BIOMARKERS ASSOCIATED WITH ENVIRONMENTAL SUBSTANCES AND ESTROGEN IN BREAST CARCINOGENESIS

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Abstract: Breast cancer is the most common cancer in women. Exogenous and endogenous agents such as environmental carcinogens and female hormones seem to be involved in the etiology of this disease. It is a multistage process involving a series of genetic alterations. Identification of potential biomarkers for breast carcinogenesis is critical for diagnosis. To gain insights into possible biomarkers an experimental breast cancer model, named Alpha model, was used (Carcinogenesis 21: 769, 2000). It was developed with the immortalized human breast epithelial cell line, called MCF-10F, exposed to low doses of high LET (linear energy transfer) alpha particles (150 keV/μm) in the presence of 17β-estradiol (Estrogen). This model consisted of human breast epithelial cells in different stages of transformation: i) a control cell line, MCF-10F; ii) Estrogen-treated cell line iii) a malignant cell line, named Alpha3; iv) a malignant and tumorigenic cell line, named Alpha5 and v) tumor cell line derived from Alpha5, named Tumor2. Results showed that double dose of 60 cGy alpha particles in the presence of estrogen induced malignant transformation of MCF-10F assessed by multiple biological assays as increase in cell proliferation, anchorage independency, invasive capabilities, tumor formation in nude mice, microsatellite instability and loss of heterozygosity in chromosomes 17, 11, 6, 8. Gene expression analysis using cancer affymetrix arrays detected alterations in the expression levels of important oncogenes as c-Ha-Ras, as well as tumor suppressor genes as p53, BRCA1, PTEN, RB and important dependent cell signaling factors for malignant transformation as TGF alpha, TGF beta receptor, MnSOD. Some cancers are caused by alteration of many genes induced by oxidative stress, therefore free radical scavengers are important to consider. Curcumin (diferuloylmethane), a yellow colored polyphenol, an important antioxidant derived from the herb Curcuma longa was used in these studies. Accumulating evidence suggests that curcumin has a diverse range of molecular targets, supporting the concept that it acts upon numerous biochemical and molecular cascades. Results indicated that curcumin as antioxidant decreased hydrogen peroxide formation in MCF-10F, Estrogen, Alpha3, Alpha5 and Tumor2 cell lines in comparison to their counterparts. Bound GDP mediated by a guanine nucleotide releasing factor, named GRF must be released by Ras proteins. Curcumin decreased RasGRF1 protein expression in Alpha3 and Alpha5. The enzyme superoxide dismutase (MnSOD) that reduces the superoxide radical to hydrogen peroxide decreased in Alpha5 in presence of curcumin. In summary, altered expression of multiple genes and proteins involved in key signaling pathways of carcinogenesis render this model an important tool for finding important biomarkers associated with environmental substances and estrogen in breast carcinogenesis.

Key words: biomarkers, environmental substances, estrogen, breast carcinogenesis

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