



## Review Article

# Role of adipocyte browning in prostate and breast tumor microenvironment

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### ABSTRACT

Prostate cancer (PC) and breast cancer (BC) are the most common cancers in men and women, respectively, in developed countries. The increased incidence of PC and BC largely reflects an increase in the prevalence of obesity and metabolic syndrome. In pathological conditions involving the development and progression of PC and BC, adipose tissue plays an important role via paracrine and endocrine signaling. The increase in the amount of local adipose tissue, specifically periprostatic adipose tissue, may be a key contributor to the PC pathobiology. Similarly, breast adipose tissue secretion affects various aspects of BC by influencing tumor progression, angiogenesis, metastasis, and microenvironment. In this context, the role of white adipose tissue (WAT) has been extensively studied. However, the influence of browning of the WAT on the development and progression of PC and BC is unclear and has received less attention. In this review, we highlight that adipose tissue plays a vital role in the regulation of the tumor microenvironment in PC or BC and highlight the probable underlying mechanisms linking adipose tissue with PC or BC. We further discuss whether the browning of WAT could be a therapeutic strategy for the treatment of PC and BC.

**KEYWORDS:** *Adipocyte browning, Breast cancer, Prostate cancer, Tumor microenvironment*

### INTRODUCTION

Prostate cancer (PC) is the most common type of cancer in men in developed countries [1]. There is growing evidence to demonstrate the association between obesity and carcinoma aggressiveness, poor treatment outcomes, and a higher risk of cancer-specific mortality for PC [2-5]. Similarly, breast cancer (BC) is the most commonly diagnosed cancer and the main cause of cancer-related deaths in women worldwide. General and central obesity are risk factors for many chronic diseases [6,7] and are often defined by the body mass index (BMI) or waist-to-hip ratio (WHR) [8]. Overweight and obesity are associated with an elevated risk of 13 types of cancers [9,10]. The aim of this review was to explore the role of adipose tissue in the regulation of the tumor microenvironment in PC or BC by discussing the following: (1) the relationship between obesity and PC or BC, (2) possible physiological mechanisms linking obesity and the progression of PC or BC, and (3) white adipose tissue (WAT) browning as a potential therapeutic strategy for PC or BC via the improvement of tumor microenvironment.

### OBESITY AND PROSTATE CANCER

Numerous studies have been conducted to understand how PC progression is affected by the consequences of an

obese environment, such as increased systemic inflammation, hyperinsulinemia, altered adipokine profiles, and upregulated lipid availability [11,12]. Augmented synthesis and uptake of lipids are important hallmarks of PC and are modulated by androgen signaling (the key driver of PC pathogenesis) [13,14]. In addition, increased local adipose tissue amounts, specifically peri-prostatic adipose tissue (PPAT), may be associated with a higher grade or aggressiveness of PC; obesity-modulated alteration to the size of this lipid depot may be a key contributor to PC pathobiology. Obesity is a condition of chronic inflammation that is characterized by enhanced secretion of inflammatory cytokine, including interleukin (IL)-6, monocyte chemoattractant protein-1, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), by adipose tissues [15] [Table 1]. These inflammatory cytokines are associated with PC progression both in clinical and *in vitro* studies [16-18]. Particularly, IL-6 secreted by PPAT in patients with PC demonstrated a concentration 375 times greater than that in the matched patient serum and was found to be associated significantly with the disease

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pathological grade [19]. Moreover, PPAT inflammation, defined by the existence of crown-like structures (CLS), was found to be associated with larger adipocyte size, higher circulating levels of insulin and triglycerides, and highgrade PC [20]. Adipose tissues are endocrine organs that synthesize, secrete, and metabolize steroid hormones from circulating precursors. In addition, adipose tissues contain several androgens and androgen precursors, including testosterone, dihydrotestosterone, androstenedione, progesterone, and dehydroepiandrosterone [21], which, in the case of PPAT, supply a valid local extragonadal source of androgens that may reinforce PC growth and metastasis. PPAT also produces aromatase enzymes, which convert androgens to estrogens [22], and several studies suggest that estradiol is a modulator in PC pathogenesis and progression [23]. In addition, estrogen can activate both wild-type and mutated androgen receptors [24]. In summary, obesity is rather consistently associated with an increased risk of aggressive PC.

**RECIPROCAL INTERACTIONS BETWEEN ADIPOSE TISSUE AND PROSTATE CANCER**

The reciprocal interaction between adipocytes and tumor cells re-shapes adipocytes to a less differentiated condition referred to as cancer-associated adipocytes, a phenotype favorable to more aggressive tumors such as PC [22,25-27]. Several studies suggest that cancer-associated adipocytes can increase the malignant features of the cancer cells, eventually leading to detrimental positive feedback [25,28,29]. Culturing human PPAT using PC3 cell-derived conditioned medium (CM) increases the secretion of adipokines, TNF- $\alpha$ , IL-6, and osteopontin and enhances matrix metalloproteinase (MMP)-9 activity [25]. Furthermore, preadipocytes primed with PC CM undergo neoplastic-like transformation such as genetic instability, mesenchymal-to-epithelial transition, and formation of prostate-like neoplastic lesions *in vivo* [30]. PC is affected by adipocyte-secreted factors that increase the cells' ability to proliferate, migrate, and/or invade [19,26,29,31-34]. The biopsies of human prostate specimens or PPAT collected after prostatectomy showed a strong concentration gradient of the adipokine CCL7, suggesting that the PPAT secretome passively diffuses away from it into the tumor tissues to increase the directed migration of PC cells [26]. The CM of PPAT demonstrates higher MMP activity compared with that seen in peri-peritoneal visceral adipose tissue [29], which degrades the extracellular matrix proteins and promotes the invasion of cancer cells into the surrounding tissues [35]. Direct adipocyte-prostate cell crosstalk has been observed in their co-culture models. Mature rat epididymal adipocytes influenced the growth and differentiation of normal rat prostatic epithelium [36] or human PC [37,38] when cocultured in a three-dimensional collagen gel matrix. These effects were accompanied by an upregulated expression (20-fold) of the cytokines, including vascular endothelial growth factor and platelet-derived growth factor [37], and activation of the phosphatidylinositol 3-kinase (PI3K) pathway [38] in the PC3 cells. However, different studies have reported considerable variability – PPAT CM showed a stimulatory effect on PC3 and LNCaP cell migration in one

study [29], and coculturing rat epididymal adipocytes with PC3 cells increased PC3 proliferation in one study [37] – but these findings were contradicted in other studies [38]. This discrepancy is probably due to the differences in the nature of the cell lines and experimental methodologies used. The functional significance of adipocyte-PC cell interactions is emphasized by a study using a subcutaneous *in vivo* tumor model, in which larger tumors were generated by co-injection of PC cells with preadipocytes than by injection of only PC cells [39]. Thus, targeting the biological modulators of the tumor microenvironment, which links PPAT and PC, has the potential to reduce PC progression.

**POSSIBLE MECHANISMS CONNECTING OBESITY AND PROSTATE CANCER**

The mechanisms connecting adiposity and the progression of PC are poorly understood, and may be multifactorial [40]. In this respect, prospective components consisting of adipokine signaling pathways, sex hormone concentrations, and variation along the insulin/insulin-like-growth-factor (IGF) axis were involved [41,42]. (1) In adipokine signaling pathways, leptin and adiponectin are the two most plentiful and well-studied adipokines. High concentrations of adiponectin inhibit PC cell growth [43,44] [Table 2] and extend a beneficial effect on PC by suppressing inflammation,

**Table 1: Adipokines with their alterations in obesity and beneficial/detrimental effects**

Adipokines	Alteration in obesity	Beneficial or detrimental effects
Adiponectin	Reduction	Anti-inflammation, insulin sensitizing
Leptin	Increase due to leptin resistance	Modulates appetite and energy expenditure
Resistin	Increase	Induces insulin resistance, pro-inflammation
TNF- $\alpha$	Increase	Impairs the insulin signaling, contributes to the pro-inflammatory state
IL-6	Increase	Enhances C-reactive protein release from the liver, causes insulin resistance, leads to the pro-inflammatory state
MCP-1	Increase	Leads to the pro-inflammatory state

TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ , MCP-1: Monocyte chemoattractant protein-1, IL-6: Interleukin 6

**Table 2: Effects of adipokines on prostate cancer and breast cancer**

Adipokine	Tumor type	Cancer development	References
Leptin	PC	Increase	[43]
	BC	Increase	[45]
Adiponectin	PC	Decrease	[44]
	BC	Decrease	[46]
MCP-1	PC	Increase	[15]
	BC	Increase	[15]
TNF- $\alpha$	PC	Increase	[25]
	BC	Increase	[47]
IL-6	PC	Increase	[19]
	BC	Increase	[46]

TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ , MCP-1: Monocyte chemoattractant protein-1, IL-6: Interleukin 6, PC: Prostate cancer, BC: Breast cancer

activating fatty acid oxidation, ameliorating insulin sensitivity and glucose metabolism [44,48], and stimulating adenosine monophosphate-activated protein kinase (AMPK) activity [49]. Conversely, high concentrations of leptin have a pro-tumor effect in DU145 and PC-3 but not in LNCaP-FGC PC cell lines [32]. The relationship between these adipokines and PC progression needs to be elucidated [50]. (2) Sex hormone: Massillo *et al.* have found that estradiol induces the proliferation of androgen-sensitive cells, whereas it diminishes the proliferation of androgen-insensitive cell lines. Furthermore, high-fat diet (HFD)-fed mice had elevated concentrations of estradiol, which was associated with increased PC cell growth [51]. Although preclinical studies have demonstrated the link between estradiol and PC progression [52], further investigation is required to substantiate the results [53]. (3) Insulin and IGF-axis: Insulin resistance is strongly associated with obesity, leading to high insulin levels circulating in the blood [54]. Insulin increases cell proliferation and glucose consumption in PC cells but not in noncancerous prostate epithelial cells [55]. The IGF-axis is composed of cell surface receptors, ligands, IGF-binding proteins, and proteases [41]. Epidemiological studies have shown that higher serum IGF-1 concentrations and downregulated circulating IGFBP-3 levels are correlated with an increased risk of developing PC [56]. IGFBP-3 has been shown to induce apoptosis in a PC-3 cell line *in vitro* [57]. In addition, previous studies have indicated that exercise and nutrition interventions could decrease the BMI and weight loss may be advantageous in ameliorating IGFBP concentrations, leading to decreased bioavailable IGF-1 and reduced risk of PC progression [58,59]. In conclusion, the regulation of adipokine signaling, sex hormones, and insulin and IGF-axis in the tumor microenvironment may have the potential for reducing PC progression [Figure 1].

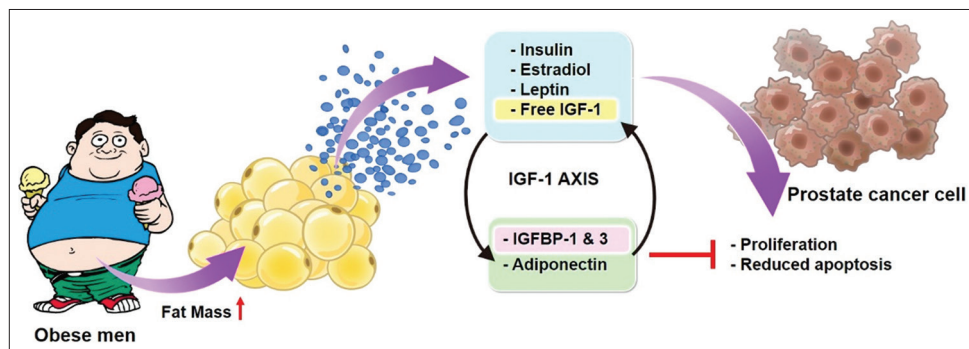
**OBESITY AND BREAST CANCER**

A meta-analysis of cohort studies demonstrated positive associations between BMI and WHR with obesity-related cancers, such as postmenopausal BC [60]. However, there is still disagreement on their influence on the risk of premenopausal BC, which may be caused by ethnic differences or/and sample size of the clinical study. Recently, a study on Korean women found that there was a negative association between obesity and BC in premenopausal women [61]. Nonetheless, several studies

showed no remarkable effect of obesity on the risk of BC in Asian premenopausal women [62,63]. In addition, an increased risk of triple-negative BC was observed in obese type II (BMI  $\geq 30$  kg/m<sup>2</sup>) premenopausal Korean women [64].

**CROSSTALK BETWEEN ADIPOCYTES AND BREAST CANCER**

Obesity is greatly related to a dysfunctional metabolism in adipocytes resulting in several chronic diseases. High levels of free fatty acids (FFA), cholesterol, glycerol, and triglycerides in serum impact breast tumor initiation, development, and migration [65-69]. *In vitro* coculture of mature adipocytes with BC cells enhances BC cell proliferation, which strongly suggests that adipocytes directly impact cancer cells by their secretions [70]. FFA are obtained from daily meals, which deposit as lipid droplets in the adipose tissue. Inflammation-induced obesity is an essential mechanism in the development and invasion of BC [66,67,71]. Saturated fatty acids reportedly activate toll-like receptor 4 to augment inflammation that leads to angiogenesis and tumor progression [72]. Inflamed microenvironment promotes adipocyte cell death, recruits macrophages, and leads to the formation of CLS [71]. The number of CLS is nine times higher in cancer patients with obesity than in lean women with BC and is often related to poor prognosis [73,74]. A study demonstrated that induced inflammation in WAT and increased CLS reduced the survival rate in patients [74]. Furthermore, saturated fatty acids can activate NF- $\kappa$ B, leading to TNF- $\alpha$  production, which affects BC cell proliferation, invasion, and metastasis [47]. FFAs induce BC invasion by activating the epidermal growth factor receptor, GTP-binding protein, and protein kinase C pathway [75], and controlling cell proliferation via PI3K [76] and cell migration through FFA receptor 1 and 4 and AKT pathway activation [77]. In addition, obesity-related factors within the tumor and the breast microenvironment are now known to regulate several important metabolic pathways: PI3K-RAC serine/threonine protein kinase (AKT), hypoxia-inducible factor 1 $\alpha$ , liver kinase B1-AMPK, and p53. Dysregulated metabolic pathways in the breast microenvironment can support tumor growth. In summary, targeting the biological regulator of the tumor microenvironment between WAT and BC has the potential to decrease BC progression.



**Figure 1:** Proposed mechanisms for the link between obesity and prostate cancer progression. IGF: Insulin-like growth factor



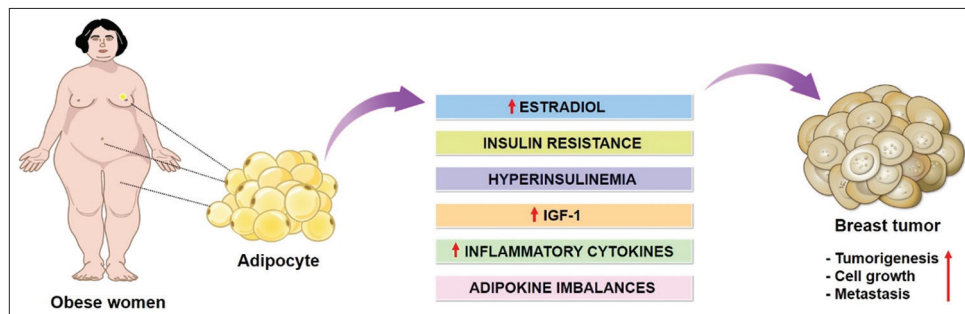
**POSSIBLE MECHANISMS LINKING OBESITY AND BREAST CANCER**

The mechanism for the obesity-driven BC is very complex, and the underlying mechanisms in this process mainly consist of adipokines, insulin/IGF, sex hormone, and chronic inflammation; their dysregulation can enhance BC incidence and progression in the following ways. (1) Adipokines: Leptin-dependent secretion of the extracellular matrix proteins such as MMP-2 and MMP-9 and invasion in a FAK and Src-dependent manner suggest that leptin boosted the development of a more aggressive invasive phenotype in BC [45] [Table 2]. In addition, serum levels of adiponectin were decreased in a diet-induced obese mouse model, which was negatively correlated with obesity and increased the BC recurrence [46]. (2) Insulin and IGF: Insulin in conjunction with inflammation can enhance BC growth and metastasis [78]. Furthermore, HFD-fed obese mice showed hyperinsulinemia, upregulated IGF-1 levels, and accelerated BC recurrence, suggesting that the insulin/IGF-1 signaling pathway is a potential regulator for obesity and BC recurrence [46]. (3) Sex hormone: Aromatase, a rate-limiting enzyme, is secreted by stromal cells of adipose tissue that converts androstenedione to estrone, subsequently forming estrogen after menopause. Aromatase upregulation in the breast tissue of obese patients resulted in an increased risk of hormone receptor-positive BC in obese postmenopausal women [79]. (4) Chronic inflammation: Studies have found that obesity decreases the local IL-10 levels in the mammary fat pad of ovariectomized mice, resulting in the upregulation of aromatase and leading to BC progression [80]. In summary, targeting of adipokines, insulin/IGF-1, sex hormones, and inflammation in the BC tumor microenvironment may have the potential to hinder BC progression [Figure 2].

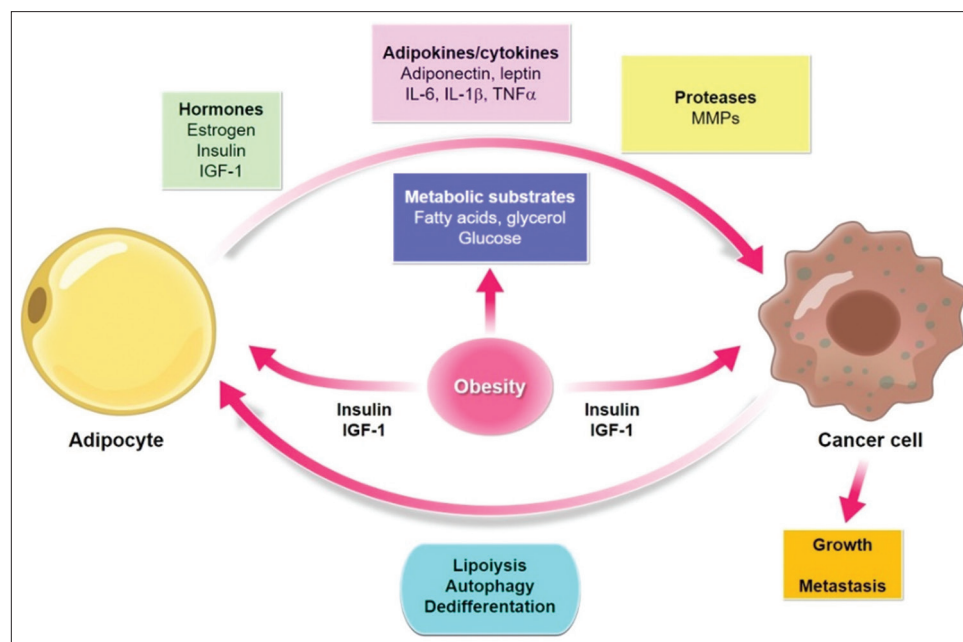
**FACTORS INVOLVED IN WHITE-TO-BROWN ADIPOCYTE CONVERSION**

There are two different types of adipose tissues – WAT, cells of which contain a large single, spherical lipid vacuoles and few mitochondria, and brown adipose tissue (BAT), cells of which contain small and multilocular lipid droplets and large number of mitochondria. BAT is the principal effector organ of nonshivering thermogenesis and can use a large amount of glucose and lipid from circulation to promote negative energy balance. Hence, it

will induce thermogenesis, dissipate heat, improve glucose metabolism, and develop insulin resistance in obese individuals [81-84]. Therefore, BAT is now known to exert anti-type 2 diabetes effects associated with improvement of dyslipidemia and decreased insulin resistance [85-88]. The metabolic adaptations during white-to-brown adipocyte conversion are not well known. Several studies have shown that another type of brown cells, known as the beige or brite (brown in white) cells, exists in both mouse and human [89-91]. Beige cells are generated postnatally within WAT in response to cold or adrenergic stimulations. Both classical brown fat and beige cells are rich in mitochondria and uniquely express UCP1. Although both share the same thermogenic function, they arise from entirely different cell lineages [89,92]. In contrast to brown cells that express both myogenic genes Myf5 and Pax7 [93,94], beige cells are generated postnatally in WAT depots and arise from Myf5-precursor lineage that expresses PDGFR $\alpha$  [89,95,96] or through transdifferentiation of mature white [96-98] adipocytes in response to cold or  $\beta$ -adrenergic stimulation. In human, beige adipocytes have been observed in white fat depots [87,99]. Morphological and histological data indicate the presence of cells with an intermediate phenotype, suggesting that conversion of white into beige adipocytes likely occurs [87]. There are three main transcriptional regulators of classical BAT development, namely PR domain containing 16 (PRDM16), peroxisome proliferator-activated receptor  $\gamma$ , and peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$ , which are key nodes in the regulation of inducible brown fat. In addition, some transcription factors and coregulators are involved in the browning process of WAT such as forkhead box protein C2 [100], steroid receptor coactivator-1, transcriptional intermediary factor-2 [101], T-box 15 (TBX15) [102], and mitochondrial transcription factor A [103]. Moreover, secreted proteins, including irisin [104], FGF21 [105], cardiac natriuretic peptide [106], and bone morphogenetic protein 7 [107], had been reported to regulate white-to-brown conversion. Furthermore, different components of the immune system have been reported to promote browning, such as eosinophils [108], macrophages [109,110] and ILC2s [111,112]; several cytokines are involved in the regulation of browning. In sum, targeting transcription factors and coregulators involved in the browning of WAT may have the potential to combat obesity or improve the tumor microenvironment and needs further investigation.



**Figure 2:** Proposed mechanisms for the association between obesity and breast cancer progression. IGF: Insulin-like growth factor



**Figure 3:** The possible mechanisms involved in the tumor microenvironment regulated by adipocyte in prostate cancer and breast cancer. IGF: Insulin-like growth factor, IL: Interleukin, TNF: Tumor necrosis factor, MMP: Matrix metalloproteinase

### THERAPEUTIC BROWNING OF WHITE ADIPOSE TISSUE IN THE TUMOR MICROENVIRONMENT

In pathological conditions such as the development and progression of PC and BC, adipose tissue plays an important role via paracrine and endocrine signaling. Although implied, the influence of WAT browning on the development and progression of PC and BC is unclear and has received less attention. Browning of WAT can be achieved with benzyl isothiocyanate and Honokiol, which increase the expression of BAT marker genes (*UCP1*, *PRDM16*, *EVOL3*, *COX7a*, and *CIDEA*) in WAT. It not only abolishes the pro-cancer effects of WAT on BC cells but also changes the secretome profile of WAT [113]. Furthermore, the *in vitro* and *in vivo* models with primary brown adipose cells (BACs) indicate that primary BACs can directly decrease the viability of H22 cells, a hepatocellular carcinoma cell line, and the growth of tumors. In conclusion, BACs may be a potential therapeutic tool for the treatment of hepatocellular carcinoma [114]. However, whether browning WAT could be a therapeutic strategy for the treatment of PC and BC needs further examination.

### CONCLUSION

Epidemiological and clinical evidence has shown a consistent association between obesity with cancer progression and increased mortality of PC and BC patients. However, the underlying mechanisms linking them remain unclear. Clinical studies found that alteration of insulin and IGF-axis, sex hormone concentrations, and adipokine signaling can increase cancer cell proliferation in individuals with obesity. In addition, these factors can also synthetically affect angiogenesis, oncogene activation, immune cell dysfunction, and oxidative stress, which can modulate the behaviors of PC or BC cells and tumor microenvironment. Targeting adipocyte-derived molecules may be a potential therapeutic

approach to ameliorate the prognosis of obese patients. Furthermore, a thorough understanding of the physiological mechanisms of obesity on treatment effectiveness and tolerance is necessary for improving the efficacy of PC or BC therapy. A summary of the possible mechanisms involved in the tumor microenvironment regulated by adipocyte in PC and BC is depicted in Figure 3. Thus, it can be concluded that regulation of adipocyte function is a novel therapeutic strategy for the treatment of PC or BC.

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### Conflicts of interest

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