REVIEW

Adipose tissue : Critical contributor to the development of prostate cancer

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Abstract : The prostate is surrounded by periprostatic adipose tissue. Although adipose tissue was thought to play limited physiological roles, it has recently been recognized as an active endocrine organ, secreting growth factors and adipokines. Epidemiologically, obesity is associated with prostate cancer progression. A major mechanism to explain the link between obesity and cancer includes the insulin and insulin-like growth factor (IGF)-1 axis, sex steroids, and adipokines. When prostate cancer cells invade periprostatic adipose tissue, adipose tissue contributes to create the tumor microenvironment, mainly via adipokine secretion. Furthermore, direct crosstalk between adipocytes and cancer cells can exist. We showed that fatty acid-binding protein 4 (FABP4) released from adipocytes was taken up into prostate cancer cells and may act as a carrier of an energy source for the invasion. Bone is an adipocyte-rich organ and is the common metastatic site of prostate cancer. In the microenvironment of bone metastases, tumor cells, osteoblasts, osteoclasts, adipocytes, and other stromal cells are interacting with one another and organizing a complex system. Thus, growing evidence implicates adipose tissue as a critical contributor to the development of prostate cancer. A deeper understanding of the mechanisms leads to more effective therapeutic strategies for prostate cancer. J. Med. Invest. 65 : 9-17, February, 2018

Keywords **:** *adipose tissue, prostate cancer, adipokine, bone metastasis*

INTRODUCTION

Prostate cancer continues to be the most common cancer and the third-leading cause of cancer-related deaths among men in the United States. Projections for 2017 indicated 161,360 new cases of prostate cancer, along with 26,730 deaths from the disease (1, 2). Prostate cancer incidence is much lower in Asian countries including Japan than that of Western countries. However, prostate cancer incidence in Asian countries has been on a steady increase during the past few decades (3, 4). Extraprostatic extension of prostate cancer is defined as pT3a in the tumor, lymph node, and metastasis staging system for prostate cancer, and it is well-established as being associated with a poor prognosis. This feature must be identified accurately for optimal patient management after radical prostatectomy (5-7). The prostate is surrounded by periprostatic adipose tissue. Therefore, an admixture of tumor cells with periprostatic adipose tissue (Figure 1) is the most common finding of extraprostatic extension (8, 9).

Adipose tissue is composed mainly of adipocytes, although additional cell types are present, including pericytes, monocytes, macrophages, lymphocytes, fibroblasts, vascular endothelial cells, and pluripotent stem cells. Previously, adipose tissue was thought to play limited physiological roles mainly as energy storage and protection from cold temperatures. Currently, adipose tissue is recognized as an active endocrine organ, secreting growth factors, chemokines, or pro-inflammatory molecules termed 'adipokines' that can regulate metabolism and the immune system. Physiologically, adipokines regulate appetite, lipid metabolism, glucose homeostasis, insulin sensitivity, angiogenesis, blood pressure, and inflammatory processes (10). Obesity is defined by increased adipose mass arising from an energy imbalance. Adipocyte hypertrophy during obesity causes adipose dysfunction and inflammation by increasing the secretion of pro-inflammatory adipokines from adipocytes (11). Alterations of adipocyte biology associated with adipocyte hypertrophy affect systemic organs. Epidemiologically, obesity is related to the risk of many types of cancers, including esophageal, gastric, colorectal, biliary, pancreatic breast, endometrial, ovarian, and kidney cancers (12-14). In addition, obesity is associated with the progression of many cancers, including prostate, breast, endometrial, kidney, pancreatic, esophageal, and thyroid cancers (15-19). Furthermore, direct crosstalk between normal adipocytes and cancer cells can exist at the front of cancer invasion to adipose tissue (20-22). Thus, growing evidence suggests crucial roles for adipose tissue in the development of several cancers.

In this article, we review the contribution of adipose tissue to prostate cancer development, including bone metastasis.

1. OBESITY AND PROSTATE CANCER

It is estimated that overweight and obesity could account for 14% of all cancer deaths in men and 20% of all cancer deaths in women in the United States (23). Epidemiologic studies have found that the relationship between obesity and the incidence of prostate cancer is unclear. On the other hand, obesity is associated with prostate cancer mortality (12-14). In addition, obesity and hypertension were each associated with an increased risk of biochemical recurrence of prostate cancer after radical prostatectomy, independent of age at diagnosis and tumor pathological features (24). Interestingly, several studies suggest that obesity reduces the risk of localized, low-grade, and nonaggressive prostate cancer, although it increases the risk of advanced, high-grade, and aggressive prostate cancer (25, 26). Obesity has also been associated with

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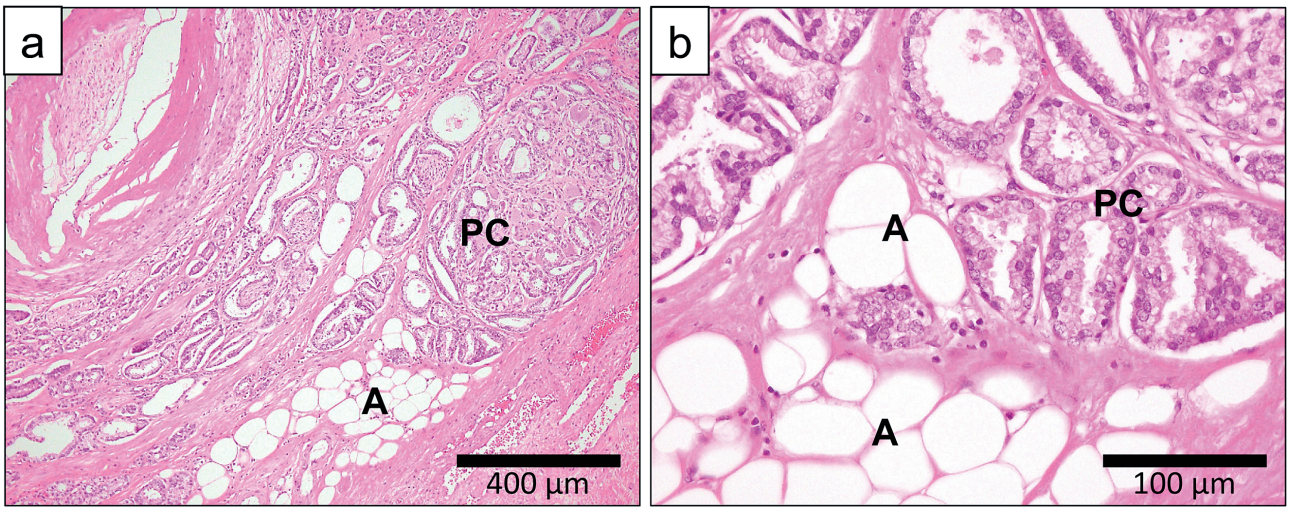

Figure 1. Extraprostatic extension of prostate cancer. (a) Prostate cancer invasion into periprostatic adipose tissue. Scale = 400 µm. PC, prostate cancer cells ; A, adipose tissue. (b) Prostate cancer cells grow in proximity to adipocytes. Scale = 100 µm. PC, prostate cancer cells ; A, adipose tissue.

the presence of prostatic intraepithelial neoplasia in benign specimens and with future prostate cancer risk after an initial benign finding. Therefore, obesity should be taken into account in the clinical follow-up plan after a benign biopsy (27).

A major mechanism to explain the link between obesity and cancer includes insulin and the IGF-1 axis, sex steroids, and adipose tissue-derived cytokines. They are linked through insulin resistance (28). Other possible mechanisms include fatty acid-induced inflammation, oxidative stress, endoplasmic reticulum stress, and hypoxia.

Insulin-IGF-1 axis

Circulating insulin levels correlate positively with increasing body mass index, and many obese persons are insulin-resistant. The evidence is mounting that insulin resistance is a risk factor for cancer development. It is suggested that hyperinsulinemia may contribute to cancer development through the growth-promoting effect of elevated insulin levels (29, 30). Obesity and prolonged hyperinsulinemia are associated with increases in the levels of free or bioactive IGF-1 due to reduced production of IGF-binding proteins, which normally bind IGF-1 and inhibit its action. Through the interaction with the IGF receptor, IGF activates downstream signaling pathways that affect the growth of cancer cells by the promotion of mitogenic pathways, induction of neovascularization, and inhibition of apoptosis. Insulin itself has anabolic, antiapoptotic, and mitotic effects (12, 31, 32).

Epidemiological data suggest that high levels of circulating IGF-1 are associated with an increased risk of prostate cancer development (33). IGF-1 signaling is elevated in prostate cancer compared to prostate epithelium and is associated with tumor progression (34, 35). In addition, overexpression of the IGF-1 receptor has been shown in prostate cancer (36).

Sex hormones

Androgens have been known to play an important role in normal prostate development and function, as well as for the growth and progression of prostate cancer. However, it has been suggested that there is no association between the plasma concentration of androgens and prostate cancer risk (37). Obesity is associated with a decrease in testosterone levels (38) and the synthesis of sex hormone-binding globulin (SHBG), which binds to sex hormones including testosterone and dihydrotestosterone and regulates their effects (39). A significant association was shown between low serum testosterone levels and tumor stage and extraprostatic tumor spread in prostate cancer patients (40). Furthermore, the levels of testosterone were significantly lower in patients with prostate cancer than in those with benign prostatic hyperplasia (41). These results suggest that the low testosterone levels in obese men may be related to prostate cancer development. However, the exact mechanisms are still unknown.

Adipose tissue-derived cytokines

Adipose tissues in obesity are infiltrated by a large number of inflammatory cells (e.g. macrophages and leukocytes), and this recruitment is linked to systemic inflammation and insulin resistance (42, 43). The inflammation induces the generation of reactive oxygen species that act as tumor promoters at a low concentrations (44). Adipocytes, other stromal cells, and infiltrating inflammatory cells in adipose tissue secrete several adipokines and other cytokines, which have been implicated to play a pivotal role in the development of obesity-related cancer (45). Adipokines are defined as hormone-like polypeptides that are actively secreted by white adipose tissue, and they include cytokines (e.g. interleukin-6 (IL-6) and tumor necrosis factor (TNF)-α), angiogenic factors (e.g. vascular endothelial growth factor (VEGF) and apelin), and other factors (e.g. leptin and adiponectin) (46). Several adipokines have been recognized to have multiple effects on prostate cancer cells.

2. MAJOR ADIPOKINES (LEPTIN, IL-6, AND ADIPONECTIN) AND PROSTATE CANCER

Leptin

Leptin, a polypeptide hormone that is mainly produced by adipocytes, acts as a major regulator for appetite and energy homeostasis via its action on specific receptors expressed in the hypothalamus (47). The levels of leptin in plasma are correlated with the percentage of body fat (48, 49). This observation suggests that most obese persons are insensitive to endogenous leptin production.

Epidemiologically, the association between serum leptin levels and prostate cancer risk is controversial. Stattin *et al.* reported that

moderately elevated plasma leptin concentrations are associated with later development of prostate cancer (50). Another study showed that elevated plasma leptin concentrations are associated with an increased risk of high-volume prostate cancer (tumors > 0.5 cc in volume or with histologic evidence of extraprostatic extension but without metastases) (51). On the other hand, several studies suggest that there is no association between serum leptin levels and prostate cancer risk (52, 53).

In human prostate tissue, leptin receptors have been detected in normal epithelium, prostatic high-grade intraepithelial neoplasia, and carcinoma by immunohistochemistry (50). DU145 and PC-3 human prostate cancer cells have also been found to express leptin receptors, and leptin treatment had mitogenic and anti-apoptotic effects on these cells with phosphatidyl-inositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathway activation (54, 55). Moreover, long-term exposure to leptin enhanced proliferation, invasion, and migration of prostate cancer cells with increased cyclin D1 expression and decreased p21 expression, suggesting the participation of leptin in cell cycle progression (56). Single nucleotide polymorphism (SNP) in exon 4 of the leptin receptor gene was significantly associated with prostate cancer-specific mortality (57).

IL-6

Serum IL-6 has demonstrated the strongest relationship with obesity and insulin resistance (58). In adipose tissue, the main sources of IL-6 are infiltrating macrophages and stromal cells. However, adipocytes also produce IL-6 (59). Serum IL-6 levels were significantly higher in patients with metastatic or hormone-refractory prostate cancer than in normal controls or patients with localized disease (60, 61), and they were associated with shorter survival time in patients with hormone-refractory prostate cancer (62). Exogenous IL-6 stimulated growth in hormone-sensitive LNCaP prostate cancer cells, but not hormone-insensitive DU145 and PC-3 cells (63). In a tumor xenograft model, when LNCaP cells continuously treated with IL-6 were inoculated into nude mice, tumor volumes were larger than those of their controls cultured without IL-6 treatment (64). Increased IL-6 receptor expression was observed in human prostate cancer tissue, compared with normal prostate tissue, and high levels of IL-6 receptor expression in prostate cancer were associated with higher rates of cell proliferation on immunohistochemistry (65). Thus, IL-6 appears to act primarily as a paracrine growth factor for hormone-sensitive prostate cancer. However, its main action may shift to an autocrine mode as hormone resistance develops in prostate cancer.

Adiponectin

Adiponectin is a protein displaying structural similarities to collagen and TNF-α, and it is mainly secreted by adipocytes (66) and regulates glucose and lipid metabolism, vascular remodeling, and bone homeostasis. In addition, adiponectin has defensive effects against inflammation and insulin resistance (67-70). In humans, plasma concentrations of adiponectin are significantly lower in obesity and insulin-resistant states (71, 72). Adiponectin can bind to three receptors, AdipoR1, AdipoR2, and T-cadherin (73). Through the interaction with AdipoR1 and AdipoR2, adiponectin shows antidiabetic effects (74).

Epidemiological studies have reported that plasma adiponectin levels were significantly lower in patients with prostate cancer than in benign prostatic hyperplasia (BPH) patients or healthy controls (75, 76). Tan *et al*. examined the immunohistochemical expressions of adiponectin in BPH cases and prostate cancer cases with low Gleason score (<7) Gleason score 7 or high Gleason score (> 7). The results suggested that decreased adiponectin expression was associated with prostate cancer progression. Furthermore, silencing of adiponectin induced proliferation and invasion in 22RV1 human prostate cancer cells via the epithelial-to-mesenchymal transition process (77). AdipoR2 expression levels in prostate cancer cells were positively associated with cell proliferation, with expression of fatty acid synthase, and with angiogenesis (78). These results suggests a positive relationship between AdipoR2 and prostate cancer development.

3. TUMOR MICROENVIRONMENT AND ADIPOSE TISSUE

Periprostatic adipose tissue was present on 48% of all prostatic surfaces. The distribution of adipose tissue in the anterior, posterior, right, and left prostatic surfaces was 44%, 36%, 59%, and 57%, respectively (79). When prostate cancer cells invade into periprostatic adipose tissue, adipose tissue contributes to create the tumor microenvironment. It has been recognized that the tumor microenvironment is crucial for tumor progression and metastasis. In such cases, adipokines play a central role. Adipokines act in paracrine, autocrine, and endocrine manners (80). However, paracrine and autocrine signaling may be a key action in the tumor microenvironment. For example, IL-6 levels in periprostatic adipose tissue harvested from prostate cancer patients undergoing radical prostatectomy were approximately 375 times higher than in patient-matched serum. In addition, a higher Gleason score was correlated with high IL-6 levels (81). Fain *et al*. reported that the levels of VEGF and IL-6 released from visceral adipose tissue were significantly higher than those from subcutaneous adipose tissue (82). Thus, in cases of extraprostatic extension, prostate cancer cells are directly exposed to huge amounts of adipokines released from periprostatic adipose tissue. Furthermore, increased periprostatic adipose tissue due to obesity etc. may modify the tumor microenvironment and accelerate tumor progression. Actually, increasing periprostatic adipose tissue thickness, measured by transrectal ultrasonography as the distance between the prostate and the pubic bone, was associated with prostate cancer and high-grade prostate cancer (83).

In the tumor microenvironment, matrix metalloproteinases (MMPs) play an important role in cancer progression, as well as adipokines. Periprostatic adipose tissue from prostate cancer patients released higher amounts of pro-MMP-9 than that from BPH patients (84). Supernatants from whole periprostatic adipose tissue showed increased activities of both MMP2 and MMP9, and they promoted proliferation and migration of PC-3 cells, compared with those from the stromal vascular fraction of adipose tissue (85). These findings suggest that MMPs from periprostatic adipose tissue modulate the tumor microenvironment and promote prostate cancer cell survival and migration.

When cancer cells invade into adipose tissue, direct contact between cancer cells and adipocytes may occur. Dirat *et al*. reported that adipocytes adjacent to cancer cells at the invasive front demonstrated a decrease in more differentiated adipose markers and overexpressions of several inflammatory cytokines in breast cancer. In addition, the levels of IL-6 in tumor surrounding adipocytes were higher in cases with tumors of larger size and/or with lymph node involvement. These adipocytes were termed "cancer-associated adipocytes" (20). Thus the cross-interactions between breast cancer cells and adipocytes modify each other's characteristics/phenotypes, leading cancer cells to become more aggressive.

Nieman *et al*. indicated another mechanism of cancer progression by direct contact between cancer cells and adipocytes. Co-culture of adipocytes and ovarian cancer cells promoted in vitro and in vivo tumor growth. In this culture system, the direct transfer of lipids from adipocytes to ovarian cancer cells, lipolysis in adipocytes, and β-oxidation in cancer cells were induced, suggesting that adipocytes act as an energy source for the cancer cells.

From the results of protein array and immunohistochemical analyses in omental metastases compared to primary ovarian tumors, FABP4 was found to play an important role in ovarian cancer metastasis (86). FABP4, also known as aP2, is a member of the cytoplasmic fatty acid binding protein multigene family that is associated with insulin resistance, type 2 diabetes mellitus, and cardiovascular disease (87-89). FABP4 is released from adipocytes and is abundantly present in human serum. Serum FABP4 levels are linked to obesity (87). We showed the involvement of FABP4 in human prostate cancer cell progression. In an in vitro study, FABP4 treatment promoted prostate cancer cell invasion, and the promoting effects were reduced by a FABP4 inhibitor, which inhibits FABP4 binding to fatty acids. Uptake of FABP4 into prostate cancer cells following FABP4 treatment was observed on immunohistochemistry. A FABP4 inhibitor also reduced subcutaneous growth and lung metastasis of prostate cancer cells in vivo. These results suggest that FABP4 may act as a carrier of an energy source for the prostate cancer cells. In addition, FABP4 treatment activated the phosphoinositide 3-kinase (PI3K)/Akt pathway, with or without a FABP4 inhibitor, suggesting that FABP4 exerts its effect on prostate cancer cells through several pathways (90). Thus, FABP4 might be a key molecule to understand the mechanisms underlying the adipose tissue-prostate cancer progression link. Possible mechanisms involving FABP4 in prostate cancer progression are shown in Figure 2.

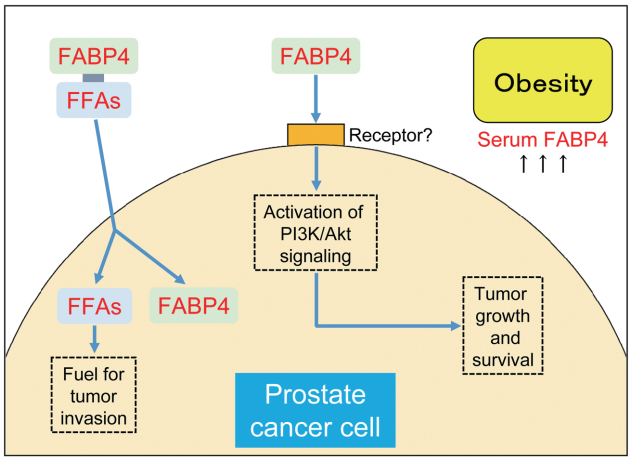

Figure 2. Possible mechanisms involving fatty acid-binding protein 4 (FABP4) in prostate cancer progression. FABP4 binding to free fatty acids (FFAs) is taken up into prostate cancer cells, and FFAs may be used as an energy source for prostate cancer development. In addition, FABP4 can activate the phosphatidyl-inositol 3-kinase (PI3K)/Akt pathway without being taken up into prostate cancer cells. Obesity increases the serum levels of FABP4.

4. BONE MARROW ADIPOCYTES AND CANCER METASTASIS

Bone is the common metastatic site of prostate cancer, and bone metastasis is seen in 90% of patients with metastatic prostate cancer. In fact, 86% of these patients had only bone metastases (91). Bone metastasis of prostate cancer is a multistep process including detachment of cancer cells from the primary tumor, travel of the cells through the blood vessels or lymphatics, attachment to bone tissue, and development of metastatic tumor in the bone. Figure 3 shows the histology of prostate cancer bone metastases. Prostate cancer metastases cause an osteoblastic, osteolytic, or mixed bone response (92-94). In osteolytic metastases, cancer cells produce osteoclastic factors such as parathyroid hormone-related protein (PTHrP) and transforming growth factor β (TGFβ), which stimulate osteoblasts and stromal cells to express receptor activator of NF kappa B (54) ligand (RANKL). The binding of RANKL to its receptor, RANK, on osteoclasts drives bone resorption and release of growth factors from the matrix, which supports cancer cell growth (95, 96). On the other hand, osteoblastic metastases are formed by cancer cell growth with new bone formation. Some tumor-associated factors, including endothelin-1 and Wnts, have been proposed to stimulate osteoblast activity directly, and other factors including urokinase-type plasminogen activator activate proteases such as PSA, which enhance the osteosclerotic process either via activation of the quiescent forms of TGFβ or via degradation of PTHrP (95, 97, 98).

Although bone contains few adipocytes at birth, aging causes an increase in the number of marrow adipocytes (99). In addition, obesity is associated with an increase of bone marrow adipose tissue (100). Therefore, it is possible that marrow adipose tissue may affect the growth and survival of metastatic cancer cells. Actually, when breast cancer cells were co-cultured with cancellous human bone tissue fragments, cancer cell migration toward tissue-conditioned medium was enhanced in association with increasing levels of leptin and IL-1β. Immunohistochemistry of fragments showed breast cancer cell colonization within the marrow adipose tissue compartment (101).

IGF-1 is the most abundant growth factor that is deposited in the bone matrix (102). Although IGF-1 is a key factor in the endocrine regulation of body composition, IGF-1 also plays an important role in the maintenance of bone mineral density. IGF-1 is released from the bone matrix in response to bone resorption. IGF-1 induces the differentiation of osteoblasts and stimulates expression and secretion of RANKL in osteoblasts. RANKL promotes osteoclastogenesis. As a result, new bone is formed at bone resorption sites (103-105). Furthermore, IGF-1 stimulates LNCaP cell growth (106). C4-2 human prostate cancer cells, a subline of LNCaP having a proclivity to form osteoblastic bone metastases, produced higher amounts of IGF-1 than LNCaP. IGF-I mRNA expression in C4-2 cells was substantially increased in the presence of exogenous IGF-I. These results suggest the contribution of the IGF-I axis to the osteoblastic metastases of prostate cancer (107).

Whereas IL-6 is one of the major adipokines, it also plays a profound role in bone metabolism. Acting via stromal/osteoblastic cells, IL-6 stimulates osteoclastogenesis. Moreover, IL-6 can promote differentiation of osteoblasts toward a more mature phenotype (108). Therefore, in the bone microenvironment, metastatic cancer cells may be exposed to large amounts of IL-6 from both stromal/osteoblastic cells and adipocytes. Actually, it has been suggested that IL-6 is involved with the mechanisms of bone metastasis. In a mouse model of bone metastasis, administration of a high-fat diet increased melanoma cell growth in the bone marrow with induction of osteopontin and IL-6. Immunofluorescence staining of IL-6 showed that higher numbers of bone marrow adipocytes expressing IL-6 were observed in the vicinity of tumor cells (109). Culture medium from PC-3 human prostate cancer cells induced IL-6 gene expression in osteoblast-like MC3T3-E1 cells and promoted osteoclastogenesis in vitro. IL-6 was highly expressed in PC-3 cells growing in the bones of SCID mice and human bone metastases (110). On the other hand, culture medium from human osteoblast-like HOBIT cells induced proliferation and PSA expression in human prostate cancer cells, LNCaP, C4-2B, and VCaP. These effects were inhibited by treatment with anti-IL-6 antibody, suggesting that IL-6 secreted from osteoblasts promotes prostate cancer growth (111).

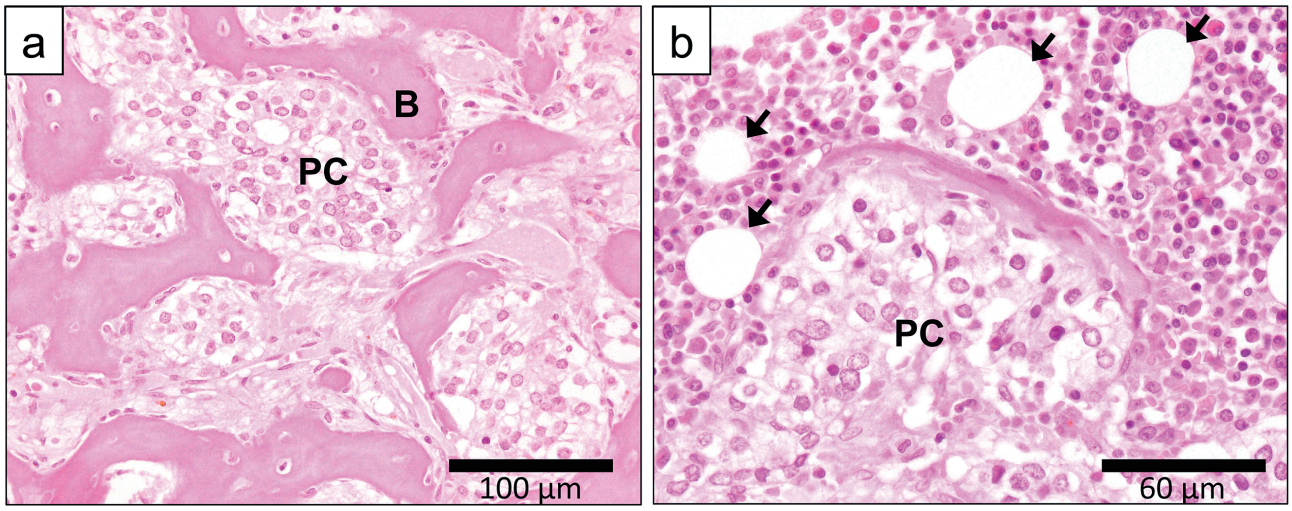

Figure 3. Bone metastases of prostate cancer. (a) Prostate cancer cells grow with bone formation. Scale = 100 μm. (b) At the periphery of bone metastases, prostate cancer cells are facing normal bone marrow cells including several adipocytes. Scale = 60 μm. PC, prostate cancer cells ; B, bone ; arrows, bone marrow adipocytes.

As thus far described, in the microenvironment of bone metastases, tumor cells, osteoblasts, osteoclasts, adipocytes, and other stromal cells interacting with each other and organize a complex system (Figure 4). Because aging is associated with both cancer risk and amount of bone marrow adipose tissue, bone marrow adipose tissue may be one of the key factors in bone metastasis. However, its roles are poorly understood.

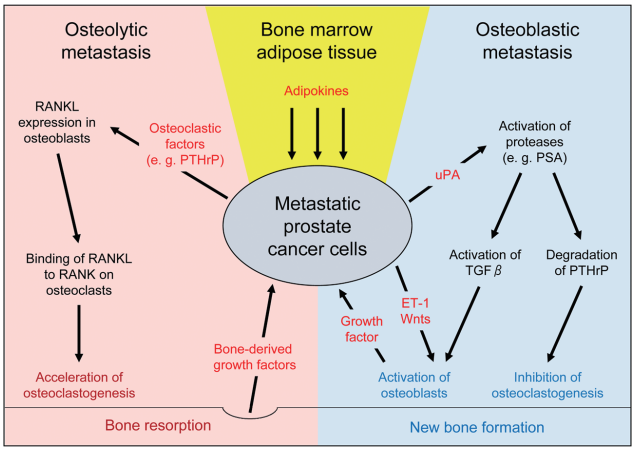

Figure 4. Interactions of prostate cancer cells with osteoblasts, osteoclasts, and adipocytes in the microenvironment of bone metastases. In osteolytic metastases, cancer cells produce osteoclastic factors such as parathyroid hormone-related protein (PTHrP) that stimulate osteoblasts to express receptor activator of NF kappa B (54) ligand (RANKL). The binding of RANKL to RANK on osteoclasts drives bone resorption and release of growth factors from the matrix, which supports cancer cell growth. In osteoblastic metastases, some tumor-associated factors including endothelin-1 (ET-1) and Wnts have been proposed to stimulate osteoblast activity directly, and other factors, including urokinase-type plasminogen activator (uPA), activate proteases such as PSA that enhance the osteosclerotic process, either via activation of the quiescent forms of transforming growth factor β (TGFβ) or via degradation of PTHrP. Adipose tissue is presumably involved in these processes via adipokine secretion.

5. CONCLUSIONS

The data presented in this review suggest that adipose tissue plays an important role in the development of prostate cancer, including tumor growth, invasion, and metastasis. Prostate cancer cells with extracapsular invasion form a new microenvironment in periprostatic adipose tissue. In the process, cancer cells are thought to have direct or indirect interactions with adipocytes. Moreover, obesity may modify these interactions and promote tumor progression. Bone is a favorite metastatic site of prostate cancer and contains increasing adipose tissue with age. Bone marrow adipose tissue interacts with tumor cells, osteoblasts, and other stromal cells, and it participates in the organization of the tumor microenvironment. Whereas adipokines seem to be key molecules in the relationship between cancer cells and adipose tissue, several other mechanisms are suggested. A deeper understanding of the roles of adipose tissue in prostate cancer progression will lead to more effective therapeutic strategies for prostate cancer.

CONFLICT OF INTEREST

None of the authors has any conflicts of interest to declare.

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