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论文

d-宁烯、丹参及姜黄素衍生物对ras基因产物膜结合和细胞间隙信息传导的影响

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摘要:

目的旨在寻找新型抗肿瘤药物,进一步研究*d*-宁烯、丹参及姜黄素衍生物的抗肿瘤机理。采用分子生物学方法及划痕标记染料示踪技术,研究了4种人实体瘤起源的细胞系的细胞间隙信息传导(GJIC)、H-ras癌基因表达以及ras癌基因产物($P21^{ras}$蛋白)表达状态,并观察了4种天然产物对它们的影响。结果表明,细胞内染料传输功能的丧失与ras基因突变率呈正相关;单萜化合物*d*-宁烯和酚类化合物丹参衍生物的抗肿瘤作用可能与抑制$P21^{ras}$蛋白膜结合和增强细胞间隙信息传导功能有关。提示Ras癌基因产物$P21^{ras}$蛋白膜结合的抑制与细胞间隙信息传导功能的增强有直接关系。

关键词: 人实体瘤细胞系 Ras癌基因产物 膜结合 细胞间隙信息传导

EFFECT OF *D*-LIMONENE, SALIVIA MILTIORRHIZA AND TURMERIC DERIVATIVES ON MEMBRANE ASSOCIATION OF RAS GENE PRODUCT AND GAP JUNCTION INTERCELLULAR COMMUNICATION

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Abstract:

Gap junction intercellular communication (GJIC), H-ras oncogene expression and Ras oncogene product ($P21^{ras}$ protein) expression were studied in four human solid tumor cell lines, W_1-38, $CACO_2$, A549 and PaCa (with the different Ras gene mutation rate), and the effects of four compounds, *Salvia miltiorrhiza* derivative (SMD), *d*-limonene, turmeric derivative I(TD-I) and turmeric derivative II(TD-II), on them. The abilities of the four solid tumor cell lines to transfer dye to adjacent cells were examined using the scrape-loading/dye transfer technique, and the H-ras oncogene expression by Northern blotting and $P21^{ras}$ protein expression by Western blotting. The results showed the loss of intercellular coupling in PaCa cells, slight GJIC in A549 and $CACO_2$ cells, and good GJIC in W_1-38 cells. The four ompounds used was shown to improve the GJIC of PaCa to different extents. The amount of total and membrane associated $P21^{ras}$ in PaCa cells were decreased after treatment with SMD, *d*-limonene and TD-I(2.5 $\mu g \cdot ml^{-1}$) for 48 h. Concomitantly, the growth of PaCa cells decreased in soft agar and GJIC was enhanced. The relative potency was found to be: *d*-limonene>SMD> TD-I=TD-II. No significant effect of the four compounds on H-ras oncogene expression was observed. These results suggest that 1. there was an excellent correlation between loss of Lucifer Yellow dye transfer and ras gene mutation rate in the four solid tumor cell lines used (ras gene mutation rate inversely correlated with average cell number couplied, r=0.98)i.e, showing that high ras gene mutation is closely correlated with loss of GJIC in these malignant human tumor cells; 2. the antitumor effect of the monoterpene *d*-limonene and the phenol compound, SMD, might be related to the inhibition of $P21^{ras}$ membrane association and enhancement of GJIC, whilst that of the others may be by a different mechanism; 3.the inhibition of $P21^{ras}$ membrane association is directly related to the enhancement of gap junction intercellular communication.

Keywords: Ras oncogene product Membrance association Gap junction intercellular communication Human solid tumor cell line

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