PREFACE

Obesity and Breast Cancer: A Multipartite Connection

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It is our great pleasure to provide a brief introduction to this special issue of the *Journal of Mammary Gland Biology and Neoplasia* that is devoted to obesity and breast cancer. This issue contains reviews discussing the impact of obesity on breast cancer and dissecting the underlying molecular networks that, in our opinion, represent key pathways mediating the effects of obese state on breast carcinogenesis. In the last few years, basic science has advanced to the point where innovative tools have been developed to study and target the key nodes of obesity-breast cancer link; these models and emerging therapeutic targets will be discussed.

This is a very timely issue. The prevalence of overweight and obesity has dramatically increased in the last two decades in the United States and many other countries. Notably, obesity is second only to tobacco as a leading risk factor for cancer and nearly 30 % of cancers are attributable to obesity. The association of obesity with breast cancer has been examined in multiple studies. It is now known that obesity is not only a risk factor for the increased tumor aggressiveness, poorer prognosis, higher rate of recurrence and poorer survival of obese breast cancer patients, but it also affects the development of new cases of breast cancer. A recent meta-analysis examining the effect of obesity on survival of women with breast cancer reported a hazard ratio (HR) of 1.30–1.35 for mortality in obese vs. non-obese subjects [1].

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Obesity at time of diagnosis was also found to be associated with a greater than two-fold increased risk of breast cancer recurrence (HR 2.43) [2]. Multiple clinical studies have been conducted to examine the factors that play a role in mediating the impact of obesity on breast cancer outcomes.

Obesity is a complex physiologic state that is associated with multiple molecular changes capable of modulating tumor cell behavior as well as aspects of the surrounding microenvironment. Gene expression analysis of breast tumors from normal, overweight and obese breast cancer patients revealed an obesity-associated breast cancer transcriptional gene signature which correlated with worse patient outcome when analyzed using various public expression data sets [3]. Obese state appears to modulate gene expression patterns of the tumor cells, potentially altering their growth and metastatic potential. Multiple factors in the breast tumor microenvironment can influence breast tumor cells. Size heterogeneity of normal adipocytes is often lost in obesity in favor of adipocyte hypertrophy (increase in cell size) and hyperplasia (increase in cell number). Increased number of hypertrophied adipocytes may produce increased levels of hormones (e.g., estrogen) to promote aggressive behavior of tumor cells [4]. Additionally, increased numbers of infiltrating TNFα and interleukin (IL)-6 secreting macrophages, endothelial cells, T-cells, mast cells and other immune cells in the tumor microenvironment alter tumor behavior in obese conditions [5, 6].

Hyperinsulinemia associated with obesity promotes the biological activity of insulin-like growth factor-1 (IGF-1) and alters the levels and activity of proinflammatory cytokines, chemokines and adipokines [7] leading to breast tumor progression and metastasis. Epidemiological studies have shown a strong relationship between high levels of circulating insulin and c-peptide and poor prognosis of breast cancer [8, 9]. Various studies of different populations, genders and age groups have found a non-linear relationship

between circulating concentrations of IGF-1 and increased BMI (reviewed in [10]) and high IGF-1 levels positively correlate with increased breast cancer risk [11, 12]. IGF-1 overexpression leads to excessive proliferation and increased survival signals for the development of breast tumors [13]. In fact, inactivation of IGF-1R results in reduced breast tumor growth and metastasis in vivo [14]. It is noteworthy that IGF-1R is overexpressed in ~50 % of primary breast tumors compared with normal tissue indicating that these carcinomas may have enhance responses to the mitogenic and anti-apoptotic effects of IGF-1 in their immediate obese microenvironment [15].

The cytokine profile associated with obesity is typically altered to show a reduction in the release of anti-inflammatory factors and an increase in the secretion of pro-inflammatory factors, which might thereby trigger a chronic inflammation state [16, 17]. In recent years, the presence of chronic inflammation in obese women, characterized by increased levels of C-reactive protein, inflammatory cytokines (TNFα, IL-6, IL-8 and monocyte chemoattractant MCP-1) and leptin, has gained increased attention as it creates a tumor-supporting inflammatory milieu [18]. Importantly, local adipose inflammation, manifesting as inflammatory foci known as crown-like structures (CLS) consisting of dead adipocytes encircled by macrophages, is observed in breast tissue of most overweight and obese women. In a feed-forward manner, saturated fatty acids are released as a result of obesity-associated lipolysis to induce macrophage activation via Toll-like receptor 4 and NF-kB activation [19]. These proceedings lead to activation of inflammatory cytokines (TNFα, IL-6, IL-8) triggering a series of events in the inflammatory process. In addition, induction of cyclooxygenase-2 (COX-2) and prostaglandin (PG) expression as a consequence of inflammation can induce aromatase expression and estrogen synthesis, further supporting breast cancer cell growth and metastatic behavior.

An additional player has been identified as a key member of the obesity-molecular network that influences several components of microenvironment as well as growth and metastatic characteristics of breast cancer cells: the adipokine, leptin. Over the last few years, multiple epidemiological studies have linked high levels of plasma leptin with increased risk and poor prognosis for breast carcinogenesis [20–24]. Circulating as a 16-kD protein, partially bound to plasma proteins, leptin exerts its biological actions through specific cell surface receptors (leptin receptors) present in a variety of tissues [25]. Breast carcinoma cells express higher levels of leptin receptor in comparison to normal mammary epithelial cells, allowing cancer cells to acquire increased sensitivity to leptin in the tumor microenvironment. Overexpression of leptin is observed in 92 % of breast tumors whereas little or no expression of leptin is found in normal mammary epithelial cells [26]. Thus, in obese conditions, leptin affects breast cancer growth via endocrine, paracrine and autocrine interactions.

With the rising obesity pandemic, its newly acquired designation as a "disease" and its strong impact on breast cancer incidence, behavior, and prognosis, it is important to understand the clinical and molecular links underlying the obesity-breast cancer connection. In this issue, experts succinctly review our current understanding of obesity-breast cancer related molecular pathways, taking into account the role of various secreted factors and microenvironment components. They also review the clinical implications of these studies, presenting the in vivo models that have proven invaluable in obesity research and discussing potential therapeutic tools to break the obesity-breast cancer connection. Our goal in assembling this issue is to provide insight into the obesity-breast cancer link at the preclinical and clinical levels, identify gaps in our knowledge and most importantly, inspire others to join us in studying the multiple faces of obesity as it impacts breast cancer.

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