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Genetic induction and upregulation of cyclooxygenase (COX) and aromatase (CYP19): an extension of the dietary fat hypothesis of breast cancer

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Summary A novel model of mammary carcinogenesis is proposed involving sequential induction and upregulation of cyclooxygenase and aromatase genes by essential fatty acids prominent in the US diet. The basic carcinogenic processes are: (1) constitutive prostaglandin biosynthesis and formation of mutagenic oxygen and nitrogen free radicals responsible for tumor initiation; (2) PGE-2-induced expression of aromatase and constitutive estrogen biosynthesis which sustains mitogenesis and tumor promotion; and (3) PGE-2-induced expression of vascular endothelial growth factor which stimulates angiogenesis and tumor metastasis.

Epidemiologic investigations suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) have chemopreventive potential against human breast cancer (1–4). This effect apparently stems from the blockade of the prostaglandin cascade by inhibition of its rate limiting enzyme, cyclooxygenase (COX).

Two primary genes are responsible for the genetic control of COX, a constitutive gene (COX-1) and an inducible isoform (COX-2) (5). Recent molecular studies of breast cancer tissues indicate that COX-2 is inappropriately induced and that both COX-2 and COX-1 are upregulated in malignant cells (6).

Prostaglandin (PG) biosynthesis is the key component of the human response to immune stimulation (7). However, inappropriate activation and upregulation of this immunoreactive pathway may lead to untoward results; namely, the intermediate genesis of free radicals (FRs) which are mutagenic (8).

Since mammary carcinogenesis is undoubtedly a function of deregulation of estrogen biosynthesis and metabolism, the above components of PG deregulation are not by themselves sufficient to constitute an important model of mammary carcinogenesis. However, it has recently been discovered that PGE-2 effectively and specifically induces the promoter II region of the cytochrome P-450 gene (CYP-19) which is transcribed and translated into aromatase, the chief enzyme in the biosynthesis of estrogen (9). Thus, the PG model of mammary carcinogenesis involves a mutagenic autocrine function of mammary epithelial cells (production of PG and FRs), and a paracrine function in contiguous adipocytes and fibroblasts (induction of CYP-19 with subsequent biosynthesis of estrogen by aromatase). It is also noteworthy that the model potentiates angiogenesis in developing tumors, since PGE-2 induces the expression of vascular endothelial growth factor (VEGF) which stimulates neovascularization (10). Figure 1 depicts the basic features of the model.

The key feature of the model is elucidation of a common mechanism by which inappropriate induction and upregulation of estrogen biosynthesis occurs with regularity in the ductal epithelium of the mammary gland. Since estrogen is under tight homeostatic regulation, it is hypothesized that the loss of control is facilitated primarily

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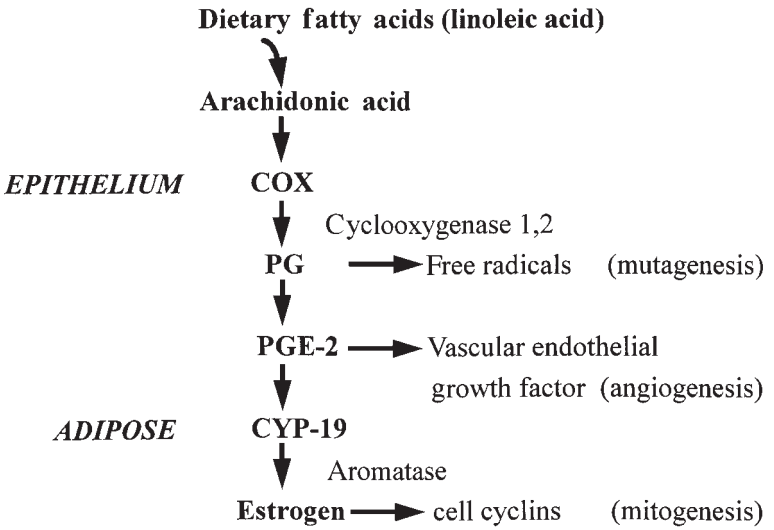

Fig. 1 Model of mammary carcinogenesis.

through a second biosynthetic pathway inextricably linked to estrogen biosynthesis. The PG cascade is sufficient for this purpose. It is ubiquitous in all cells including mammary epithelium and its controlling genes (especially COX-2) are readily induced and upregulated by a number of intra- and intercellular effector molecules including viral and bacterial antigens, growth regulatory factor and, most importantly, arachidonic acid, which serves as the pathway's primary substrate (11). In US women, the sustained presence of excess arachidonic acid results from excess consumption of red meat and certain vegetable oils rich in the essential polyunsaturated fatty acid, linoleic acid (12,13). Upon entering adipose and muscle cells, linoleic acid is converted to arachidonic acid which, in turn, activates constitutive transcription and translation of COX genes in the mammary epithelium, thereby leading to autocrine and paracrine effects of mutagenesis (tumor initiation), mitogenesis (tumor promotion), and angiogenesis (tumor metastasis). The model is therefore an extension of the dietary fat hypothesis of breast cancer and, since NSAIDs selectively inhibit cyclooxygenase, it portends an important new area of research in breast cancer chemoprevention (14,15).

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