9， -12蛋白剪切活化、GRP78蛋白表达增强。以上结果表明，内质网作为细胞凋亡的重要途径参与了辛伐他汀诱导K562细胞的凋亡。辛伐他汀将可能被用于临床治疗白血病。

关键词： 辛伐他汀 内质网 应激 K562细胞 凋亡

Simvastatin-induced apoptosis of K562 cells is mediated by endoplasmic reticulum stress

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Abstract:

To explore the apoptotic effect of simvastatin on K562 cells through endoplasmic reticulum stress, morphological change of apoptotic cells was observed by Hoechst33258 fluorescent staining under fluorescent microscope. Apoptosis rate of cells was determined with annexinV-FITC/PI double staining by flow cytometry; Intracellular calcium concentration ($[Ca^{2+}]_i$) was measured by laser scanning confocal microscope (LSCM); The expression levels of glucose regulated protein 78 (GRP78) and calpain gene mRNA were determined by RT-PCR; The expression levels of caspase-3, -6, -7, -9, -12, calpain and GRP78 proteins were evaluated by Western blotting. In this study, K562 cells treated with simvastatin for 72 h exhibited typical morphological change of apoptosis cells. After 72 h exposed to 10, 20, 30 μmol·L^{-1} simvastatin, the apoptotic rates of K562 cells were 12.41%, 19.08% and 23.41%, respectively. Simvastatin induced the increase of $[Ca^{2+}]_i$ in K562 cells, fluorescent intensities were 43, 54, and 64, respectively. The expression levels of GRP78 and calpain gene mRNA were up-regulated. The cleavage and activation of caspase-3, -6, -7, -9, -12 and upregulation of GRP78 expression were determined by Western blotting. These findings suggest that endoplasmic reticulum is an important pathway of apoptosis in cells and participates simvastatin-induced apoptosis in K562 cells. It is implied that simvastatin may be suitable for clinical usage in the treatment of myeloma patients.

Keywords: endoplasmic reticulum stress K562 cells apoptosis simvastatin

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