IN THE SPOTLIGHT

The Role of the PGE_2–Aromatase Pathway in Obesity-Associated Breast Inflammation

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Summary: Subbaramaiah and colleagues present the first evidence indicating that a cyclooxygenase-2–prostaglandin E_2–aromatase pathway promotes obesity-associated inflammation in women's breast tissues. Their findings shed new light on obesity-associated inflammation in general and provide a rationale for developing effective chemopreventive and therapeutic strategies targeting this pathway for obese women with breast inflammation and patients with hormone-dependent breast cancer. *Cancer Discov*; *2(4)*; 308–10. *©2012 AACR.*

Commentary on Subbaramaiah et al., p. 356 (3).

It is assumed that weight increase and obesity are mostly caused by a combination of excessive consumption of energy-dense foods and lack of physical activity. A few cases are attributable primarily to genetics (endocrine disorders), medical reasons, or psychiatric illness. The correlation between obesity and several life-threatening diseases such as type 2 diabetes and cardiovascular disease has been well established. In addition, recent epidemiologic studies reveal that obesity is also a risk factor for multiple types of cancers, including breast cancer, and is associated with a poor prognosis of breast cancer (1, 2). However, the mechanisms underlying the association of obesity with cancer are poorly understood. Obesity-associated inflammation is thought to be one of the most important factors connecting obesity to cancer. In addition, several specific obesity-associated factors correlate with an increased risk of organ-specific cancers. For example, obesity-induced esophageal reflux, hypertension, insulin resistance, and hormone alterations could contribute to an increased risk in esophageal, kidney, colorectal, and breast cancer, respectively. In breast cancer, approximately two thirds of patients have tumors that express estrogen receptors (ER) and require estrogens for tumor growth. Estrogens are female sex hormones, including estrone, estradiol, and estriol, which are synthesized from androgens by aromatase, a cytochrome P450 enzyme. In this issue of *Cancer Discovery*, Subbaramaiah and colleagues (3) report for the first time that overweight/obesity-associated aromatase expression and activity (hormone alterations) correlate with the status of inflammation in breast tissues of women. These findings suggest that aromatase may mediate the crosstalk of obesity-associated inflammation and hormone alterations.

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It has been well established that a proinflammatory gene, cyclooxygenase 2 (COX-2), plays important roles in inflammation and cancer progression (4). For example, COX-2 is elevated in approximately 43% of human invasive breast cancers and 63% of ductal carcinomas *in situ* and its expression is also associated with decreased survival in patients with invasive breast cancers (5, 6). Currently, the best agents for targeting COX-2 enzyme are nonsteroidal anti-inflammatory drugs (NSAID), including nonselective NSAIDs and selective COX-2 inhibitors. NSAIDs are some of the most commonly used drugs in the United States and around the world because of their anti-inflammatory and pain-relieving effects. The epidemiologic and clinical evidence demonstrates that regular use of NSAIDs over a 10- to 15-year period reduces the relative risk of developing colorectal cancer by 40% to 50%. In addition to colorectal cancer, a recent extensive meta-analysis of 38 studies (16 case–control studies, 18 cohort studies, 3 case–control studies nested in well-defined cohorts, and 1 clinical trial) showed that NSAID use reduced breast cancer risk (7). Importantly, daily NSAID use for over 5 years decreased a relative risk for developing breast cancer by 39% (8). Multiple lines of preclinical evidence demonstrate that COX-2 contributes to obesity and obesity-induced muscular insulin resistance. For example, loss of COX-2 led to reduced total body fat in mice by attenuating adipose tissue differentiation and decreased infiltration of macrophages into epididymal adipose tissue (9). Similarly, inhibition of COX-2 by selective inhibitors resulted in a reduction of adipose tissue mass development and obesity-induced muscular insulin resistance in murine models of nutritionally induced obesity (10, 11). The report in this issue of *Cancer Discovery* provides the first clinical evidence that COX-2 levels are significantly associated with breast inflammation in women, although its expression is substantially higher in the breast tissue of obese as compared with lean women. Moreover, this report shows for the first time that the levels of COX-2–derived prostaglandin E_2 (PGE_2) in the breast tissue is positively correlated with obesity and breast inflammation in women. PGE_2 is a known proinflammatory mediator and plays a predominant role in promoting inflammation and tumor progression. Their findings indicate that PGE_2 may be one of the proinflammatory mediators connecting obesity to breast cancer.

In addition to being an energy storage depot, adipose tissue also serves as an active endocrine organ. Excess adipose tissue secretes growth factors and cytokines such as adiponectin, leptin, plasminogen activator inhibitor, VEGF, TNF-α, resistin, interleukin-6, and interleukin-8 (12). Some inflammatory mediators produced by adipose tissue, as mentioned previously, have been shown to contribute to obesity-associated chronic inflammation. However, the findings reported by Sabbaramaiah and colleagues (3) have extended our current knowledge of obesity-associated inflammation. The data from this study showed that each molecule of the PGE_2→cyclic AMP (cAMP)→protein kinase A (PKA)→aromatase pathway is significantly associated with both obesity and breast inflammation in women. Their findings provide another potential mechanistic explanation for the contribution of obesity to inflammation in human breast tissue. Given that COX-2–derived PGE_2 upregulates aromatase through a cAMP–PKA cascade in human breast tissue, inhibition of COX-2 could result in reduction of estrogen production. Indeed, a strong association between COX-2 and aromatase expression has been found in human breast cancer specimens (13). Moreover, recent results from the National Institutes of Health–AARP Diet and Health Study indicated that daily aspirin use lowered circulating estradiol levels in a postmenopausal women and significantly reduced risk of ER-positive but not ER-negative breast cancer (14). Additional research is needed to determine whether the levels of COX-2 are higher in ER-positive breast cancer than in ER-negative breast cancer and whether COX-2 expression is associated with the inflammation in breast tissue of obese women.

The adipose tissue in breast consists of adipocytes, macrophages, and undifferentiated fibroblasts. Adipocytes serve as active endocrine cells producing hormones, growth factors, and cytokines. Subbaramaiah and colleagues (3) present the first *in vitro* evidence that PGE_2 secreted from macrophages induced aromatase expression and activity through a cAMP–PKA cascade in preadipocytes. Their findings suggest a novel function of the COX-2–PGE_2 signaling in mediating cross-talk between macrophages and adipocytes during obesity-associated inflammation.

Therapies targeting estrogen activity or synthesis are commonly used for both the prevention and treatment of hormone-dependent breast cancer. For example, tamoxifen as an inhibitor of estrogen activity is one of the first-generation drugs for the prevention and treatment of hormone-dependent breast cancer. Exemestane, which is one of the third-generation aromatase inhibitors, is used to treat postmenopausal women with hormone-dependent breast cancer and patients who have already been treated with tamoxifen for 2 to 3 years without beneficial effects. However, these drugs have significant side effects. Similarly, long-term use of high doses of selective COX-2 inhibitors and nonselective NSAIDs (except for aspirin) is associated with unacceptable cardiovascular side effects in certain patients, especially in those individuals with a history of atherosclerotic heart disease. One way to avoid these undesired side effects is to use lower doses of drug through adjuvant treatment. For instance, combined treatment using aromatase inhibitors and selective COX-2 inhibitors may improve the efficacy of a single agent in breast cancer prevention and treatment with less toxicity. Indeed, recent clinical trials showed that combined treatment with celecoxib (a selective COX-2 inhibitor) and exemestane had more of an effect on reducing tumor size than either drug alone in postmenopausal women who have breast cancer (15) or in postmenopausal patients with invasive ER-positive breast cancer (16). This newly reported work by Subbaramaiah and colleagues (3) supports further clinical studies to evaluate the relative benefits and risks of this approach for chemoprevention in obese postmenopausal women and for therapy in patients with hormone-dependent breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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