# White adipose tissue-derived factors and prostate cancer progression: mechanisms and targets for interventions

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## Abstract

Obesity represents an important risk factor for prostate cancer, driving more aggressive disease, chemoresistance, and increased mortality. White adipose tissue (WAT) overgrowth in obesity is central to the mechanisms that lead to these clinical observations. Adipose stromal cells (ASCs), the progenitors to mature adipocytes and other cell types in WAT, play a vital role in driving PCa aggressiveness. ASCs produce numerous factors, especially chemokines, including the chemokine CXCL12, which is involved in driving EMT and chemoresistance in PCa. A greater understanding of the impact of WAT in obesity-induced progression of PCa and the underlying mechanisms has begun to provide opportunities for developing interventional strategies for preventing or offsetting these critical events. These include weight loss regimens, therapeutic targeting of ASCs, use of calorie restriction mimetic compounds, and combinations of compounds as well as specific receptor targeting strategies.

**Keywords** Prostate cancer · Chemokines · Adipose tissue · Obesity

## 1 Introduction

Prostate cancer (PCa) is the most frequently diagnosed non-skin cancer and is the second most common cause of cancer death in men in the United States (US). Approximately 1 in 8 men will be diagnosed with PCa during their lifetime and about 1 in 41 will die of PCa. It is estimated that ∼268,490 new cases of PCa will be diagnosed and ∼34,500 PCa-related deaths will occur in the US in 2022. Concurrently,

obesity is a major public health crisis, with 42–46% of men over age 40 with obesity [1]. While there is a high prevalence of both obesity and PCa among men, data associating obesity and PCa risk are inconclusive [2, 3]. Although most men with localized PCa are cancer-free for 5 years after radical prostatectomy (RP), 20–30% of these men show signs of biochemical recurrence (BCR) after the 5-year mark [4, 5], and recently reported studies have shown obese men, particularly with androgen-responsive PCa and who rapidly gained weight after RP, have increased risk of metastatic progression, development of BCR, and decreased overall survival [6]. Men with obesity and PCa are at increased risk of lymphedema, positive surgical margins, BCR, and fatal PCa [7–9]. Being overweight at the time of diagnosis also increases the likelihood of dying from PCa by 50% [10]. Weight gain after RP is associated with higher risk of BCR [11, 12] and PCa-specific mortality [13, 14]. The role of weight loss after RP is less clear with observational data suggesting a lower risk of BCR [11] while other data show increased risk of death, likely due to reverse causality [15]. Detriments associated with being overweight/obese at RP include longer operative times, higher blood loss during RP, and slower recovery to continence and potency [9]. Also, RP is more difficult to perform in men with higher BMIs [9]. In contrast, several studies have shown that men with a

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smaller waist-to-hip ratio, lower BMI, and low body fat have low-volume PCa in comparison to men with high-volume PCa [16, 17]. Since the prevalence of obesity is increasing continuously [18], a clear knowledge of the mechanism(s) underlying disease aggressiveness as well as interventions designed to disrupt the obesity-PCa link are urgently needed to reduce morbidity and mortality associated with PCa.

## 2 Mechanisms associated with obesity and PCa progression

A number of mechanisms have been suggested for the effects of obesity on PCa progression. These include hyperinsulinemia, higher levels of growth factors in the circulation, inflammation and increased inflammatory mediators such as cytokines and chemokines, as well as changes in levels of steroid hormones and adiponectin as well as other factors (e.g., changes in microbiome, angiogenesis) [19, 20]. Obesity and particularly abdominal obesity are associated with abnormal and excessive expansion of white adipose tissue (WAT). Multiple studies have confirmed the link between PCa progression and WAT overgrowth [21–23]. In addition, excessive WAT expansion leads to a pathological state of chronic inflammation thought to play a leading role in the obesity-cancer link [24–26]. Although WAT was considered previously as an inactive organ for fat storage, numerous recent studies now confirm its secretory and endocrine function to serve an essential physiological role and maintenance of various signaling events [27, 28]. Adipocytes are by far the major component of WAT along with vascular endothelial cells; immune cells including monocytes, macrophages, fibroblasts, pericytes, and stem; and importantly adipocyte progenitor cells. The mesenchymal adipocyte progenitor cells with stem cell-like properties are known as adipose stromal cells (ASCs) and together with other cells in the WAT, produce numerous adipokines [26, 29] such as various cytokines (IL-1α, IL-1β, IL-6, TNFα), chemokines (CCL2, CCL3, CCL5, CCL7, CXCL1, CXCL8, CXCL12, CXCL16), growth factors (IGF-1), leptin, steroid hormones, and angiogenesis-related factors (VEGFA, VEGFB, VEGFC) [30–32]. These factors are associated with various essential cell signaling pathways for cancer development and progression and their higher secretion by WAT during obesity leads to progression of various cancers including PCa.

As noted above, in addition to ASCs, other cells of the WAT may also play essential roles in driving PCa progression. These include adipocytes, leukocytes (including various immune cells such as macrophages), and lymphocytes that are expanded in obesity [33]. For example, obesity is associated with increased accumulation of macrophages in WAT and these cells can further transform to cancer-associated macrophages and are recruited in tumor stroma [34,

35]. In addition, macrophages in obese conditions acquire a more proinflammatory phenotype and secrete various proinflammatory mediators leading to chronic low-grade inflammation, growth promotion, and angiogenesis [35]. The inflammatory states of WAT also contribute to activation of T-lymphocytes leading to secretion of various proinflammatory chemokines and cytokines such as TNF-α, IL-6, IL-1α, CXCL2, and various angiogenesis factors including VEGF and MMPs [33]. Finally, adipocytes in the WAT are also involved in cancer progression [36]. Adipocytes in peri prostatic WAT (ppWAT) come in direct contact with cancer cells and upon lipolysis, they serve as the energy source for cancer cells [36–38].

ppWAT is the fat layer that surrounds the prostate surface and plays an essential role in cancer progression [39–43]. During the cancer progression, invasion of cancer cells into the ppWAT of the tumor microenvironment leads to tumor-adipocyte crosstalk and facilitates PCa aggressiveness and leads to poor prognosis [43–45]. It was reported that the number of pre-adipocytes is higher in ppWAT of PCa patients compared to BPH patients [46]. These pre-adipocytes are also present in larger quantities in ppWAT compared to visceral WAT [47] and their interaction with cancer cells leads to formation of cancer-associated adipocytes that contribute to development of aggressive PCa [48, 49]. Taken together, the various cell types in the WAT/ppWAT that are increased in number and activated during obesity and that interact either directly or by secreting various mediators ultimately drive aggressive cancer.

## 3 ASCs as important drivers of PCa progression in obesity

ASCs constitute an important cellular component of periprostatic WAT (ppWAT), increase in number in obesity, and are mobilized from their perivascular niche. The recruitment of ASCs into the tumor microenvironment in obesity leads to increased cancer cell proliferation and tumor angiogenesis [50]. The migrated ASCs in the tumor microenvironment increase tumor viability by enhancing the tumor vasculature which provides oxygen and essential nutrients while removing toxic metabolites [51]. ppWAT proliferation during obesity is linked with a gene expression profile that stimulates proliferation, inhibits apoptosis and lipolysis, and increases matrix remodeling, lipid metabolism, and metastasis leading to increased PCa mortality [48, 52, 53]. Numerous animal studies have shown that ASCs, which are expanded in obesity, migrate from WAT to adjacent tumors [51, 54–59]. Once there, they become part of the cell population in the tumor stroma [51]. Trafficking of WAT-derived ASCs into tumors of obese PCa patients has been linked with decreased survival [60]. Recent studies have also shown that human

PCa cell–derived CXCL1 serves as a ligand for CXCR1 and CXCR2 receptors on ASC [60] and that activation of this CXCL1-CXCR1 signaling axis in obesity drives recruitment of ASC to the tumor microenvironment [60].

Recent studies have also shown that ASCs play several roles in PCa progression stages. In this regard, paracrine signals for ASCs lead to anti-apoptotic, mitogenic, angiogenic, and immunosuppressive signals that together promote cancer progression [54, 61, 62]. ASCs can acquire perivascular localization which promotes tumor vascularization [51]. MCP-1 secreted by ASCs [63] recruit macrophages [64] that also contribute to PCa progression [65] as well as effects on T cells that can inhibit anti-tumor immune responses [35, 63, 66]. ASCs can facilitate remodeling of ECM leading to stimulation of cancer cell invasiveness through alterations in mechanotransduction and desmoplasia [67]. Studies in mice with grafted PCa tumors showed differentiation of ASCs into adipocytes further stimulating growth of nearby cancer cells [68]. The reported effects of ASCs on cancer progression [51, 57, 58] have been reproduced by several research groups [69–71]. In addition, ASCs have the ability to stimulate metastasis [70–74] and therapy resistance of multiple cancer types [75–78]. Recent studies using co-culture model systems have also revealed that ASCs induce EMT in PCa cells [79]. Obesity has also been shown to induce EMT in a mouse PCa allograft tumor model [64]. Notably, in this study, WAT invasion into the tumor microenvironment was observed. These latter studies also provided evidence for involvement of ASC in oxidative stress signaling in cancer cells [79] and have further clarified the induction of cancer cell invasiveness and chemoresistance mediated by ASCs.

# 4  WAT and ASC-derived factors in obesity-driven PCa progression

A number of adipokines and cytokines and their role in obesity-driven PCa have been previously reviewed by us and others [27, 30, 31, 80–84]. Here, we will focus the discussion mainly on chemokines (both CXC and CC chemokines) and on lipids implicated in obesity-driven PCa progression.

## 4.1  CXC chemokines

**CXCL12 and its receptors CXCR4 and CXCR7**  Mouse models have proven invaluable in understanding the role of obesity on cancer progression, including PCa [85–89]. We have shown, using the HiMyc mouse PCa model, that obesity drives disease progression while continuous calorie restriction (cCR) inhibits disease progression [85]. Obese HiMyc mice exhibited a dramatic infiltration of inflammatory cells and elevated inflammatory gene expression compared to mice on control and cCR diets [85, 86]. Further analyses of

the prostate tumor microenvironment in obese HiMyc mice support the hypothesis that CXCL12 derived from ASCs stimulates invasiveness of PCa cells and plays an important role in obesity-induced PCa progression [79, 86]. CXCL12, an extensively studied chemokine, acts as a potent chemotactic factor for hematopoietic cells [90, 91] and is involved in metastatic progression of several cancer types including PCa [reviewed in 92]. CXCL12 binds with its receptors CXCR4 and CXCR7 to modulate various downstream cell signaling events [reviewed in 92]. For example, when CXCL12 binds with CXCR4, it induces trimeric G protein signaling and stimulates numerous downstream signaling events including PI3K/Akt, MAPK (ERK and JNK), and Src/STAT3, leading to increased invasiveness and migration of cancer cells [92–96].

Although CXCR7 was initially considered a decoy receptor due to lack of a specific G protein recruiting motif, more recent evidence suggests that binding of CXCL12 with CXCR7 stimulates downstream signaling, including MAP-kinase signaling pathway, by recruiting β-arrestin and subsequent ligand-receptor internalization [97]. CXCR4 and CXCR7 are expressed in cells either individually or together [92]. It is important to note that when co-expressed, they can form both homo and heterodimers; the heterodimers appear to play an essential role in modulating downstream signaling [97–99]. CXCL12 signaling is associated with progression of several cancers, including prostate, breast, pancreatic, and lung cancers [reviewed in 92]. Recent studies have also shown that CXCL12/CXCR4 signaling activates epidermal growth factor receptor family members [93, 100, 101]. Wang et al. [102] further reported that higher CXCR7 expression in human PCa cells was associated with more aggressive tumors. In addition, higher CXCR7 levels led to increased expression of pro-angiogenic factors (IL-8 and VEGF), activation of Akt, and were associated with increased xenograft tumor growth.

CXCL12 and its receptors have also been linked to metastasis of PCa to bone and are considered a poor prognostic marker [103–106]. CXCL12/CXCR4 has been shown to participate in localizing PCa to the bone marrow which can be blocked by neutralizing antibody to CXCR4 [107]. Bone marrow adipose tissue (BMAT) is present in the bone marrow space and bone tissue and constitutes approximately 10% of total adipose tissue in humans and also plays an important role in cancer progression including PCa [108]. Although BMAT shares some phenotypic characteristics with other WAT depots and serves as an energy storage in addition to secreting various adipokines and fatty acids, it is actually increased in young calorie restricted mice and in lean anorexia nervosa patients [109–111]. Several recent studies have confirmed the importance of BMAT in driving cancer progression by promoting survival, proliferation, migration, and invasion of various cancer cells [112, 113]. In

particular, Herroon et al. showed that BMAT stimulated PCa growth in bone marrow by induction of fatty acid binding protein 4 [112]. Furthermore, CXCL1 and CXCL2 derived from BMAT are also involved in osteolysis in metastatic PCa [114]. Finally, a population of CXCL12^{+} pre-adipocyte like stromal cells has been identified in bone marrow that expresses CXCL12 and regulates marrow adipogenesis [115]. These CXCL12-producing stromal cells in bone marrow may also participate in driving PCa aggressiveness and metastatic disease.

We recently reported that treatment of cultured mouse PCa cells (HMVP2 cells isolated from HiMyc mice) with CXCL12 significantly increased migration, invasion, and activated several signaling events associated with development and progression of PCa [86]. We further showed that inhibition of both CXCL12 receptors (CXCR4 and CXCR7) attenuated the effect of CXCL12 on PCa progression [86]. Collectively, these studies suggest that CXCL12 is highly expressed and secreted from ppWAT and ASCs in obesity and plays an important role in PCa progression.

**CXCL1 and CXCL8 and their receptors CXCR1 and CXCR2** CXCL1 and CXCL8 are two additional chemotactic chemokines secreted by a variety of cells in the WAT and involved in progression of cancers including PCa [116–118]. Both chemokines have also been shown to induce migration, angiogenesis, metastatic progression and PCa aggressiveness [119, 120]. CXCL1 and CXCL8 share the common receptors CXCR1 and CXCR2 and Zhang et al. showed that both chemokines facilitated the migration of ASCs that express CXCR1 and CXCR2 into the tumor microenvironment [60]. Multiple animal and human studies also have confirmed higher CXCL1 and CXCL8 expression in obesity and high-grade PCa [120, 121]. Numerous cytokines and chemokines (CXCL12, TNF-α, IL-1, and IL-6) that are highly upregulated in obesity further stimulate the expression of CXCL8 [122, 123]. Binding of ligand with CXCR1/CXCR2 causes activation of numerous cell signaling events mediated via pertussis toxin-sensitive G protein signaling [124]. This includes dissociation of GTP-bound Gα subunit from Gβγ subunit leading to activation of phospholipase C (PLC) and protein kinase C (PKC) and subsequent cytosolic mobilization of $Ca^{2+}$ from endoplasmic reticulum [124, 125]. In addition, activation of CXCR1/2 leads to induction of PI3K/AKT, RhoA, Src kinases, FAK, and MAPKs including ERK1/2, JNK, and p38 ultimately playing important roles in regulation of various cellular processes including migration and chemotaxis [126–129]. In addition to binding with CXCL1 and CXCL8, CXCR2 also binds with the chemokine CXCL5 that is released from various cell types in the SVF of adipose tissue [130, 131]. Expression of CXCL5 is also elevated in obese patients as well in prostate tumor samples and is associated with

activation of JAK/STAT, PI3K, and MAPK signaling pathways that ultimately leads to higher migration, invasion, and cell survival [131, 132]. In summary, CXCL1, CXCL5, and CXCL8 acting through their receptors CXCR1 and CXCR2 play important roles in obesity-induced PCa progression.

**CXCL13 and its receptor CXCR5** The chemokine CXCL13 secreted by adipocytes and other cells of the TME plays important role in cancer progression including induction of cell survival, migration, invasion, angiogenesis, and metastasis [133–135]. CXCL13 triggers its effect by binding with the G protein-coupled receptor CXCR5. Like other G protein-coupled chemokine receptors, CXCL13/CXCR5 interaction leads to G protein subunit dissociation and subsequent induction of different downstream signaling events including activation of ERK1/2, JNK, Src, FAK, and PI3K/AKT signaling [136, 137]. CXCL13 is also involved in the induction of PCa cell survival, migration, invasion, and metastasis [136–138]. Hypoxia increases the expression of both CXCL13 and CXCR5 in adipocytes and WAT isolated from mice on obesity inducing diet showed increased expression of CXCL13 [134]. Taken together, CXCL13 along with its receptor CXCR5 also play an important role in obesity-induced PCa progression.

**CXCL16 and its receptor CXCR6** CXCL16 is another chemokine that has been shown to be involved in obesity and cancer and is expressed in various cells including adipocytes and tumor cells. The effect of CXCL16 is mediated through its interaction with the GPCR, CXCR6 which when bound with CXCL16 leads to activation of multiple downstream cell signaling pathways such as PI3K/AKT, NFκB, ERK1/2, and GSK3β. In addition to binding with CXCR6, recent studies have also shown an alternative transmembrane-mediated signaling called "Inverse signaling" [139]. In this type of signaling, membrane-bound CXCL16 acts like a receptor and CXCL16 in soluble form binds with the transmembrane CXCL16 and induces activation of AKT and ERK and stimulates various biological effects including induction of proliferation and reduction of apoptosis [139]. WAT of obese mice showed increased CXCL16 levels compared to non-obese mice and mice undergoing calorie restriction appear to show lower level of CXCL16 [140]. CXCL16 also involved in PCa metastasis and development of chemoresistance [141, 142].

## 4.2 CC chemokines

In addition to CXC chemokines, various CC chemokines derived from WAT are also involved in obesity-related PCa cancer progression. Several of these are summarized in this section.

**CCL2** CCL2 is expressed in various tissues including adipose tissue and preadipocytes [143–145] and is associated with macrophage mobilization in adipose tissue, chronic inflammation particularly inflammation of the adipose tissue, and is considered a promising biomarker of human PCa [146]. Various proinflammatory mediators such as TNFα, interferon γ (IFNγ), IL-1, IL-6, transforming growth factor β (TGFβ), vascular endothelial growth factor (VEGF), lipopolysaccharide (LPS), and platelet-derived growth factor (PDGF) increase the expression of CCL2 [147]. The expression of CCL2 also increases with higher BMI and weight loss decreses circulatory levels of CCL2 [148]. Like many CXC chemokines, CCL2 also mediates its effect by binding with a GPCR, CCR2. CCR2 serves as the receptor for CCL2 and this receptor ligand interaction leads to activation of different cell signaling pathways including STAT3, PI3K, and MAPK leading to increased survival, anti-apotosis, therapy resistance, and tumor metastasis [149, 150].

**CCL3, CCL4, and CCL5** The chemokines CCL3, CCL4, and CCL5 share common receptor, namely CCR5, in addition to their other binding receptors and all three ligands are highly expressed in WAT and serum of obese mice compared to their non-obese counterparts [86, 151, 152]. WAT of obese mice also showed higher CCL3 level compared to lean mice. We also found higher CCL5 level in ppWAT of obese HiMyc mice compared to control mice [86]. CLL4 and CCL5 are also associated with promoting PCa progression through activation of the STAT3 signaling pathway [153, 154].

**CCL7** CCL7 or monocyte chemoattractant protein-3 (MCP-3) is a chemokine produced by various cells including adipocytes and cancer cells and functions as chemoattractant for immune cells [36, 155–158]. There are several receptors for CCL7, for example, CCR1, CCR2, CCR3, CCR5, and CCR10 [159, 160]. During obesity, adipocytes including periprostatic adipocytes produce higher amount of CCL7 [155, 161] leading to increased migration of CCR3 expressing cancer cells including PCa cells into the ppWAT of tumor microenvironments [36]. The expression of CCL7 is higher in the adipose tissue of patients with severe obesity compared to their lean counterparts and it is also associated with increased migratory potential of PCa cells by induction of ERK and high MMP3 level mediated through CCR3 [162]. The level of CCR3 also shown to be higher in adipose tissue of obese subjects and in PCa patients and involved in poor prognosis [36].

### 4.3 Fatty acids

Long chain fatty acid (LCFA) is mainly stored in WAT [163] and undergoes lipolysis due to activation of catecholamines and β3 adrenergic signaling [164, 165]. Hydrolysis of triglycerides via various lipases such as adipose triglyceride lipase, monoacylglycerol lipase, and hormone sensitive lipase is responsible for the release of free LCFAs [166]. It was reported that monoacylglycerol lipase which serves in the final step of lipolysis is highly expressed in androgen-independent PCa cells (DU145 and PC3) compared to androgen-dependent cells (LNCaP) [167]. Monoacylglycerol lipase is also associated with a gene signature that involves EMT and cancer stem cell-like properties and inhibition of this enzyme reduces PCa aggressiveness [167]. Animal studies demonstrated that loss of body fat during aggressive cancers and growth of tumors stimulates lipolysis in adipocytes [168–170]. Lower free LCFA levels reduce cancer pathogenicity [166] due to decreased lipolysis. Several cancers including pancreatic, breast, and ovarian cancers show increased invasive potential due to alteration in adipose tissue lipolysis in tumor microenvironment [171–173]. Cancer cells acquire LCFAs derived from lipolysis of adipocytes [38] that leads to accelerated proliferation and invasion of breast cancer cells [74, 174, 175]. LCFAs from adipocyte also cause AMPK-mediated induction of mitochondrial biogenesis [168, 176]. Recent studies in animal models have shown the potential importance of adipocyte-derived LCFAs for PCa progression [177, 178].

## 5 Brown adipose tissue (BAT) in PCa

BAT, named based on the color, was initially thought to be present only in infants. However, recent advancement of imaging techniques has led to accurate identification and distribution of BAT in human adults [179]. BAT plays an essential role in non-shivering thermogenesis. Recent evidence suggests that formation of beige/brown adipose tissue from WAT may play a role in PCa progression [35, 180]. Browning of WAT is associated with higher expression of PPARγ or PGC-1 as well as activation of the sympathetic nervous system, leading to stimulation of β-adrenergic signaling [181, 182]. Although the role of WAT in PCa progression has been extensively studied and is well recognized, the impact of BAT and the browning of WAT in PCa progression are not clearly understood at the present time. Further studies are clearly warranted to understand the role of BAT in PCa progression.

## 6 Strategies to offset obesity effects on PCa progression

### 6.1 Calorie restriction

Calorie restriction (CR) is a very potent and broad acting dietary intervention for weight loss and cancer inhibition in

experimental studies, including studies in non-human primates [183]. Using the HiMyc mouse model of PCa, a 30% continuous CR (cCR) diet significantly decreased *in situ* adenocarcinoma (AC) formation and completely inhibited the progression of AC to locally invasive PCa compared to both overweight control and obese mice [85]. This was associated with a marked reduction in mRNA expression of various inflammatory and angiogenesis-related genes. cCR further decreased various important cell signaling pathways in prostate lobes such as AKT/mTORC1, STAT3, NFκB, and CXCL12/CXCR4/CXCR7 signaling involved in cancer progression and metastasis [85, 86]. Galet et al. also showed that cCR decreased growth of 22Rv1 xenograft tumors by modulating IGF-1 signaling [184]. Similarly, cCR with a no carbohydrate ketogenic diet prolonged survival and reduced LAPC-4 PCa tumor growth in SCID mice by modulating insulin and IGF-1 axis compared to mice on a Western diet [185].

Translation of CR studies to human cancer prevention strategies is of great importance because of the high prevalence of overweight/obesity and the essential role of obesity on metabolic changes and progression of multiple cancers, including PCa [186]. Several funded clinical trials have addressed whether the potential benefits of cCR reported in preclinical studies translate to humans. The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) Study evaluated the impacts of a 2-year cCR regimen (25% less energy than controls) in nonobese, healthy individuals [187]. Results from this study indicated that humans showed many similar cCR-induced endocrine and metabolic changes observed in rodents and monkeys. The results are consistent with studies in patients at high risk for breast cancer showing better reduction in insulin, metabolic, and growth factor signaling pathways by cCR or 2 days/week of calorie restriction (hereafter referred to as intermittent CR or iCR) [188–190]. The observed metabolic effects of iCR are particularly important, since it is much easier, attainable, and more feasible to restrict calories for 2 days/week, than to chronically restrict calories. While iCR data show better insulin and body fat/weight reduction in the short-term in women [188], effects in older men and long-term sustainability of the weight/fat loss and metabolic improvements are unknown.

In contrast, clinical trials show that intentional weight loss of greater than 5% by cCR with exercise in men prior to RP is feasible. In an RCT, 25–30% cCR with exercise led to 5.5% of weight loss (95% CI, 4–7%) from baseline to RP (mean = 5 weeks) [191]. Furthermore, 26 weeks post-RP, the cCR group maintained or kept losing to a net loss of 11% initial body weight (95% CI, 8–14%). The cCR regimen decreased insulin, leptin:adiponectin ratio (LAR), and visceral adipose tissue (VAT) associated with inflammation (Hamilton-Reeves, unpublished data). In an earlier study, a novel finding of lower level of CXCL12, CXCR7, and CXCR4 comparing biopsy to RP tissue with cCR was observed [192, 193], which agrees with other evidence of altered gene expression of CXCR4, CCL2, and IGF-2 receptor in prostate tissue with 5% weight loss by cCR diet in four men prior to RP [194]. VAT, LAR, and chronic inflammation are parameters to which cCR weight loss studies report inconsistencies with a higher degree of variability. Henning et al. showed significant decrease in insulin and body fat, without alteration in LAR or trunk fat mass in a similar study design with combined cCR (1200–1500 kcal/day) and 60 min/day exercise [195]. Alternatively, Demark-Wahnefried et al. showed no change in insulin or body fat but a significant decrease in leptin, with intentional weight loss by cCR of a 1000 kcal/day deficit and additional 250–500 kcal expenditure through aerobic exercise in men prior to RP compared to the control group [196]; participants' microbiota changed in response to types of foods but not due to cCR [197]. Wilson et al. showed a significant decrease in VAT and fat mass in a retrospective analysis of patients following cCR of 750–1000 kcal/day and 90 min/day of aerobic exercise for up to 12 weeks before RP [198]. Although cCR improves health overall, it is possible that iCR may have as great or greater impact on molecular pathways and may be easier for adherence; thus, efficacy in men with obesity and PCa needs to be tested.

Data from some human studies suggest that compared to cCR, iCR shows greater increases in insulin sensitivity [188, 189], faster weight loss [188], greater reductions in fat mass [188], better retention of lean mass [199], alterations in gut microbiota [200, 201], inflammation reduction [188, 202], and better LAR [188], while systematic reviews deem iCR and cCR equivalent for weight/fat loss and metabolic changes [203, 204] although primarily only women were studied [205]. While it seems plausible that iCR may allow more flexibility for adherence and for avoiding weight regain, long-term effects in humans are unknown. Currently, there are no published human iCR intervention studies in patients with cancer. It is also unknown if greater metabolic benefits occur when the two fasting days are consecutive or if the carry-over effects of spontaneous CR observed on normal eating days persist long term [188, 189]. Restricting calories mostly from carbohydrates for 2 days/week is appealing for simplicity and also to mitigate risk by allowing sufficient protein intake on restricted days to prevent muscle/function loss [206]. Some benefits may be independent from weight loss, with one study in healthy men showing improved insulin sensitivity from iCR without weight/fat loss [207], which is particularly interesting since men and women have different acute effects to fasting [208]. iCR may make greater improvements than cCR on the cancer biomarkers that contribute to PCa progression and BCR.

Since one of the major impacts of obesity is the extensive alteration of WAT and its secretory status, it is important to look at the role of CR on WAT. Several studies reported that cCR provides beneficial effects by modulating the WAT. This includes a significant decrease in adiposity leading to lower level of various secretory components, biosynthesis of fatty acid, mitochondrial biogenesis, and alteration in adipose tissue metabolism. In this regard, using the HiMyc mouse model of PCa, 30% cCR significantly decreases ppWAT mass as well as complete inhibition of the infiltration of adipocytes into the prostate gland compared to control or obese mice [86]. Miller et al. recently showed that cCR in mice significantly decreased adiposity and high molecular weight adiponectin levels. CR also activated downstream signaling of adiponectin receptor such as increased expression of peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α), SIRT1, and nicotinamide phosphoribosyl transferase (NAMPT) in adipose tissue of cCR mice [209]. These authors also found a greater oxidative metabolic state of the adipose tissue microenvironment [209]. In addition, adipose tissue lipid metabolism was altered with cCR in mice with differences in free fatty acid (FFA), monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) as well as decreases in desaturation, elongation, and omega-3 metabolism in cCR mice [209]. cCR also increased mitochondrial biogenesis, mitochondrial DNA, and oxidative phosphorylation in WAT [210–212]. Decreases in IL-15 signaling and TNF-α expression were also observed in WAT of cCR mice [213]. AMPK and SIRT1 are modulated by cCR and both of them act as positive regulators of PGC-1α. In addition, recent studies showed that induction of PGC-1α in WAT during cCR is mediated by sterol regulatory element-binding protein 1c (SREBP1c) and fibroblast growth factor 21 (FGF21) [214, 215]. Taken together, cCR produces an array of changes in WAT including metabolic reprogramming leading to reversal of the harmful effect of obesity.

## 6.2 Physical activity

Exercise training is a potential strategy to offset PCa progression. Data from several studies have demonstrated that a higher level of physical activity is associated with a lower risk of PCa progression [216] and cancer-specific mortality [217–219]. There is growing evidence linking the molecular pathways underlying these associations. Postulated mechanisms of exercise training include indirect effects by modulating cytokines, improving glucose regulation, reducing insulin resistance, reducing adiposity, and modulating hormones [220]. Physical activity may also directly suppress tumors and the tumor microenvironment by lowering chronic inflammation [221], altering tumor vascularization,

modulating growth factors, and improving immune function [220, 222].

Physical activity is prescribed with recommendations for the frequency, intensity, time/duration, and type of activity; however, the understanding of how these different variables inhibit carcinogenesis is not fully understood. Exercise physiology elicits acute effects after a single bout of exercise and different effects after weeks of consistent exercise training. These differences are summarized in a review by Kim et al. comparing the changes in PCa cell lines treated with serum obtained after a single exercise session showing reductions in AKT, mTOR, ERK, and mitogenic activity to the changes in PCa cell lines treated with serum obtained after consistent long-term exercise training showing increased p53, reduced PCNA, and increased apoptosis [223]. Interestingly, after single bouts of exercise, several groups have reported increased circulating CXCL12 directly after moderate to vigorous exercise [224–230] while no changes in plasma CXCL12 were found after a single bout of strength training [231, 232] suggesting intensity and type may impact this outcome in the plasma. Effects of acute or prolonged exercise on the prostate tissue expression of CXCL12 or related pathways are unknown. Wedell-Neergaard et al. demonstrated that IL-6 signaling is required for exercise to reduce visceral adipose tissue mass; IL-6 increases acutely after a bout of exercise [233]. In general, prolonged exercise interventions have been purported to lower inflammation and improve immune editing, and although these outcomes are known to be highly variable, a meta-analysis by Khosravi et al. of 27 exercise intervention trials in cancer (prostate cancer = 4) reported that exercise training decreased circulating pro-inflammatory markers CRP and TNF [234]. As proposed by Rocha-Rodrigues et al., exercise training may also alter the tumor microenvironment by the effects on the secretions of adipokines from WAT/ppWAT and on secretions of myokines by skeletal muscle and the crosstalk between the two [235]; however, these effects have not yet been tested in patients with PCa or in animal models of PCa. Idorn et al. proposed the idea of using exercise to help hone T cells for immunotherapy through its effects of promoting infiltration of immune cells into the tumor [236]. These data open several future exciting areas of research, including adjuvant exercise with cancer therapy.

A meta-analysis by Bourke et al. found that exercise interventions across all stages of PCa improved cancer-specific quality of life and cancer-specific fatigue in men with up to 6 months of follow-up [237]. A more recent meta-analysis by Anderson et al. confirmed that exercise improved cancer-specific quality of life with a greater magnitude than previously reported and significantly improved cardiovascular fitness as well [238]. An interesting sub-study of INTERVAL-GAP4 trial [239] which uses moderate to high intensity exercise training for 6 months showed tumor suppressive

effects in the supervised exercise arm compared to the control arm when serum obtained from participants with metastatic PCa was added to the human PCa cell line, DU145 [240]. In summary, exercise training is a potential strategy to offset the progression of PCa with or without obesity and there are several potential areas of research opportunities to further evaluate the impact of frequency, intensity, duration, and type of exercise training to benefit patients with PCa at various stages of disease.

## 6.3 Calorie restriction mimetics (CRM)

Although numerous studies have established the potential benefit of cCR from animal studies to humans for a large number of diseases including obesity and cancer, it is extremely difficult to maintain a certain level of cCR for a long period of time to get a desired clinical outcome. In addition, since there are no prolonged cCR studies in human, it is still unclear whether long-term dietary restrictions might cause any adverse side effects. An alternative approach is the use of agents that can provide the similar benefits of CR without altering the dietary manipulations. This has led to recently developed concept of CRM to describe the agents or molecules that mimic the beneficial effects of CR. In order to be an ideal candidate, CRM agents are proposed [241] to have several key characteristics including (i) exert the similar physiological, metabolic, and hormonal effects produced by CR; (ii) not significantly decrease long-term food intake; (iii) produce similar levels of stress response pathways and show protection against a variety of stressors seen in CR; and (iv) reduce age-related diseases as well as inflammation and autoimmunity. Based on these criteria, several agents have been identified as CRM agents including 2- Deoxy-D-Glucose, metformin, rapamycin, peroxisome proliferator-activated receptor (PPAR) activators, and certain natural phytochemicals such as resveratrol, curcumin, EGCG, and quercetin. Here we will briefly discuss the potential benefits of some of the CRM agents in reversing the effects of obesity and PCa progression.

**Resveratrol** The plant-derived polyphenol resveratrol is found in grapes, berries, peanuts, and red wine. Numerous studies reported the potential health benefits of resveratrol including its effects as anti-cancer, anti-aging, anti-diabetes, and as an anti-obesity agent [242]. Recently, resveratrol has been considered as an ideal CRM agent for its role in metabolic effects and effects on adipose tissue. In this regard, Lagouge et al. showed that dietary administration of resveratrol significantly decreased the body weight and WAT deposits in mice maintained on a high-fat diet [243]. Several other reported studies also confirmed that resveratrol decreases body weight and WAT mass in mice on HFD [244–246]. Although there are only a few human trials to evaluate the

effect of resveratrol in comparison to vast majority animal studies, the beneficial effect of resveratrol was still evident. For example, administration of resveratrol at a dose of 500 mg $3\times$/day for 3 months in patients with metabolic syndrome [247] showed significant decrease in body weight, BMI, fat content, and waist circumference (WC) compared to patient with placebo group. Similarly, several other clinical trials found positive outcomes of resveratrol intake and body weight reduction as well as decrease in adipose tissue mass [248–250]. In addition to its effect on obesity and WAT mass, resveratrol has shown potential benefit as an anti-cancer agent for several cancers including PCa [251–255]. Preclinical studies using both cultured cells and transgenic animal models of PCa showed that resveratrol decreases PCa cell growth and metastasis by modulating multiple cell signaling pathways [251, 252, 256, 257]. For example, Seth et al. reported that oral administration of resveratrol decreases xenografted PCa tumor growth and lung metastasis by modulating AKT/miRNA-21 pathway [251].

**Curcumin** Curcumin is another plant-derived polyphenolic compound with CRM activity. It is present in the rhizome of the plant *Curcuma longa*, widely consumed as a food additive and several studies showed potential anti-obesity effect of curcumin. Dietary administration of curcumin showed significant weight loss in both DIO and ob/ob mice [258]. Curcumin also showed reduction of macrophage infiltration in WAT, reduced NFκB activity, and increased adiponectin production [258]. Shao et al. similarly reported that curcumin feeding reversed the HFD-induced weight gain in mice [259]. In addition, curcumin administration increased insulin sensitivity, decreased oxidative and inflammatory signaling in adipocytes, and decreased lipogenic gene expression in the liver [259]. Additionally, Ejaz et al. reported that supplementation of 500 mg/kg of curcumin per day in 22 kcal% HFD significantly reduced body weight, adipose tissue mass, and microvessel density in adipose tissue along with decreased expression of VEGF and VEGFR2 compared to mice fed in HFD [260]. Numerous cell culture and preclinical animal model studies also showed the ability of curcumin to inhibit growth and progression of various cancers including PCa [261]. In addition, several completed and ongoing clinical studies with curcumin show promise for its effect on cancer treatment [261].

**Quercetin** Quercetin is a widely studied polyphenolic compound present in a diverse range of fruits and vegetables including apple, berries, onion, broccoli, cherries, and red grapes [262]. Quercetin is considered as a CRM because of its potential to modulate many cellular changes that are similar to changes observed with cCR. For example, several studies have reported that administration of quercetin causes activation of AMPK, reduction in inflammation, induction of

autophagy, and lifespan increase [263–267]. In mice maintained in 40 kCal% HFD, dietary supplementation of quercetin (0.33%) produced significant decrease in body weight gain, lipid level in serum, and liver without modulation of energy intake [268]. In another study, oral administration of 100 μg/day quercetin produced a 29% decrease in body weight of C57BL6 mice. Additionally, quercetin together with exercise showed further decrease in body weight with 43.5% reduction compared to control mice [269]. Recently, Pei et al. reported that dietary administration of 1% quercetin decreased inflammation in brown adipose tissue (BAT) in HFD-induced obese mice by modulation of NFκB and SIRT1 signaling [270]. Furthermore, Dong et al. showed that 0.1% quercetin decreased body weight gain in C57BL/6 mice fed a HFD and improved glucose intolerance and insulin sensitivity. Quercetin administration also decreased expression of proinflammatory cytokines and activated AMPK and SIRT1 in epididymis adipose tissue of HFD-fed mice [265]. In comparison to a vast majority of animal studies, there are only a few human studies [271, 272] to evaluate the potential CRM benefits of quercetin. For example, in a randomized, double-blind, placebo-controlled study, Lee et al. reported that daily intake of onion peel extract capsules containing 100 mg of quercetin significantly decreased the body weight, BMI, and percentage of body fat in subjects in the treated group compared to the subjects in the placebo group [271]. Thus, in order to fully elucidate the beneficial effect of quercetin as a CRM agent, further properly designed human studies are necessary.

**Metformin** Worldwide, metformin is a highly prescribed agent used for the treatment of type II diabetes and several studies identified its potential as a CRM agent [88, 241, 273, 274]. In this regard, several animal studies showed anti-cancer, anti-aging, and lifespan extension after treatment with metformin. For example, Martin-Montalvo et al. reported that long-term administration of 0.1% metformin in drinking water increased survival of mice compared to control and was associated with better physical performance, higher insulin sensitivity, lowered LDL and cholesterol levels, and activation of AMPK [273]. In another study, Anisimov et al. showed that female outbred SHR mice treated with 100 mg/kg of metformin in drinking water produced a decrease in body weight and extension of the mean lifespan by 37.8% compared to control mice [274]. Numerous published data in preclinical models including our own studies suggested the potential anti-cancer effect of metformin in part due to modulation of multiple cell signaling pathways as well as its effect on body weight reduction [88, 275, 276]. Although there is a growing interest for the potential anti-cancer and anti-obesity effects of metformin, the results in human studies have been inconsistent. A review by Lev M Berstein nicely pointed out some of the factors related to

the inconsistency [277]. However, future, more carefully designed long-term human clinical studies will be needed to provide definitive information related to the use of metformin as a CRM agent in treating cancer and obesity. In this regard, multiple clinical studies are currently ongoing in several countries with metformin to clarify its role in cancer and obesity.

**Rapamycin** Rapamycin is a potent bacterial derived macrolide compound used widely for its role as immunosuppressant treatment for organ transplant recipients as well as in autoimmune disorders. Rapamycin possesses many characteristics of cCR and numerous reports including our own studies showed the potential anti-aging, anti-obesity, anti-cancer, and lifespan extension effect of rapamycin in animal models [275, 278–280]. Chang et al. showed that rapamycin treatment decreased body weight and epididimal fat pad in obese C57BL/6 mice maintained on HFD compared to control treatment [279]. We also showed that rapamycin treatment reduced TPA-induced skin tumor promotion as well as reduction of PCa progression in HiMyc mouse model with complete inhibition of adenocarcinoma formation in this mouse model [275, 280]. Similar to cCR, rapamycin exerts it effect by inhibiting mTORC1 signaling pathways with subsequent decrease in activation of downstream signaling pathways, including p70S6K and ribosomal S6 kinase [85, 275], and might serve as a potential CRM agent for treating obesity and cancer including PCa.

**Phytochemical combinations as CRM** The use of combinations of agents including phytochemical combinations for various diseases such as cancer has received considerable recent interest due to the potential to (i) provide synergistic effects, (ii) target multiple cell signaling pathways leading to better beneficial effects, and (iii) produce less toxic effects due to smaller dose requirements. Several recent studies including our own studies with combinations of agents have shown effects on obesity as well as modulation of key signaling such as AMPK [275, 281]. In this regard, one recent study by Lee et al. showed that treatment with a combination of phytochemicals containing p-octopamine hydrochloride, p-synephrine, and hispidulin significantly lowered the body weight of HFD-induced obese mice compared to control mice with concomitant decrease in the expression of various adipogenic markers such as CCAAT/enhancer-binding protein alpha (C/EBPα), CCAAT/enhancer-binding protein beta (C/EBPβ), and peroxisome proliferator-activated receptor gamma (PPARγ) [281]. Furthermore, combinations of several phytochemicals (resveratrol, genistein, and quercetin) together with vitamin D showed decreased body weight and adiposity compared to control diet in aged ovariectomized rats. We also showed that combinations of curcumin + ursolic acid, resveratrol + ursolic acid, curcumin + resveratrol,

and metformin + rapamycin produced significant decreases in tumor growth in a PCa allograft tumor model as well as in the HiMyc mouse model of PCa [275, 282]. In addition, these combinations of agents have shown induction of AMPK, a signaling pathway previously shown to be activated by cCR and considered as a marker of CRM [275, 282]. Taken together, the concept of using combinations of agents including phytochemical combinations has shown promise and should be considered as potential CRM approach for treating obesity-related cancer, including PCa.

### 6.4 Targeting ASC in WAT and the tumor microenvironment

As noted above, ASCs are believed to play a major role in obesity-driven PCa progression. Targeting ASC in WAT and the tumor stroma could be a strategy for offsetting the effects of obesity on PCa progression. By screening a combinatorial library *in vivo*, Kolonin and colleagues isolated a cyclic peptide called WAT7 with a sequence of CSWKYWFGEC that attacks ASCs that are found in both WAT and tumor stroma [283, 284]. This peptide was attached to another peptide (KLAKKLAK) to generate the "Hunter-Killer" peptide and ultimately targeting and killing ASCs. This hybrid peptide, called D-CAN, has been used to selectively deplete ASCs *in vivo* [284, 285]. In this regard, D-CAN has been tested *in vivo* for suppression of EMT and tumor growth in obese mice [79]. D-CAN injected into mice harboring HMVP2 allograft tumors led to significant inhibition of tumor growth, reduced periprostatic WAT, and a reversion of EMT-related changes in the tumors [79]. In addition, targeting ASC has been shown to reverse chemoresistance in both mouse allograft and human xenograft PCa models [79]. Further studies have revealed that targeting ASCs with D-CAN *in vivo* in obese HiMyc mice significantly reduced the number of CXCL12 producing cells in tumor stroma and reversed EMT changes associated with obesity [178]. These and other data have provided strong evidence that ASCs are the source of CXCL12 involved in driving PCa progression in obesity and that targeting ASCs could be a novel strategy for offsetting the effects of obesity on PCa.

### 6.5 Targeting FAs

In PCa, higher lipogenesis is a characteristic feature of more advanced PCa [286]. As noted above, reduced levels of free LCFA have been shown to reduce cancer pathogenicity [166] due to decreased lipolysis. These observations have prompted investigation into whether lipogenesis enzymes might represent therapeutic targets in obesity and PCa [166]. FA synthase (FASN) inhibitors have been shown to reduce cancer cell viability and have demonstrated promise in studies using animal models of PCa [287]. Unfortunately, systemic toxicity has been a problem with lipogenesis inhibitors as well as the observation that cancer cells can switch to extracellular LCFA utilization thereby resisting the effects

**Table 1** Strategies to offset obesity effects on PCa progression

| Strategies | Effects | Signaling changes | Ref |
|---|---|---|---|
| Calorie restriction | • Reduction of body weight<br>• Alteration in gut microbiota<br>• Reduction of inflammation<br>• Reduction of WAT and ppWAT<br>• Changes in metabolism | • Reduction of PI3K/AKT/mTOR signaling<br>• Inhibition of JAK/STAT pathway<br>• Decreased NFκB signaling<br>• Decreased CXCL12/CXCR4/CXCR7 signaling<br>• Decreased insulin/IGF1/growth factors | [85, 86, 184, 188, 191, 195, 200–202] |
| Physical activity | • Reduction of PCa progression<br>• Improvement of metabolic function<br>• Improved insulin sensitivity<br>• Improved cancer-specific quality of life and cancer-specific fatigue | • Reduction of AKT/mTOR, ERK signaling<br>• Induction of p53 | [216, 223, 237] |
| Calorie restriction mimetics (CRM) | • Decreased body weight, BMI, and WAT<br>• Reduction of macrophage infiltration in WAT<br>• Increased insulin sensitivity<br>• Reduction of inflammation<br>• Induction of autophagy<br>• Lowered LDL and cholesterol | • Reduced NFκB activity<br>• Decreased expression of VEGF and VEGFR2<br>• Activation of AMPK and SIRT1<br>• Inhibition of mTORC1 signaling | [244–246, 259, 260, 263–267, 270, 273, 275] |
| Targeting ASCs | • Suppression of EMT<br>• Inhibition of tumor growth<br>• Reduction of periprostatic WAT<br>• Reversal of chemoresistance | • Decreased CXCL12 signaling | [79, 178] |
| Targeting chemokine receptors | • Suppression of EMT<br>• Inhibition of PCa progression | • Reduction of STAT3, ERK, and JNK signaling | [92–96] |

# Obesity Driven PCa progression and intervention Strategies
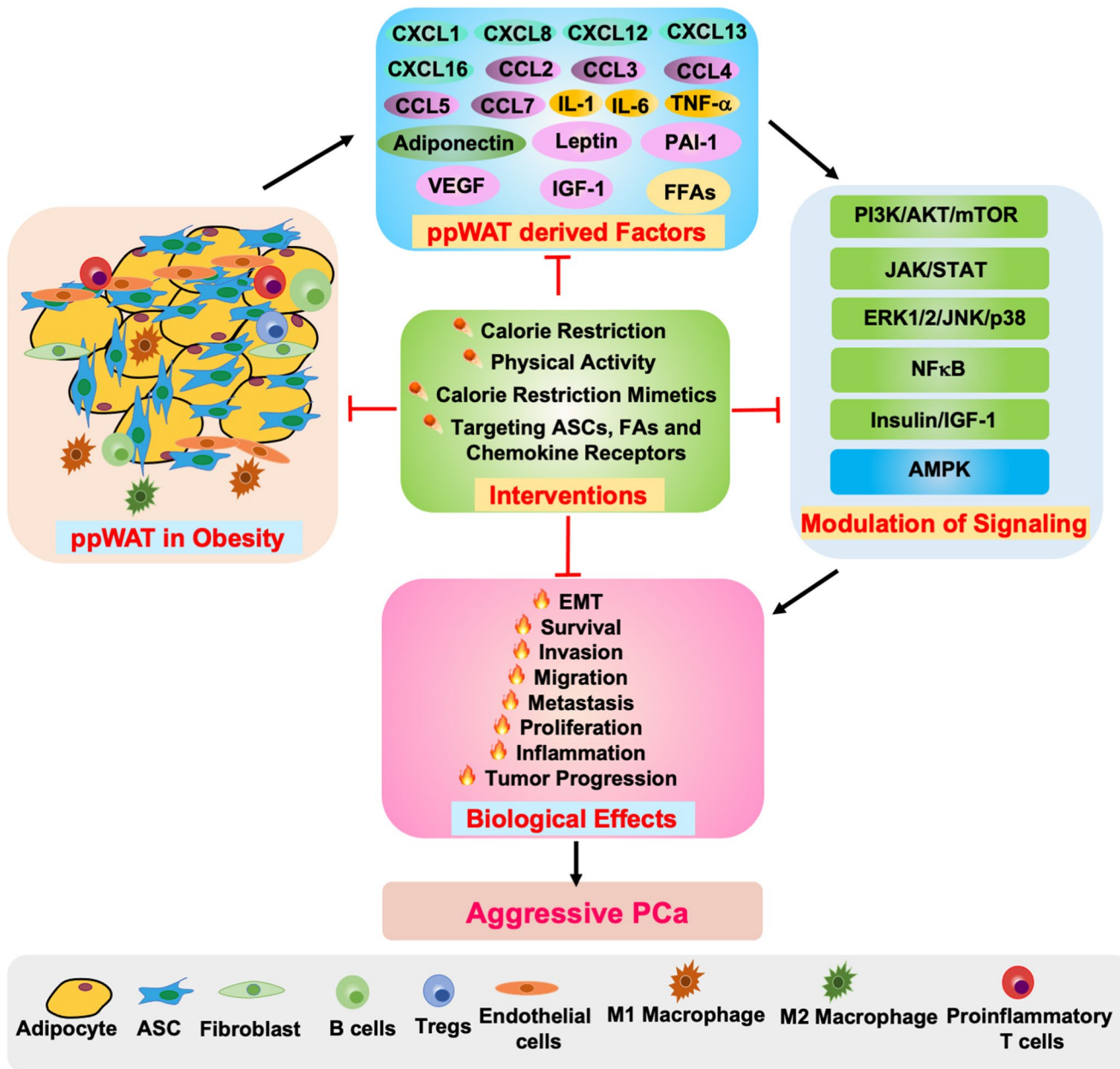


**Fig. 1** Obesity-driven PCa progression and intervention strategies. Obesity is associated with adipocyte hypertrophy and hyperplasia along with the presence of higher number of other cells such as ASCs, immune cells, and endothelial cells. These increased number of cells produce and secrete excessive amount of various signaling molecules and factors including various inflammatory chemokines (CXCL1, CXCL8, CXCL12 etc.), cytokines (IL-1, IL-6, TNFα), and growth factors (IGF-1, VEGF). These factors modulate multiple cell signaling pathways such as PI3K/AKT/mTOR, JAK/STAT3, ERK/ JNK/p38 MAPK, NFκB, insulin/IGF-1, and MAPK signaling leading to higher EMT, proliferation, survival, angiogenesis, inflammation, migration, invasion, and tumor progression that ultimately results in development and progression of aggressive PCa. There are several interventional strategies such as use of CR and CRM, physical activity, and approaches that target ASCs, FAs, and chemokine receptors that could be utilized to reverse the effect of obesity on aggressive PCa

of these types of inhibitors [288]. Further development of agents and research in this area is warranted to determine whether targeting FAs is a viable approach for treating obesity-driven PCa progression.

## 6.6 Targeting chemokine receptors

As noted above, various chemokines have been shown to play a role in obesity-driven PCa progression. ASCs produce CXCL12 which has been linked, at least in part, to PCa aggressiveness in obesity [79, 86, 178]. CXCL12 binds to both CXCR4 and CXCR7 [92]. Both CXCR4 and CXCR7 are highly expressed in various tumors [103, 104, 289, 290] and have been proposed as important players in cancer progression [291, 292]. CXCL12 binding to CXCR4 activates several signaling pathways related to cell survival, angiogenesis, and cell proliferation, such as JAK-STAT, PI3K-AKT-NFκB, and MEK-ERK signaling [293–295]. CXCR7 is an atypical chemokine receptor, and its role in cancer progression has been somewhat controversial [95, 296]. Previously, we reported a correlation of CXCR4 and CXCR7 expression in obesity with increased HiMyc tumor growth and also demonstrated the importance of CXCL12 signaling for cancer cell invasiveness as noted above [86]. Notably, blockade of either CXCR4 (either genetically or pharmacologically) or CXCR7 (pharmacologically) suppresses obesity-driven EMT and PCa progression in mouse models [297].

A summary of the various strategies discussed above, to offset the effects of obesity on PCa, is presented in Table 1.

## 7 Conclusions and future perspectives

While not completely defined, it is clear from current research that ppWAT and cells within this compartment, especially ASCs, are critical drivers of PCa progression in obesity. Multiple mechanisms likely play a role in obesity-driven PCa progression but secreted factors, especially chemokines appear to play a significant role. In addition to chemokines, other molecules such as cytokines, angiogenesis factors, growth factors, and lipids [27, 30, 84] also likely contribute to the effects of obesity with the possibility that multiple pathways that are activated may synergize to drive PCa aggressiveness and chemoresistance. The accumulating knowledge of mechanisms has led to research into strategies to offset the effects of obesity on PCa and other cancers and include weight loss interventions, CRMs, and more targeted approaches to block specific signaling pathways. Figure 1 summarizes some of the relevant mechanisms associated with obesity-driven PCa progression and potential prevention/treatment strategies discussed in this review. Further understanding of the cellular and molecular mechanisms underlying the activity of ppWAT and in particular ASCs, as well as other components of the ppWAT, will allow further development of strategies for their inhibition and will

facilitate the development of strategies to reduce obesity-associated PCa progression.

## Declarations

**Competing interests** The authors declare no competing interests.

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