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Obesity and Breast Cancer: mechanisms and therapeutic implications

Kristy A. Brown[1,2], Evan R. Simpson[1,3]

[1]Metabolism and Cancer Laboratory, Prince Henry's Institute, Clayton, Australia, 3168, [2]Department of Physiology, Monash University, Clayton, Australia, 3168, [3]Department of Biochemistry and Molecular Biology, Monash University, Clayton, Australia, 3168

TABLE OF CONTENTS

1. ABSTRACT

Obesity is a known risk factor for postmenopausal breast cancer, whereby factors produced by the adipose tissue are known to directly and indirectly affect tumour growth. It is now becoming increasingly clear that both obesity and cancer arise as a consequence of dysregulated metabolism, both in response to altered energy status and endocrine factors, and to intrinsic changes within cells. Moreover, both obesity and cancer lead to localised inflammation, whereby inflammatory cytokines and prostaglandins are produced by adipose tissue and tumour cells. Obesity is also a risk factor for type 2 diabetes, with a consequential increase in circulating insulin and insulin-like growth factor-I (IGF-I) known to promote tumour cell growth. Interestingly, these factors converge to increase aromatase expression within the breast and hence, estrogen production, thereby increasing the risk of breast cancer and the growth of breast tumour cells. Therapies aimed at treating obesity/diabetes are therefore attractive options for the treatment of postmenopausal breast cancer.

2. INTRODUCTION

Obesity is a risk factor for breast cancer. Factors produced by the adipose tissue are known to directly and indirectly affect tumour cell growth. Moreover, both obesity and breast cancer are accompanied by a number of common features, including being a consequence of dysregulated metabolism, resulting in inflammation, causing and responding to changes in adipokines, insulin, IGF-1 and estrogen signalling. This review will examine how these common features and risk factors develop in and affect function of cells within the adipose and breast tumour epithelium. We will not go in depth into the role of the adipokines leptin and adiponectin in breast cancer as it has recently been reviewed in this journal (1). Suffice it to say that recent work has shown that higher leptin levels such as those found in obesity are significantly associated with an increase in breast cancer risk. On the other hand, with increased obesity, adiponectin serum levels decrease and these levels are inversely correlated with breast cancer risk. We will, however, discuss how these adipokines have been shown to affect estrogen production within the breast,

a topic mentioned only briefly in the previous review. The present review also aims to provide the reader with an insight into how these common features and risk factors may impact future therapy development.

3. PRE- VERSUS POST-MENOPAUSAL BREAST CANCER

In developed countries, over two thirds of newly diagnosed cancers are in individuals aged over 55 (2), and obesity is a recognised risk factor for breast cancer in postmenopausal women (reviewed in 3, 4). In particular, a body mass index (BMI) of 30, categorised as obese, carries a two-fold increased risk of developing breast cancer, and the risk increases exponentially with increasing BMI (4-7). Changes in the hormonal milieu at the menopause are associated with an increase in total adiposity (8, 9) and increased breast cancer risk (10). Moreover, the majority of obesity-related postmenopausal breast cancers are hormone receptor positive (reviewed in 11, 12, 13). As estrogens are no longer produced in postmenopausal ovaries, this suggests that locally produced estrogens and/or other endocrine factors are affecting tumour cell proliferation within the breast (14, 15). Conversely, data for premenopausal women has been conflicting. Although it was once believed that obesity was associated with a decreased risk of breast cancer in younger women, a number of studies now indicate that a BMI > 30 increases the risk of hormone receptor negative tumours in women prior to menopause (16-18), indicating that these tumour cells are not dependent on estrogens for proliferation but rather, may rely more heavily on insulin, IGF-I and adipose-derived factors for growth. Interestingly, gaining weight prior to menopause, particularly from 30 years of age to menopause, has been associated with an increased risk of developing breast cancer postmenopausally (19).

4. COMMON FEATURES AND RISK FACTORS

4.1. Dysregulated metabolism

Adipocytes within white adipose depots are responsible for storing energy in the form of triglycerides in times of high energy supply and mobilising these lipids in times of high energy demand. The storage of lipids in adipocytes helps to prevent excess circulating free fatty acids (FFA) being stored ectopically as triglycerides in tissues such as the pancreas, liver, muscle and kidneys which would lead to various pathologies, including hypertension, dyslipidemia, glucose intolerance and insulin resistance (20). Catecholamines, which increase intracellular cAMP, cause an increase in lipolysis, whereas insulin inhibits it (21). Obesity results when there is an imbalance between energy intake and energy expenditure and is accompanied by an increase in the number and size of adipocytes, leading to hyperplasia and hypertrophy, respectively (22). In obesity, leptin no longer elicits satiety signals from the central nervous system, thereby leading to increased energy uptake despite already high stores of energy in the adipocytes and further favouring triglyceride accumulation (23). Furthermore, the protein expression of lipolytic enzymes ATGL (adipocyte triglyceride lipase) and HSL (hormone sensitive lipase) are decreased in obese patients compared to lean individuals. AMP activated protein kinase (AMPK) is a master regulator of energy homeostasis in a number of tissues including the muscle, liver, central nervous system and adipose tissue and is suppressed in many diseases, including obesity, metabolic syndrome and cancer (24). AMPK functions as an energy sensor, directly binding AMP and ATP, and responding to energy deficiencies by conformational changes allowing the upstream kinase Liver Kinase B1 (LKB1) to phosphorylate the alpha subunit at Thr172. This leads to an increase in activity of pathways of energy production (oxidation of fatty acids, for example) and inhibition of pathways of energy utilisation (e.g. fatty acid and cholesterol synthesis and gluconeogenesis). In adipocytes of lean individuals, adiponectin activates AMPK and stimulates glucose uptake and oxidation of fatty acids and leads to an increase in available energy (25). Sex hormones have also been shown to influence AMPK activity in adipocytes where estrogens activate and androgens inactivate, and the relationship between the two appears to be a crucial determinant of fatty acid accumulation (26, 27). These findings provide one mechanism whereby hormonal changes during the menopausal transition may lead to dysregulated metabolism and weight gain.

Dysregulated metabolism is also a common feature of tumour cells. Much work has been done to characterise ideas first proposed by Warburg 80 years ago whereby it was suggested that the origin of cancer depended not on genetic changes but rather on a shift in how energy was produced (28). Although it is clear that genetic changes to oncogenes and tumour suppressors, for example, play an important role in tumour development and growth, the idea that tumour cells also acquire a metabolic advantage is now largely supported. The complexities involved in a cell's ability to shift from mitochondrial respiration to aerobic glycolysis (Warburg effect) are beyond the scope of this review, but they have been beautifully reviewed in (29). Rather, we will focus on common features of obese adipocytes and breast tumour cells, centralising around fatty acid metabolism. Noteworthy is the observation that fatty acid synthase expression, important for *de novo* lipogenesis, is increased in many types of cancer, including breast (30, 31) and consistent with this observation, LKB1 and pAMPK, known to inhibit lipogenesis, are suppressed in breast cancer cells (32-34). The inhibited activity of AMPK in obesity may be involved in carcinogenesis of breast cancer. In addition to its role in energy homeostasis, AMPK can suppress cell proliferation by inhibiting protein biosynthesis via inhibition of the mTOR (mammaliam target of rapamycin) pathway, and activation of p53 and cell cycle arrest. Much work has been done to characterise the role of p53 in mediating cell senescence and apoptosis, however, it also has an established role in maintaining energy homeostasis (35). Namely, in states of limited nutrient availability, p53 expression is induced, and p53 protein is stabilised and has an increased binding affinity to DNA, and as a consequence its downstream targets promote oxidative phosphorylation to increase energy production and inhibit glycolysis. Mutations in p53 are frequent in several types of cancer, including breast.

Inactivation of p53 thereby increases cell proliferation not only due to impairments in its pro-apoptotic capacity, but also as a consequence of shifting from mitochondrial respiration to aerobic glycolysis. Little is known of the role of p53 in adipocyte biology although it has been suggested to be anti-adipogenic (36).

4.2. Inflammation

It is now clear that obesity is associated with low grade chronic inflammation as a direct result of energy accumulation within the body. Excessive fat storage leads to stress reactions within adipocytes which in turn lead to the release of pro-inflammatory cytokines, including TNF-alpha and IL-6, from adipocytes themselves and immune cells within the adipose tissue (37). One mechanism whereby this occurs is via the increased secretion of leptin, a pro-inflammatory adipokine, which induces the production of chemokines, TNF-alpha and IL-6 from macrophages and monocytes (38, 39). Indeed, adipocytes are not the only cell type within the adipose tissue to initiate and respond to inflammatory signals. The stromal vascular fraction, which includes preadipocytes or adipose stromal cells (ASCs), endothelial cells, smooth muscle cells, multipotent stem cells, and immune cells, surrounds the adipocytes and actively participates in inflammatory responses within the adipose tissue. Macrophages in particular have been shown to infiltrate adipose tissue of obese individuals and directly associate with overly stressed or necrotic adipocytes, leading to histologically visible crown-like structures (40, 41). The number of these crown-like structures is directly related to the degree of inflammation within the adipose tissue, and is associated with the release of free fatty acids, pro-inflammatory cytokines, activation of NF-kB signalling and the increased expression of aromatase (42). Furthermore, the increased local production of IL-6 leads to an increase in circulating levels of the pro-inflammatory marker C-reactive protein, a strong predictor of the development of type II diabetes (T2D) (43). Moreover, TNF-alpha has been shown to decrease fatty acid oxidation via the downregulation of AMPK (44). Interestingly, the release of fatty acids from adipocytes has also been shown to stimulate the release of TNF-alpha and increase the expression of the inducible cyclooxygenase, COX-2, the rate limiting enzyme in prostaglandin synthesis (45). Prostaglandins act via their cognate G-protein coupled receptors to mediate autocrine and paracrine actions and have been shown to act on many physiological systems, including the adipose tissue (46). Namely, *in vitro* studies have demonstrated that prostaglandins stimulate adipocyte differentiation by increasing the clonal expansion phase (47); (48, 49) and *in vivo* data using knockout mice suggests that inhibiting prostaglandin E2 (PGE2) results in the disinhibition of lipolysis, and protects animals from high fat diet-induced obesity (50).

Inflammation also occurs in many tumour types and in some instances, precedes tumour formation (reviewed in 51). Many lines of evidence have been offered to support a direct and causative link between inflammation and cancer, and the increased prevalence of cancer at sites of chronic inflammation suggest that the inflammatory nature of obesity may contribute to the predisposition of obese women to develop breast cancer. TNF-alpha and IL-6 are well characterised for their tumour-promoting effects via the activation of oncogenic transcription factors NF-kB, AP-1 and STAT3 in epithelial cells (reviewed in 52). The intrinsic pathway of inflammation, however, is activated as a consequence of the activation of oncogenes, which then leads to the secretion of chemokines, cytokines and prostaglandins from the tumour cells themselves. This process is also accompanied by the recruitment of inflammatory cells, the increased vascularisation and the remodelling of the affected tissue (reviewed in 51, 53). Interestingly, tumour cells from invasive and *in situ* breast cancer also have increased expression of COX-2 (54). Moreover, inflammatory mediators act to stimulate cell proliferation, migration and invasion, and have been shown to affect hormone production in the adjacent stroma (reviewed below).

4.3. Insulin and IGF-I

It is well accepted that obesity is associated with an increased risk of insulin resistance and diabetes. In 2010, it was estimated that 285 million people between the ages of 20 and 79 had diabetes worldwide (reviewed in 2). Type II diabetes (T2D) which accounts for 95% of cases is characterised by hyperinsulinemia, hyperglycemia and insulin resistance, and is a risk factor for several types of cancer, including breast, colon and pancreas. Insulin and insulin-like growth factor-I (IGF-I) are peptide hormones which mediate metabolic and mitogenic effects via binding to their cognate receptors, the insulin receptor (IR) and the IGF-I receptor (IGF-IR), although actions via hybrid receptors (insulin/IGF-I receptor) have also been described.

Changes in receptor abundance and the increased formation of hybrid receptors on tumour cells have been associated with decreased patient survival. Insulin has been shown to increase the proliferation of breast cancer cells, perhaps via activation of the hybrid receptors. Interestingly, the increased growth of tumour cells in T2D appears to be independent of obesity. A-ZIP/F-1 mice, which are a lipoatrophic model of T2D demonstrate increased tumour incidence despite having no white fat and the MKR model of T2D, which is hyperinsulinemic, insulin-resistant and glucose-intolerant, displays increased growth of orthotopically inoculated mouse mammary carcinoma cells compared to control mice, despite not being obese (reviewed in 55). Furthermore, elevated fasting insulin levels are positively associated with breast cancer risk, independent of obesity in women. Interestingly, IGF-I is expressed at a higher level in ER-positive tumours than in ER-negative breast tumours (56).

4.4. Estrogens

The regulation of estrogen production within the breast is emerging as a central linking factor between obesity and breast cancer. Total and free plasma estrogen concentrations are elevated in postmenopausal obese women compared to their healthy weight counterparts (5, 57-59). Moreover, the majority of postmenopausal breast cancers are estrogen receptor (ER)-positive and their dependence of estrogens is emphasised by the efficacy of

current endocrine therapy. Noteworthy is the fact that the ovaries no longer produce measurable levels of estrogens after menopause, and the major source then becomes the adipose tissue. Aging is also associated with an increase in the ability of adipose tissue to intrinsically synthesise estrogens via the increased expression of aromatase, the enzyme responsible for catalysing the rate-limiting and one of the last steps in estrogen biosynthesis. This does not occur within adipocytes, rather, in the undifferentiated preadipocytes or adipose stromal cells (ASCs). Not only is the expression of aromatase under the control of adipose-derived factors, its expression is largely increased in response to tumour-derived factors, thereby creating a positive feedback loop between the tumour and the adipose stroma. Noteworthy is the observation that obese breast cancer patients have 130% higher circulating estradiol than their normal weight counterparts (58). Interestingly, adipokines, insulin and IGF-I, inflammatory factors and dysregulated metabolic pathways have all been shown to affect aromatase expression.

The structure of the gene which encodes aromatase, *CYP19A1*, is complex (reviewed in 60). It is composed of 9 coding exons, as well as a number of untranslated first exons driven by tissue-specific promoters. In normal breast adipose tissue, activity of promoter I.4 accounts for approximately half of total aromatase transcripts, with the remaining half being under the control of promoters I.3 and PII (61). The relative contribution of these promoters changes in the presence of a tumour, where promoters I.3 and PII are the main promoters utilised to drive aromatase expression (62).

Inflammatory factors, including prostaglandins and class I cytokines, produced by both the adipose and tumour cells are known to potently induce aromatase expression in human breast ASCs. TNF-alpha and a number of class I cytokines, including IL-6, IL-11, leukemia inhibitory factor, oncostatin-M, induces the promoter I.4-driven expression of aromatase in the presence of glucocorticoids,, whereas PGE2 causes the upregulation of promoter I.3 and PII-specific transcripts (63-65).

This review has already emphasised the role of LKB1/AMPK signalling in energy homeostasis. Interestingly, LKB1/AMPK is also a potent inhibitor of aromatase expression within breast ASCs (66). The mechanism whereby this occurs relies on the fact that AMPK inhibits the expression of CREB-target genes by directly phosphorylating the CREB co-activator CRTC2, thereby preventing its nuclear translocation and ability to bind CREB (67). Tumour-derived factors such as PGE2 are dependent on CREB activity for increased activation of promoters I.3 and PII and hence, expression of aromatase (68, 69). Interestingly, both leptin and PGE2 decrease the expression of LKB1 and the phosphorylation of AMPK, and lead to the nuclear translocation of CRTC2 and its increased binding and activation of aromatase PII in human breast ASCs (66), providing one mechanism behind the observation that obese cancer patients have higher estrogens than normal weight women. Interestingly, research performed in p53-inactivated primary cultures of mouse mammary epithelial cells demonstrated that aromatase expression and CREB phosphorylation and nuclear accumulation were increased compared to control cells (70).

The effect of insulin and IGF-I on estrogen production has also been characterised. In addition to increasing the bioavailability of estrogens via the downregulation of sex-hormone binding globulin (SHBG), insulin also acts directly on estrogen production and significantly increases aromatase activity in human ASCs in culture (71, 72). Moreover, IGF-I increases the activity of aromatase in stably transfected breast cancer cell lines (73). Interestingly, insulin and IGF-1 potentiate the actions of dexamethasone but inhibit the stimulatory effect of cAMP on aromatase activity (74). *In vivo*, SHBG also correlates negatively with insulin and IGF-I (75).

5. PERSPECTIVES AND EMERGING THERAPIES

In a world where 1.5 billion adults are overweight and of these, over 300 million women are obese, it is difficult to imagine the economic and societal impacts of aging and increased susceptibility to disease. The need to take action to manage obesity and prevent the emergence of a breast cancer epidemic is upon us. Furthermore and due to the commonalities between obesity and breast cancer, it is predictable that therapies which target obesity may also play an important role in treating and preventing breast cancer.

Weight loss has been shown to lower the level of pro-inflammatory proteins in obese women (76-79), decrease the incidence of diabetes and restore euglycemia in patients with T2D (reviewed in 2), decrease circulating leptin (80) and increase SHBG levels (81). Curiously, one study reported no change in sex hormone levels after weight loss (81) whereas an earlier study examining the effect of weight loss on sex hormones levels in women with PCOS, demonstrated a significant decrease (82). However, the association between weight loss and breast cancer risk is less clear and this is largely due to difficulties in defining the amount of weight loss and the duration necessary when designing clinical studies, and results in difficulties in interpreting conflicting studies and more so in designing more comprehensive ones. Moreover, many individuals struggle to lose weight via traditional methods focussed on healthy eating and exercise, and resorting to alternative methods of weight loss or disease control becomes a necessity. Weight loss as a result of bariatric surgery is also associated with improvement of insulin resistance, decreased inflammation, as well as beneficial modulation of adipokines and sex hormones (reviewed in 83). As a result women who have undergone this procedure have a reduced risk of developing many obesity-related cancers, including that of the breast (84).

Laboratory-based evidence suggests that adiponectin protects against obesity-related dysregulated metabolism, by increasing insulin sensitivity (85) and reducing blood glucose, triglycerides and free fatty acids

(86). Furthermore, adiponectin prevents the PGE2-mediated induction in aromatase expression in human breast ASCs (66).

Anti-inflammatory and anti-diabetic drugs are now attractive therapies to treat and prevent breast cancer. Not only do they act to reduce symptoms of metabolic syndrome, but also tend to have direct and indirect effects on tumour growth. Direct effects occur via alterations in energy production and protein synthesis pathways, and indirect effects by decreasing insulin, IGF-I, leptin, estrogens, and increasing adiponectin. Case-control and cohort studies suggest that aspirin and ibuprofen, widely used non-selective COX-1/COX-2 inhibitors, and other non-steroidal anti-inflammatory drugs (NSAIDs) decrease the incidence of breast cancer by 10-40% (reviewed in 87).

AMPK-activating drugs are also attractive therapies for obesity and breast cancer. It has been suggested that use of AMPK agonists may mimic the effect of exercise to enhance running endurance (88). The AMP analogue 5-Aminoimidazole-4-carboxamide 1-β-D-ribofuranoside (AICAR) has also been shown to decrease adiposity (89) and have anti-inflammatory properties (90) in rodents. Moreover, treatment of the breast cancer cell line MDA-MB-231 with AICAR results in the inhibition of lipogenesis, protein translation, and DNA synthesis, and as a consequence, inhibits cell proliferation (91). AICAR also inhibits the PGE2-mediated expression of aromatase in human breast ASCs (66). The biguanide metformin is the most commonly prescribed anti-diabetic drug and its use causes a decrease in circulating glucose by inhibiting gluconeogenesis in the liver via the activation of AMPK. Metformin also decreases plasma lipids and improves insulin sensitivity in patients with T2D (92). Moreover, metformin has also been shown to decrease TNF-alpha and C-reactive protein (93), which has a number of implications with regards to inflammation, insulin resistance and estrogen biosynthesis. Interestingly, recent epidemiological evidence also suggests that metformin may lower cancer risk and reduce the incidence of cancer-associated death in diabetic patients treated with the drug (94). A number of clinical trials are currently underway (95). Moreover, recent studies from our laboratory suggest that metformin would inhibit aromatase expression in a promoter-specific manner, thereby targeting adipose and tumour estrogen production and protecting other sites of estrogen action, including the brain and bone where other promoters are employed (1f and I.4, respectively) (96, 97). Consequent to these findings, we have initiated a prevention study aimed at determining the effects of metformin on estrogen production within the breast of mid-life women and are in the process of designing a neo-adjuvant study to explore the effect of metformin on aromatase expression in breast cancer.

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Send correspondence to: Kristy A. Brown, Metabolism and Cancer Laboratory, Prince Henry's Institute, 246 Clayton Road, Clayton, Victoria, 3168, Tel: 61 3 9594 4333, Fax: 61 3 9594 6125, E-mail: kristy.brown@princehenrys.org