DRUG RESISTANCE INDUCED BY GENOMIC INSTABILITY IN BREAST CARCINOGENESIS

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Abstract: Breast carcinogenesis is a multistage process that involves numerous mutations and cellular phenotypic alterations attributed to exposure to exogenous environmental substances as well as endogenous agents as female hormones. The aim of this study was to evaluate resistance to drugs in breast carcinogenesis induced by environmental substances and estrogen. An in vitro model, called Alpha model, was developed with the immortalized breast epithelial cell line, MCF-10F that it was exposed to low doses of high LET (linear energy transfer) alpha particles (150 keV/µm) of radiation, and cultured in presence of 17β-estradiol (estrogen). This model consisted of: i) MCF-10F, ii) Alpha3, a malignant non-tumorigenic, radiation-treated, iii) Alpha5, radiation-and estrogen-treated cell lines and iv) Tumor2 (derived from Alpha5 injected into the nude mice), both malignant and tumorigenic cell lines. Previous results showed that Alpha5 and Tumor2 increased cell proliferation, anchorage independency, invasive capabilities and tumor formation in nude mice, microsatellite instability and loss of heterozygosity in chromosomes 6, 8, 11 and 17 and mutations of c-Ha-ras and Rho-A among others. The effect of three drugs such as pamidronate, paclitaxel and docetaxel were studied in this model and in other malignant breast cancer cell lines, as MCF-7, MDA-MB-231, ZR-75-1. Results indicated that pamidronate was drug resistance in all cell lines that were positive for c-Ha-ras and Rho-A protein and gene expression. Paclitaxel induced apoptosis in all cell lines of the model but MCF-7, MDA-MB-231 and ZR-1 cell lines were resistant when positive for c-Ha-ras and Rho-A. Docetaxel induced apoptosis in all cell lines but had not affect on MCF-10F, Alpha5, MDA-MB-231 and ZR-75-1 cell lines and induced apoptosis in Alpha3, Tumor2 and MCF-7, all positive for Rho-A. It can be concluded that resistance of the malignant breast cancer cells depends upon genomic instability and progression of malignancy.

Key words: Breast, carcinogenesis, apoptosis, drug resistance

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