DRUGS AND CURCUMIN INHIBIT EPITHELIAL-MESENCHYMAL TRANSITION IN BREAST CARCINOGENESIS

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Abstract. Breast cancer remains the major cause of global female mortality despite substantial progress in prevention, diagnosis and treatment. Drugs as 5-Fluorouracil (5-FU) is a widely used anticancer drug, a heterocyclic aromatic organic compound with a structure similar to pyrimidine molecules of nucleic acids that interferes with nucleoside metabolism, cell cycle arrest and induction of apoptosis in cancer cells. Curcumin is an antioxidant known as a dietary natural yellow pigment derived from the rhizome of the herb Curcuma longa. Curcumin has demonstrated antioxidant and antiproliferative properties in breast cancer. Evidence strongly implicate that Epithelial-Mesenchymal Transition (EMT) is involved in malignant progression inducing genes such as Axl, Twist1 and Slug. Since such genes are aberrantly expressed in multiple tumor types and are known to favor the metastatic dissemination process the effect of drugs and curcumin was evaluated in breast cancer cell lines by qRT-PCR. The aim of this study was to evaluate genes that could be targeted by several drugs and curcumin in relation to EMT in a breast carcinogenesis in vitro model induced by radiation and estrogen. An established breast cancer in vitro model was used. It was developed with the normal immortalized breast epithelial cell line, MCF-10F that was exposed to low doses of high LET (linear energy transfer) alpha particles (150keV/um) of radiation, and cultured in presence of 17β-estradiol. This model consisted of the following cell lines: i) MCF-10F, ii) Alpha5, pre-tumorigenic, and iii) Tumor2, derived from Alpha5 injected in nude mice. Curcumin effect in breast cancer cell lines was studied with 10 and 30µM for 48 hrs. The expression of genes implicated in EMT was evaluated by qRT-PCR. Results showed that 5-FU and curcumin decreased expression of genes related with EMT as Axl, Slug, Twist1, E-Cadherin and increased mesenchymal-related genes as N-Cadherin, Vimentin, Fibronectin, as well as those related with metastasis such as c-Ha-ras, Rho-A, p53, Caveolin-1 and others. MicroRNA expression was analyzed in breast cell lines by the same method. Curcumin increased miR-34a expression, which in turn repressed several genes that are situated at the core of several signaling pathways known to mediate EMT. The migratory and invasive capabilities were decreased by drugs and curcumin. Thus, our studies showed that drugs and curcumin may prevent or the delay in cancer progression and dissemination through its ability to disrupt EMT. It can be concluded that drugs and curcumin influenced biochemical changes associated with EMT, and among microRNAs the miR-34a and its downstream genes Axl, Slug and Twist1 seems to promote such transition.

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