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DOWN-REGULATION OF RAF-1 KINASE IS ASSOCIATED WITH PACLITAXEL RESISTANCE IN HUMAN BREAST CANCER MCF-7/ADR CELLS

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Experiments were carried out to determine the role of Raf-1 kinase in the development of drug resistance and apoptosis induced by paclitaxel. In the present study, paclitaxel sensitivity, Raf-1 activity and MAPKs activation were compared in 2 cell lines: parental human breast cancer cells and its drug resistant variant (MCF-7/Adr) cells. MCF-7/Adr cells were significantly more resistant to the cytotoxic effects of paclitaxel than parental cells. MCF-7/Adr cells have lower basal Raf-1 activity, yet have much higher basal ERK activity than parental cells. In addition, it appeared that PD 98059, which turns off ERK through MEK inhibition, enhanced basal Raf-1 kinase activity in MCF-7/Adr cells. On the other hand, paclitaxel treatment of parental MCF-7 cells resulted in marked increase of JNK activity with concurrent phosphorylation of Raf-1 protein kinase. The findings suggest that down-regulation of Raf-1 kinase, which can be induced through the sustained ERK activation, may contribute to the development of acquired resistance in MCF-7/Adr cells, and Raf-1 and JNK MAP kinase cooperate as inducers of apoptosis in response to paclitaxel in parental MCF-7 cells.

Keyword : Paclitaxel, Raf-1, JNK, Breast cancer, drug resistance