RECENT ADVANCES IN BREAST CARCINOGENESIS INDUCED BY ENVIRONMENTAL SUBSTANCES

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Abstract: Environmental substances seem to be involved in the origin of breast cancer. Organophosphorous compounds are the most widely used pesticides because of extensive use in agriculture, medicine and industry. Breast cancer risk is associated with prolonged exposure to female hormones. Among these hormonal influences a leading role is attributed to estradiol since prolonged stimulation by steroid hormones may increase cell division, and therefore the risk of breast cancer. This cancer may be induced by radiation, for example the Japanese female survivors of the A- bomb attacks, young women treated by radiotherapy for Hodgkin’s lymphoma. Cancer development is a multistep process that it manifests itself as a sequence of defined stages. In vitro model with the immortalized human breast epithelial cell line, MCF-10F exposed to (a) low doses of high LET (linear energy transfer) alpha particles (150 keV/μm) (Carcinogenesis 21: 769, 2000) and (b) organophosphorous pesticides, either with Parathion (P) or Malathion (M) alone and combination of either P or M in the presence of estrogen (E). Results showed that MCF-10F cells treated either with double dose of 60 cGy alpha particles in the presence of E or pesticides induced malignant transformation of MCF-10F. The malignant transformation was determined by multiple biological assays: increased cell proliferation, anchorage independency, invasive capabilities and tumor formation in nude mice. Gene expression analysis using cancer pathway specific and affymetrix arrays detected alterations in the expression levels of p53, ErbB2, BRCA1, c-Ha-ras, Rho-A, PTEN, RB, c-Ha-ras, transforming protein Rho-A, F, GDP, among others. In addition to the in vitro human model (c) an in vivo rat mammary gland model was also generated: (I) control (II) either P or M (III) E and (IV) P or M and E. Animals were treated for 5 days. These combined treatments induced significant progressive morphological and molecular changes. Alterations in the protein expression levels were observed for mutant c-myc. c-jun, c-fos, p53, CYP1A1 gene in the rat mammary gland after 240 days of treatment in comparison to control. Such stimulation led to mammary tumor formation. Thus, our study shows the molecular changes indicative of oncogenic deregulation of breast cancer progression induced by the combination of environmental substances and estrogen. Thus, aberrant expression of multiple genes involved in key signaling pathways renders these models as important tools for monitoring carcinogenic progression induced by environmental substances.

Key words: Environmental substances, breast cancer cells, gene and protein expression

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