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Leptin and cancer: from cancer stem cells to metastasis

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Abstract

There is growing evidence that obesity is a risk factor of cancer incidence and mortality. Hence, the identification of the mechanistic links between obesity and cancer progression is emerging as a topic of widespread interest. Recently, several groups have addressed the functional roles of leptin, an adipocyte-derived adipokine, for mammary tumor progression. In this issue of *Endocrine-Related Cancer*, Zheng *et al.* study the role of leptin on tumor growth in a xenograft model of MMTV-Wnt1-derived cancer cells. They study growth of these cancer cells in the context of obese animals, such as *ob/ob* mice (lacking leptin) and *db/db* mice (lacking functional leptin receptors (LEPR)) and find that leptin triggers LEPR-positive cancer stem cell differentiation, thereby promoting tumor cell survival. These findings highlight the therapeutic potential for leptin and leptin signaling in the context of mammary tumor growth.

Introduction

A large number of epidemiological studies on cancer incidence link the propensity to develop certain types of cancers (e.g. colon, thyroid, esophagus, renal, endometrial, and postmenopausal breast cancer) with an individual's excess body fat/obesity (Bianchini *et al.* 2002, Calle *et al.* 2003). Adipokines, i.e. adipocyte-derived secretory proteins, represent likely candidates to mediate at least in part the increased cancer risk and enhanced progression associated with obesity. Other contributors to obesity-related cancer progression are the insulin/IGF1 pathways and sex hormones (summarized in Park *et al.* (2011a)).

Among the adipokines, leptin is the most intensively studied factor, both in metabolism in general and in obesity-related cancers due to the fact that leptin levels increase in proportion to fat mass. In this issue of *Endocrine-Related Cancer*, Zheng *et al.* (2011) show that tumor cells derived from a widely used mammary tumor model, the MMTV-Wnt1 mouse, grow

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less effectively in leptin-deficient, obese mice (generally referred to as ‘*ob/ob* mice’) compared with obese mice with an intact leptin pathway. This suggests that leptin signaling plays an essential role in MMTV-Wnt1 tumor cell growth and survival. They conclude that these leptin effects are mediated through a comprehensive set of responses of leptin receptor (LEPR)-positive tumor cells that include a cancer stem cell (CSC) population defined by characteristic cell surface markers that expresses the LEPR as well (Zheng *et al.* 2011).

Leptin: just in your head?

Leptin is encoded by the *ob* gene and is a well-established adipokine influencing appetite control and energy expenditure through its actions on the hypothalamus and other regions in the brain where LEPR are highly expressed (Frederich *et al.* 1995, Halaas *et al.* 1995, Vaisse *et al.* 1996). A single transcript encoded by the *db* gene produces at least five different variants of the LEPR protein through alternative splicing (Lee *et al.* 1996). However, only the long form of LEPR-B has a cytoplasmic domain that transduces the leptin-mediated downstream signaling events, such as activation of the PI3K, ERK1/2, and Jak2/Stat3 pathways (Baumann *et al.* 1996, Morris & Rui 2009). In addition to the neuronal actions, leptin also exerts other physiological responses in peripheral tissues. These include effects on the immune response, angiogenesis, reproduction, and an intracellular cross talk with signaling pathways of growth hormones, such as insulin, and lipid metabolism pathways (Sierra-Honigmann *et al.* 1998, Margetic *et al.* 2002, Muoio & Lynis Dohm 2002). Adipose tissue with its well-appreciated endocrine functions takes advantage of leptin as a potent signaling molecule that profoundly impacts multiple peripheral tissues. Tumor tissues have been demonstrated to have cells that are leptin responsive, including tumor cells. A number of reports indicate that LEPR are highly abundant in many tumor tissues compared with benign or normal tissues. Leptin-responsive tumors include mammary carcinoma, pancreatic tumor, and gastrointestinal tumors, such as esophageal, gastric, and colon cancer cells (Ishikawa *et al.* 2004, Garofalo *et al.* 2006, Howard *et al.* 2010).

Leptin and the breast cancer axis

Leptin is a growth factor that plays an important role in development, differentiation, and cell growth under normal physiological conditions. It affects a number of cell types, including neuronal cells, immune cells, pancreatic β -cells, endothelial cells, and adipocytes. Leptin exerts its effects through LEPR-B-mediated downstream pathways, such as PI3K, ERK1/2, and Jak2/Stat3 (Morris & Rui 2009). With respect to breast cancer, leptin is an attractive target due to its involvement in cell proliferation, migration, and invasion, giving rise to more aggressive and metastatically more potent tumor cells (Cirillo *et al.* 2008). *In vitro* studies using human breast cancer cell lines indicate that differential leptin responses among various cell lines may primarily depend on receptor levels of LEPR-B among those cell lines studied.

Numerous attempts have been made to evaluate leptin effects on breast cancer progression *in vivo*. Genetic loss-of-function mutants for leptin or the LEPR (i.e. *ob/ob* or *db/db* mice) develop systemic metabolic abnormalities that include obesity, diabetes, infertility, and immune defects (Friedman 2009). Manipulation of leptin levels with these genetic mouse

models in MMTV–transforming growth factor α (TGF α) mice failed to develop mammary tumors because these mice completely lack a ductal mammary epithelium. As most tumors arise from the ductal epithelium, it is not possible to use these mice for the study of mammary tumor development (Cleary *et al.* 2003, 2004). Recently, more compelling *in vivo* evidence was provided with a hypothalamic LEPR-B reconstitution in *db/db* mice (*db/db^{Nse+/+}*), which restores metabolic abnormalities in *db/db* mice, such as obesity, diabetes, and infertility. These mice also develop a normal mammary epithelium (Chua *et al.* 2004). Therefore, they can be crossed with a mammary tumor model, such as the MMTV-PyMT mouse. Results from these crosses suggest that an LEPR-B-mediated signal promotes tumor growth and metastasis. Cancer cell metabolism is affected in these mice by orchestrating downstream pathways, such as PI3K, ERK1/2, and Jak2/STAT3 (Park *et al.* 2011b). In addition, diet-induced obese mouse models have been used to modulate leptin levels *in vivo*. From these diet studies, it is apparent that mammary tumors grow faster under high-fat diet conditions. Consistent with a possible involvement of leptin, obese MMTV–TGF α mice do indeed display elevated circulating leptin levels (Dogan *et al.* 2007). However, for obvious reasons, it is challenging to discern distinct leptin effects from other metabolic changes associated with obesity-induced metabolic dysregulation.

Xenografts of MMTV-Wnt1 breast cancer cells transplanted into diet-induced obese mice (which maintain high levels of circulating leptin over prolonged periods of time) grow faster, in further support of a tight association between obesity and mammary tumor growth (Nunez *et al.* 2008). To assess whether this obesity-associated increase is solely due to leptin or a combined effect of other metabolic parameters that change under these conditions, Zheng *et al.* (2011) in this issue of *Endocrine-Related Cancer* demonstrate that xenografts of MMTV-Wnt1 cancer cells transplanted into leptin-deficient obese mice (*ob/ob*) displayed a stunted tumor growth. In contrast, transplants into obese *db/db* mice (lacking the LEPR and as a result displaying high leptin levels) augmented tumor growth. This is a clear indication that tumor cell behavior heavily relies on leptin signaling, even if cancer cells are exposed to other mitogenic signals and excessive nutrients, such as hyperinsulinemic, hyperglycemic, and hyperlipidemic conditions prevailing in obesity (Zheng *et al.* 2011).

LEBR-B⁺ cell populations in mammary tumor tissues

Cancer progression is a multistep process that involves tumor initiation, primary tumor growth, invasion, and metastasis, with minimally the latter three relying on interactions with stromal tumor components that include endothelial cells, immune cells, fibroblasts, and adipocytes (Hanahan & Weinberg 2011). The mechanistic details underlying the association between obesity and cancer as they relate to leptin are still elusive despite the vast literature on the topic. A key question remains as to whether leptin contributes to cancer initiation or whether its role is restricted to promoting the growth of existing tumor cells? Numerous *in vitro* studies with breast cancer cell lines indicate that leptin directly contributes to LEPR-B-positive cancer cell proliferation, migration, and invasion. Furthermore, leptin has been known to regulate the immune response and angiogenesis through targeting immune cells and endothelial cells respectively (Sierra-Honigmann *et al.* 1998, La Cava & Matarese 2004), an effect that clearly affects cancer cell growth as well, albeit only indirectly. Despite these potent leptin-induced cellular changes on mammary tumor progression at various

stages, the specific leptin-responsive cell populations in tumor tissues have not yet been adequately defined.

As xenografts of MMTV-Wnt1 cell into *ob/ob* mice failed to thrive, Zheng *et al.* (2011) analyzed these regressed tumor tissues and compared them to tumor cells isolated from wild-type mice to identify a leptin-responsive cell population missing in the *ob/ob* population but present in the wild-type isolates (Zheng *et al.* 2011). Xenograft tumor tissues from transplants into *ob/ob* mice were analyzed by fluorescent-activated cell sorting for markers characteristic of CSC-rich populations, such as CD29 (integrin β 1), CD49f (integrin α 6), and CD24 (heat stable antigen) on depletion of CD45- and Ter119-positive cells (Mani *et al.* 2008, Charafe-Jauffret *et al.* 2009). Interestingly, they found that the survival of CD29⁺CD24⁻ CSC population is efficiently increased in response to leptin. They measured this by using a ‘tumor sphere formation’ assay. A leptin-responsive CD29⁺CD24⁻ CSC population expresses high levels of LEPR-B. These findings are highly provocative but will require a more in-depth evaluation of this CSC population to strengthen the hypothesis that leptin is a mammary tumor-initiating factor on the basis of its ability to stimulate CSC survival.

Concluding remarks

These results shed new light on the role of leptin and its receptor in mammary tumors (and potentially other LEPR-B⁺ tumor types). These observations touch on the important question whether obesity can be ‘tumor initiating’ and highlights that leptin may be an important contributing factor. Based on these results, an emerging model for the role of leptin on tumor progression is raised (Fig. 1). Obesity via LEPR-B-mediated signaling pathways promotes mammary tumor growth at various stages, affecting different tumor cell types that include a spectrum of cells from early CSCs through metastatic tumor cells. In this model, leptin is involved at early stages in CSC survival. Once the primary tumor is established, leptin triggers cancer cell proliferation, migration, and invasion. Furthermore, it exerts effects on tumor-associated stromal cells, such as endothelial cells, immune cells, and fibroblasts, to enhance angiogenesis and inflammatory processes that support tumor growth. Considering all of these potential roles for leptin on cancer progression, the leptin signaling pathway emerges as an attractive therapeutic target for the obese cancer patients. Can the peripheral leptin actions effectively be targeted without deteriorating the prevailing central leptin resistance under those conditions? In light of the life-threatening circumstances in the context of rapid growth of a tumor mass, a transient deterioration of central leptin action may be a price well worth paying.

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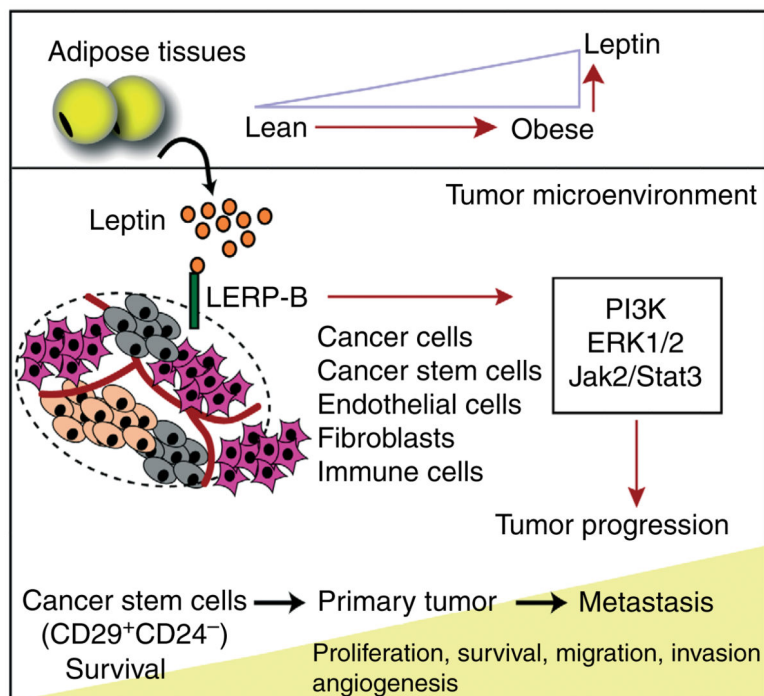


Figure 1.

The potential role of leptin in mammary tumor progression. Leptin levels are increased in proportion to adipose tissue mass over the course of obesity. Leptin produced by adipose tissues binds to LEPR-B expressing cells within the tumor microenvironment, which include epithelial cancer cells, cancer stem cells, immune cells, endothelial cells, and potentially fibroblasts. LEPR-B-mediated pathways include activation of downstream kinases, such as PI3K, ERK1/2, and Jak2/Stat3. These pathways contribute to various steps of tumor progression, from cancer stem cell survival and proliferation to metastatic tumor growth.