256~261.舒尼替尼诱导耐药鼻咽癌CNE2/DDP细胞表达NKG2DLs的机制[J].黄宇贤,王 杨,李玉华,杨玉莲,赵同峰,何庆梅,卢惠芳,贺艳杰,黄 睿,郭坤元.中国肿瘤生物治疗杂志,2010,17(3)

舒尼替尼诱导耐药鼻咽癌CNE2/DDP细胞表达NKG2DLs的机制 点此下载全文

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基金项目：国家自然科学基金资助项目（No. 30973454）；广东省自然科学基金重点项目（No. 9251051501000007）

DOI：10.3872/j.issn.1007-385X.2010.3.003

摘要：

目的：初步探讨舒尼替尼诱导高、低表达ABCG2(ATP binding cassette superfamily G member 2)分子的耐药鼻咽癌CNE2/DDP细胞（简称ABCG2 high CNE2/DDP细胞、ABCG2 low CNE2/DDP细胞）中NKG2D配体（natural killer group 2 member D ligands，NKG2DLs）表达的分子机制。方法：Caspase 8活化试剂盒和线粒体膜电位法分别检测NK细胞处理后ABCG2 high CNE2/DDP细胞和ABCG2 low CNE2/DDP细胞caspase 8活化水平和线粒体膜电位。RT PCR检测舒尼替尼处理前后两种CNE2/DDP细胞DNA损伤修复系统相关信号分子mRNA的表达。结果：CNE2/DDP细胞+NK细胞组中两种CNE2/DDP细胞caspase 8活性均明显增强；舒尼替尼处理后的ABCG2 low CNE2/DDP细胞+NK细胞组和ABCG2 high CNE2/DDP细胞＋NK细胞组中caspase 8的活性是处理前的2～2.5倍（ P <0.01）。舒尼替尼预处理后，CNE2/DDP细胞和NK细胞共培养体系中两种CNE2/DDP细胞的线粒体膜电位分别为(76.58±2.32)%和(73.11±1.93)%，较舒尼替尼处理前明显降低（ P <0.05）。舒尼替尼可上调两种CNE2/DDP细胞中ATR、CHK1和CHK2 mRNA的表达，并诱导P53和NF κB mRNA的表达。结论：舒尼替尼可能通过激活DNA损伤修复系统相关信号分子和NF κB的表达，诱导耐药鼻咽癌CNE2/DDP细胞NKG2DLs的表达，同时经由死亡受体信号通路和线粒体信号通路增强NK细胞诱导的肿瘤细胞凋亡。

关键词：舒尼替尼 鼻咽肿瘤 NKG2D配体 自然杀伤细胞 DNA损伤

Mechanism of sunitinib inducing NKG2DLs expressions in multidrug resistant nasopharyngeal carcinoma CNE2/DDP cells Download Fulltext

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Fund Project:Project supported by the National Natural Science Foundation of China (No. 30973454), and the Key Program of Natural Science Foundation of Guangdong Province (No. 9251051501000007)

Abstract:

Objective: To investigate the mec hanism by which unitinib induces up regulation of NKG2D ligands(NKG2DLs) expressions in nasopharyngeal carcinoma CNE2/DDP cells with high or low ABCG2 expression (ABCG2 high CNE2/DDP cells or ABCG2 low CNE2/DDP cells). Methods: Caspase 8 activity and mitochondrial membrane potential were detected by caspase 8 activity kit and mitochondrial membrane potential assay kit in ABCG2 high CNE2/DDP cells or ABCG2 low CNE2/DDP cells after co cultured with NK cells. Expressions of signal molecules involved in DNA damage and repair system were detected by RT PCR in ABCG2 high CNE2/DDP cells and ABCG2 low CNE2/DDP cells before and after sunitinib treatment. Results: Caspase 8 activities in ABCG2 high CNE2/DDP cells and ABCG2 low CNE2/DDP cells were ignificantly increased after co cultured with in NK cells. After treatment with sunitinib, caspase 8 activities in the co culture system were 1-1.5 times higher than those in the untreated ABCG2 high and ABCG2 low CNE2/DDP cells (P <0.01). Sunitinib inhibited mitochondrial membrane potentials of ABCG2 high and ABCG2 low CNE2/DDP cells in NK cell co culture systems, with the potentials in two kinds of sunitinib treated CNE2/DDP cells decreased to (76.58±2.32)% and (73.11± 1.93)%, respectively, which were markedly lower than those in the untreated ABCG2 high and ABCG2 low CNE2/DDP cells (P <0.05). Sunitinib could increase mRNA expressions of ATR, CHK1 and CHK2 in ABCG2 high and ABCG2 low CNE2/DDP cells, and induce P53 and NF κB mRNA expressions. Conclusion: Sunitinib can up regulate NKG2DLs expressions in CNE2/DDP cells by activating signaling molecules related to DNA damage and repair system and NF κB, and enhance NK cell induced apoptosis of tumor cells through death receptor and mitochondrial pathways.

Keywords:sunitinib nasopharyngeal neoplasms natural killer groups 2 member D ligand (NKG2DL) natural killer cell DNA damage