UNIVERSIDADE BEIRA INTERIOR

Obesity and Prostate Cancer: Tumor Microenvironment

Alexandre Silva Mortágua

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Orientador: Prof. Doutor Bruno Alexandre Guerra Jorge Pereira

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Declaração de Integridade

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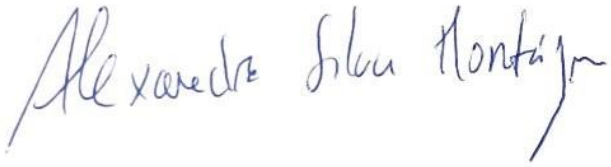

Alexandre Silva Mortágua
(41383)

Dedicatória

Aos meus pais.

Sem eles não seria possível.

Agradecimentos

Quero agradecer aos meus pais, cujo apoio incondicional e encorajamento foram a âncora que me sustentou nos momentos árduos. A sua dedicação foi a força responsável por cada conquista. Este trabalho é dedicado a vocês, que sempre estiveram ao meu lado, compartilhando alegrias e superando desafios.

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Resumo

A obesidade é uma doença crónica caracterizada por uma acumulação excessiva de gordura corporal, frequentemente resultante de uma combinação de fatores genéticos, ambientais e sociais. Vários estudos demonstram uma estreita relação entre a obesidade e o risco de desenvolvimento de carcinoma da próstata e, deste modo diferentes mecanismos biológicos têm sido propostos para explicar esta mesma associação. Nos últimos anos, a inflamação crónica induzida pelo tecido adiposo periprostático tem sido assinalada como um dos principais mecanismos envolvidos na transformação epitélio-mesenquimal para um fenótipo maligno, que promove a invasão, a agressividade e o potencial risco metastático do cancro da próstata. Este microambiente inflamatório culmina em *stress* oxidativo, ativação de citocinas inflamatórias, desregulação da sinalização de adipocinas e aumento dos níveis circulantes de insulina, assim como de outos fatores de crescimento, que podem estar envolvidos no processo de carcinogénese tumoral prostático. Deste modo, a compreensão destes mecanismos constitui um alicerce basilar na apreensão dos processos patológicos desta doença, assim como no desenvolvimento de estratégias eficazes de prevenção e tratamento para o carcinoma da próstata.

A presente revisão reflete uma análise do tecido adiposo periprostático como um órgão secretor e dinamicamente ativo, elucidando o impacto de seus produtos e os seus mecanismos na génese do carcinoma da próstata.

Palavras-chave

Obesidade;adipócitos;tecido adiposo periprostático;carcinoma da próstata; microambiente tumoral

Abstract

Obesity is a chronic disease characterized by an excessive accumulation of body fat, often resulting from a combination of genetic, environmental, and lifestyle factors. Several investigations report evidence of a connection between obesity and the risk of prostate cancer and different biologic mechanisms have been proposed to explain this association. In recent years, the chronic inflammation induced by the periprostatic adipose tissue in an obesity state has been appointed as a potential causative agent of epithelial to mesenchymal transformation into a malignant phenotype that promotes invasiveness, aggressiveness, and metastatic potential of prostate cancer. This inflammatory microenvironment results in oxidative stress, activation of inflammatory cytokines, deregulation of adipokines signaling and increased circulating levels of insulin and other growth factors that could be the physiological agents responsible for the process of carcinogenesis. Hence, the comprehension of these mechanisms may be a valuable step in the comprehension of the disease and in the development of effective prevention strategies and treatments for prostate carcinoma.

This review presents a comprehensive examination of the periprostatic adipose tissue as a dynamically active secretory organ, elucidating the impact of its derivatives and their underlying mechanisms in the tumorigenesis of prostate cancer.

Keywords

Obesity;adipocytes;periprostatic adipose tissue;prostate cancer;tumor microenvironment.

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List of abbreviations

BMI	Body Mass Index
PCa	Prostate Cancer
SAT	Subcutaneous Adipose Tissue
VAT	Visceral Adipose Tissue
WAT	White Adipose Tissue
BAT	Brown Adipose Tissue
UCP-1	Mitochondrial Uncoupling Protein-1
CAA	Cancer-associated Adipocytes
PPAT	Peri-prostatic Adipose Tissue
PAI-1	Plasminogen Activator Inhibitor-1
MCP-1	Monocyte Chemoattractant Molecule
TME	Tumor Microenvironment
EMT	Epithelial-mesenchymal Transition
MMP	Matrix Metalloproteinase
TNF- α	Tumor Necrosis Factor-alpha
NK cells	Natural Killer Cells
ROS	Reactive Oxygen Species
TAMs	Tumor-associated Macrophages
MAPK	Mitogen Activated Protein Kinase
IL-6R	IL-6 Receptor
IL-1RI	IL-1 Receptor Type 1
IRAK-1	IL-1 Receptor-associated Kinase-1
TRAF6	Tumor Necrosis Factor Receptor-associated Factor 6
HIFa	Hypoxia inducible transcription factor-1a
COX-2	Cyclooxygenase-2
VEGF	Vascular Endothelial Growth Factor
MIC-1	Macrophage Inhibitory Cytokine 1
TGF-β	Transforming Growth Factor-β
GFRAL	Glial-derived Neurotrophic Factor Receptor α-like
ERK	Extracellular Signal-regulated Kinase
PI3K	Phosphatidylinositol 3-kinase
AMPK	Adenosine Monophosphate-activated Protein Kinase
PPAR-α	Peroxisome Proliferator-activated Receptor alpha
IGFBP	Insulin-like Growth Factor-binding Protein

IGF-1	Insulin-like Growth Factor-1
PBEF	Pre-B Cell Colony Enhancing Factor
NAMPT	Nicotinamide Phosphoribosyltransferase
NAD+	Nicotinamide Adenine Dinucleotide
BMP	Bone Morphogenic Proteins
AR	Androgen Receptor
IGF-1R	IGF-1 Receptor
BC	Breast Cancer
CAFs	Cancer-associated Fibroblasts

1. Introduction

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) over 25 is considered overweight, and over 30 represents obesity.(1) The issue has grown to epidemic proportions and rates of overweight and obesity continue to grow in adults and children. Overweight and obesity are major risk factors for several chronic disorders, including cardiovascular diseases such as heart disease and stroke, metabolic (such as diabetes), respiratory, and musculoskeletal (such as osteoarthritis) and is also associated with some cancers, including endometrial, breast, ovarian, liver, gallbladder, kidney, colon, and prostate.(1) The risk of these noncommunicable diseases increases even when a person is only slightly overweight and grows more serious as the BMI climbs.(1) Although not all studies support a relationship, it is generally believed that obesity increases the risk for advanced prostate cancer (PCa) stage and grade at diagnosis, younger age at diagnosis, biochemical failure (disease recurrence) after treatment, and PCa-specific mortality.(2) However, the mechanisms by which obesity affects poor PCa outcomes are not completely understood.(2) One possible link in the relationship between obesity and PCa progression is inflammation.(2) Multiple theories have been advanced for the role of excessive body fat in carcinogenesis. The proposed mechanisms are based broadly on changes in the adipose tissue microenvironment that favor and contribute to the induction of fibrosis and angiogenesis, stem cell abundance, expansion of proinflammatory immune cells, as well as systemic production of metabolic and inflammatory mediators.

According to the Global Cancer Observatory, in 2020, PCa was among the most diagnosed cancers worldwide, with around 1.4 million men affected by the disease (7.8%), being surpassed by breast (2.2 million), lung (2.2 million) and colorectal cancer (1.9 million).(3) Simultaneously, the number of diagnoses appears to be influenced by the Human Development Score (the higher the index, the higher the frequency of PCa), as well as by rising age (average age of diagnosis is 66 years).(4) Furthermore, specific regions around the world tend to have a positive or negative relationship with PCa, with higher frequency in Europe, the Caribbean, Australia, North America, and Southern Africa.(4) The prostate is a glandular-structure, embryologically derived of the urogenital sinus in the male reproductive system. It is responsible for including an alkaline fluid, rich in nutrients, that enriches and preserves the ejaculated semen, promotes healthy ejaculation, and stimulates fertility.(4) The most common type of prostate cancer is acinar adenocarcinoma, which originates from the glandular epithelium.(5) Although the main etiology remains a gap in the scientifical community, there are some risk factors

positively associated with PCa pathology, including age, ethnicity, sexually transmitted diseases, genetic factors, diet, smoking, sexual hormones, hyperglycemic state, chronic inflammation, obesity, and hyperinsulinemia.(4) Consequently, recent investigations have centered on pinpointing the genes and mutations responsible for PCa, and understanding the risk factors that can impact this progression. Familiarity with the aforementioned may also play a role in uncovering novel therapeutic strategies. Nonetheless, obesity and PCa affect substantial proportions of the male population, the association between these conditions is of great public health significance.(6) In the last decade, multiple epidemiologic studies have suggested that obesity is associated with an increased risk of death from numerous cancer types including PCa. Several reported a positive association between obesity and PCa incidence and, although modest, the relative risks were consistent. Obesity has also been associated with worse prognostic and malignant transformation of epithelial cells.(6)

This review presents a comprehensive examination of adipose tissue as a dynamically active secretory organ, elucidating the impact of its derivatives and their underlying mechanisms in the tumorigenesis of prostate cancer.

2. Materials and Methods

The development of this narrative literature review embarked with a state-of-the-art search in the repositories of Portuguese universities, including the Integrated Master's in Medicine. The primary objective of this initial search was to ascertain the existence of dissertations on this theme. Since no results were obtained in this regard, the analysis shifted to works focusing on the periprostatic tumor microenvironment, resulting from an interaction between adipocytes and prostatic tumor cells.

The main sources for bibliographic research were the PubMed and b-on platform, from which the majority of references were retrieved. The research employed the following keywords: "Obesity", "Adipocytes", "Peri-prostatic Adipose Tissue", "Prostate Cancer", "Tumor Microenvironment" and was limited to articles published between 01/01/2013 and 01/01/2023, written in English and Portuguese. The initial search yielded a total of 114 articles, which were reduced to 90 articles after excluding the duplicates. Subsequently, the most relevant articles in the field of urology were selected for their relevance and impact, resulting in the final collection of a total of 33 articles. From this final set, we hold 23 systematic reviews and 10 randomized controlled trials (RCTs).

The official websites such as the World Health Organization and Global Cancer Observatory were used for epidemiological and theoretical information on the topic.

3. Results and Discussion

3.1 Adipose Tissue

Adipose tissue is both a metabolically active organ and an energy depot that can be broadly classified based on anatomical location (as subcutaneous or visceral) or physiological function (such as white, beige, and brown adipose tissue).(4,7,8) Subcutaneous adipose tissue (SAT), which accounts for 85% of human body fat, is present under the skin and provides thermal insulation and mechanical protection.(8) Visceral adipose tissue (VAT), present in the abdominal cavity adjacent to organs, protects these vital organs against trauma and localized infections. Furthermore, it releases more inflammatory and growth factors compared with SAT, although visceral adipose make up only 10% of total body fat.(4,8–10)

Moreover, white adipose tissue (WAT) consists mostly of mature adipocytes, but other cells from the stromal vascular fraction are present, including adipose progenitor cells, lymphocytes, macrophages, fibroblasts, and vascular cells.(11) In contrast, brown adipose tissue (BAT), which is rich in mitochondria, oxidizes chemical energy to produce heat, through the actions of mitochondrial uncoupling protein-1 (UCP-1), as a defense against hypothermia.(12) Beige adipose tissue appears to be a hybrid between WAT and BAT, sharing the biologic capabilities of both.(12) It functions for energy storage, but it can express UCP-1, which indicates that it can have thermogenic activity.(12) Not surprisingly, infants have a higher abundance of brown and beige fat depots to protect them from hypothermia since they lack a shivering response.(8)

Adipocytes are the most frequent cell type in adipose tissue.(13) A mature adipocyte is a large cell containing one lipidic vacuole made mainly of triacylglycerides, which is able to store and deliver lipids such as free fatty acids to other cells, through lipolysis.(13) Other lipids stored in adipocytes, such as phospholipids, are vital components of membranes and can be hydrolyzed to generate signaling molecules.(8) As previously stated, the adipocyte is a metabolically active cell, that can secrete numerous adipose-derived factors called adipokines, such as steroid hormones, growth factors including pro-angiogenic factors, chemokines, and cytokines, that are mainly pro-inflammatory.(13)

Cancer-associated adipocytes (CAA) are smaller than “standard” adipocytes and are defined as the result of interactions between adipocytes and tumor cells, leading to a phenomenon of remodeling into a more poorly differentiated state, consistent with the finding that peri-prostatic adipose tissue (PPAT) is richer in precursor adipocytes than

other visceral adipose tissues.(13,14) Hence, this precursor cell phenotype is associated with more aggressive tumors, including PCa.(14) When CAA undergoes dedifferentiation, it acquires a fibroblast-like phenotype in cancer cells, especially at the front of tumor invasion. This phenotypic change is often accompanied by increased secretion of adipocyte differentiation marker proteins (adiponectin, leptin, fatty acid binding proteins and intestinal proteins) as well as the pro-inflammatory cytokines IL-6 and PAI-1 (plasminogen activator inhibitor-1).(14) Adipokines secreted by CAAs have an increased pro-inflammatory phenotype when compared to standard adipocytes.(13)

Obesity has been linked to PCa aggressiveness.(13,15) Adipocytes from obese men are hypertrophic, with remodeling of the extracellular matrix that induces fibrosis and inflammation in the adipose microenvironment, leading to hypoxia and adipocyte stress.(13) These changes lead to increase fatty acid release and modification in adipokine production that favors the production of pro-inflammatory cytokines over anti-inflammatory cytokines, inducing an inflammatory microenvironment.(13) Concomitantly, more systemic disorders associated with obesity, such as dyslipidemia and insulin resistance leading to increased circulating levels of insulin, are also likely to be involved in PCa aggressiveness.(4,13)

3.2 Obesity, Chronic inflammation, and Prostate Cancer

Obesity driven by excessive calorie intake leads to both the hypertrophy of existing adipocytes and adipocyte proliferation, which play an important role in the progression of several epithelial cancers.(8) As obesity increases, hormone dysfunction ensues, and adipocytes become stressed, causing a characteristic inflamed state, which distinctly differentiates adipose tissue in obese individuals from lean individuals. With obesity, adipose tissue becomes resistant to the actions of insulin and secretes proinflammatory cytokines (IL-6, IL-8, PAI-1, MCP-1), adipokines and growth factors (FGF21, TGF-β, VEGF).(4,8,16)

Moreover, it is essential to remark that in obesity, given a concomitant increase in leptin, hypoxia, due to impaired tissue perfusion, and decrease in adiponectin, the tumor microenvironment (TME) becomes favorable for tumor initiation, development, progression, and metastasis, affecting the therapeutic response.(8) Hence, we acknowledge PPAT as a site of invasion of PCa and as part of the microenvironment. It was shown that PPAT secretes protein factors and fatty acids that alter this microenvironment.(14) Studies of PPAT thickness, expression of inflammatory factors, and the involvement of obesity in PCa progression have shown that changes in local adipose tissue in the prostate body can influence the behavior of PCa, for example tumor-

-like transformations, genetic variability, and epithelial-mesenchymal transition (EMT).(14) Such findings suggest the continuous positive feedback process between PCa and PPAT accelerates the continuous deterioration of PCa.(14) PPAT contains matrix metalloproteinase (MMP [zinc-dependent endopeptidases]) with higher activity than abdominal visceral adipose tissue.(14) Activated MMP can degrade extracellular matrix proteins and thus promote the invasion of cancer cells into surrounding tissues.(14)

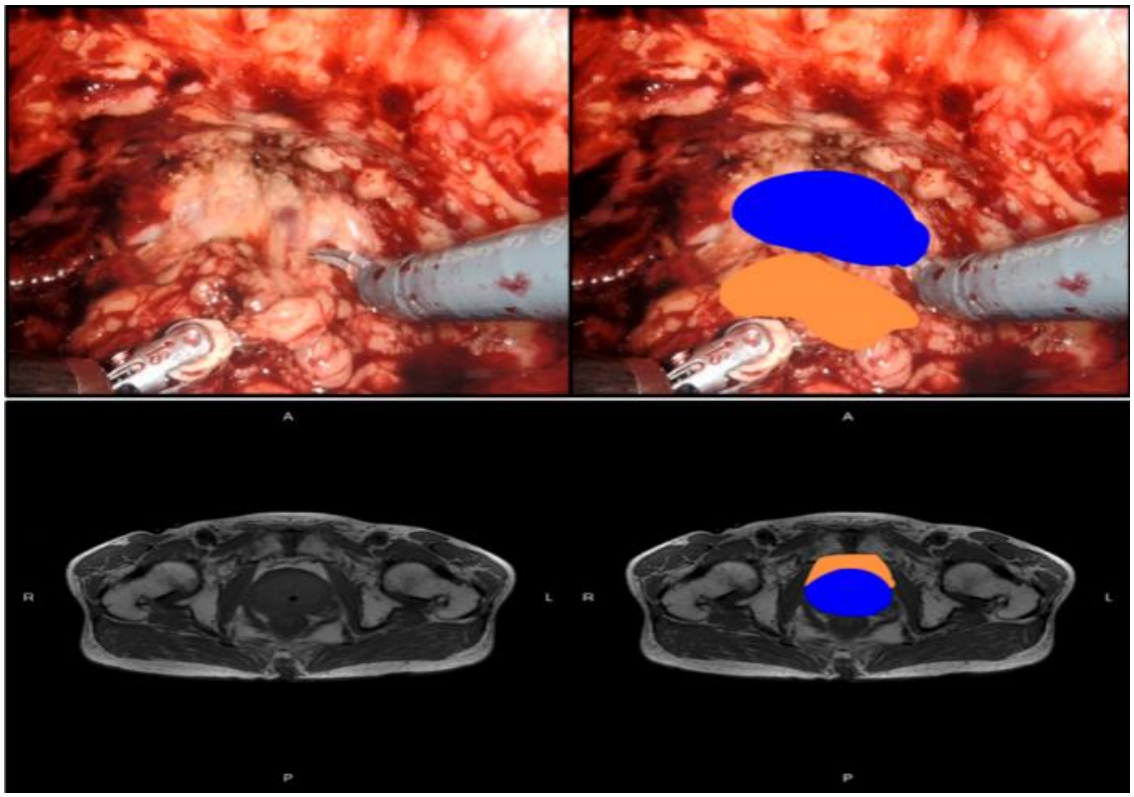

Figure 1: PPAT in robot-assisted radical prostate cancer surgery. Anatomical relationship between the prostate and PPAT. Orange color: PPAT. Blue color: Prostate cancer.(14)

As previously stated, obesity is associated with increased fat storage in the adipose tissue. Interestingly, several tumors grow in anatomic proximity to adipose cells. This is the case of PCa, which grows adjacent to the PPAT, and adipocytes can act as driving force to promote PCa cells migration.(17) (Figure 1)

The prostate stromal microenvironment is an interconnected network that consists of various types of stromal cells and has emerged as a key factor in the growth and development of PCa.(18) Macrophages are plastic cells that compose this prostate stromal microenvironment.(18,19) They can be differentiated into certain phenotypes depending on the signals present within their process of differentiation. This differentiation process is called polarization, and it produces, generally, macrophage populations which are classified into M1 and M2 subtypes. It has been widely established

that M1 macrophages are also known as classically activated and display pro-inflammatory functions, whereas M2 macrophages are alternatively activated and are mainly involved in anti-inflammatory processes.(18,19) Alternatively, M2 macrophages contribute to immunosuppression and pro-tumorigenic activities correlating with PCa aggressiveness and the development of castration resistance.(20)

As aforementioned, the constituents of this TME align with factors that amplify the process of prostatic carcinogenesis. Therefore, a better understanding of their mechanisms and physiological interconnections will provide us with improved insights into the pathological processes of PCa, as well as the potential to establish novel therapeutic tools.

3.2.1 TNF- α

Tumor necrosis factor (TNF)-alpha is a pro-inflammatory cytokine secreted by adipocytes with increased secretion levels in obese subjects.(6) The role of TNF-α in the context of PCa is complex and often contradictory. This molecule is primarily produced by cells involved in immune response processes including natural killer cells (NK cells), macrophages, and T cells however other cells including adipocytes and endothelial cells can also produce TNF-α.(15)

At the molecular level, TNF-α-induced inflammation has been shown to generate reactive oxygen species (ROS) capable of damaging DNA and generating adverse gene fusions.(15) Studies show TNF-α also plays a crucial role in invoking phenotypical characteristics of EMT such as cell motility, invasiveness, decreased E-cadherin, and upregulation of vimentin in PCa cells.(15) Given the proximity between the prostate and PPAT, PCa cells may be particularly subject to PPAT-derived TNF-α rendering PCa increasingly susceptible to TNF-α-induced EMT and subsequent migration.(6,15)

TNF-α activity can further facilitate the metastatic process, by promoting the production of extracellular matrix digesting MMP via NF-κB signaling and stimulating expression of genes regulating selectin ligands which facilitate cell adhesion to selectins located on secondary-site epithelial tissue following metastasis.(6,15)

Additionally, research has also revealed that TNF-α derived from tumor-associated macrophages (TAMs) can stimulate the production of IL-6 in tumors, which serves to establish a TAM-attracting cytokine gradient, tumor growth, promote skeletal metastasis, pro-inflammatory gene expression and angiogenesis.(4,15) Thus, interplay between macrophage-derived TNF-α and tumor-derived IL-6 establishes a cycle of

inflammation, contributing to a positive feedback loop, of tumor growth and TAM recruitment to the TME.(4,15)

TAMs are crucial drivers of tumor promoting inflammation and are generally associated with poor prognosis in solid tumors, including PCa. Subsequently, they contribute to tumor progression at different levels by promoting genetic instability, cell proliferation, angiogenesis, and metastasis, as well as suppressing protective adaptive immunity.(21)

3.2.2 IL-6

IL-6 is one of the promising adipokines that may modulate PCa through a paracrine and autocrine effect. It is a multi-functional cytokine that can be produced by various cell types, including immune/inflammatory cells (monocytes, macrophages, B cells, T cells, NK cells), fibroblasts, keratinocytes, endothelial cells, adipocytes, and tumor cells, and very abundant in periprostatic tissue.(4,11,13,16) Furthermore, numerous studies indicate it has increased both ligand and receptor production in advanced PCa cells, creating a functional autocrine loop.(11,13,16)

Research further suggests IL-6 may be a viable PCa prognostic factor.(15,16) Histological analyses reveal higher serum- and tissue-IL-6 levels are associated with increased aggressiveness of PCa, poorer prognosis, progression of malignancy, metastatic PCa, and higher Gleason score.(9,15) Hence, it has been shown to facilitate PCa progression to androgen-independent disease and potentially to promote bone metastasis and neuroendocrine differentiation.(16,22)

IL-6 signaling is mediated primarily through JAK/STAT3 and MAPK (mitogen activated protein kinase) pathways following IL-6 binding to the IL-6 receptor (IL-6R) complex, initiating the downstream activation cascade.(4,15,16) These pathways regulate cell growth, apoptosis, proliferation, survival, and metastasis, for this reason mutations resulting in constitutive signaling of these pathways may promote oncogenic activity.(4,15)

Nevertheless, it is also crucial to mention, IL-6 promotes PCa progression by attracting TAMs to the TME thus establishing an inflammatory loop fueling tumor growth and osteolytic activity.(15) TAMs secrete a multitude of factors contributing to angiogenesis, suppression of the immune system, metastasis, and carcinogenesis such as TNF-α and IL-1b.(15)

3.2.3 IL-1b

The pro-inflammatory cytokine IL-1b is transcribed via the IL1B gene and is produced by a variety of cell types including monocytes, dendritic cells, endothelial cells, tissue macrophages, and fibroblasts.(15) It binds to the ubiquitously expressed IL-1 receptor type 1 (IL-1RI), resulting in recruitment of IL-1 receptor-associated kinase (IRAK)-1 and tumor necrosis factor receptor-associated factor (TRAF) six.(15) Recruitment of IRAK-1 and TRAF6 potentiates expression of genes relating to cytokine and chemokine production, cell survival, proliferation, apoptosis, and other factors that can promote carcinogenesis and disease progression, primarily via NF-kB activation.(15)

PCa patients, regardless of disease stage, display significantly higher serum levels of IL-1b compared to healthy males suggesting serum IL-1b may be a viable prognostic factor.(15) Available research suggests this cytokine is in fact capable of stimulating multiple disease-promoting mechanisms including angiogenesis, sustained inflammatory signaling, and skeletal lysis and metastasis.(15) It is capable of promoting onset of angiogenesis through the activation of transcription factors such as NF-kB and AP-1, and via upregulation of hypoxia inducible transcription factor-1α (HIF-α), a transcription factor for vascular endothelial growth factor (VEGF), and cyclooxygenase-2 (COX-2), a pro-inflammatory enzyme that promotes angiogenic activity and migration of COX-2-expressing macrophages to sites of inflammation.(15,23)

3.2.4 MCP-1

The complex tissues that comprise solid tumors are more than just cancer epithelial cells.(19) Fibroblasts, adipose cells, and TAMs are some of the main non-cancer cells present in the TME of solid tumors.(19) It should be emphasized that in an obese state, with the presence of increased fat tissue, the recruitment of these cell types, especially macrophages, may be induced. Macrophages originate as blood monocytes and get recruited by tumor-derived chemokines, such as CCL2 (also known as monocyte chemoattractant molecule or MCP-1). This molecule is a chemotactic factor for monocytes and other immune cells such as NK cells and memory T lymphocytes, hence being one of the main modulators of macrophage recruitment and it has been significantly correlated with macrophage accumulation in tumors and associated with cytokines typically secreted by TAMs.(4,6,19,24) Its biological effects are mediated through its receptor, CCR2, which has both pro-inflammatory and anti-inflammatory effects.(24) The pro-inflammatory effects are dependent on antigen presenting cells and T cells, while the anti-inflammatory effects are dependent on regulatory T cells(24). The

ability of MCP-1 to induce angiogenesis is based on its chemoattractant effect on monocytes and its induction of VEGF-A gene expression.(24)

Over-expression of MCP-1 and CCR2 has been observed in both primary and metastatic PCa cells, moreover higher levels of MCP-1 can be found in obese subjects compared with lean subjects, and aggressive cancer cells express higher levels of CCR2 in comparison to less aggressive or benign prostatic cells.(6,24)

MCP-1 acts through the activation of the PI3K/Akt pathway, which provides cancer cells with a survival advantage through the upregulation of survivin [a protein that is essential for cell division and can inhibit cell death].(24)

3.2.5 MIC-1

Macrophage inhibitory cytokine-1 (MIC-1) is a divergent member of the transforming growth factor-β (TGF-β) family of cytokines and is a multifunctional and secretory molecule that can exist as either dimeric or monomeric forms.(18) In addition, it represents a pro-tumorigenic and progressive marker of PCa, and recent reports have shown that MIC-1 is expressed in PCa tissues, where it can significantly influence cancer cell growth, invasion and be involved in anti-cancer therapy resistance.(18)

Recent findings suggest that a high fat diet enhances MIC-1 expression and secretion in PCa cells and that the enhanced MIC-1 stimulates the prostate stromal cells to increase the expression and secretion of pro-tumorigenic cytokines, such as IL-8 and IL-6.(18) (Figure 2)

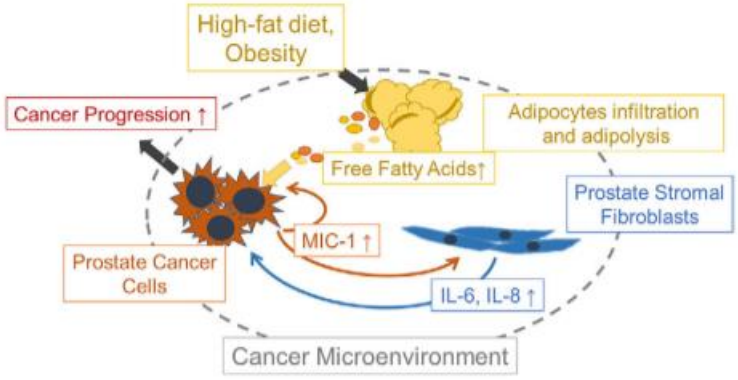

Figure 2: Schematic role of MIC-1 signaling in the PCa microenvironment induced by obesity. MIC-1 production was increased in PCa cells, which was affected by adipocyte infiltration and adipose lipolysis. MIC-1 directly stimulated surrounding prostate stromal fibroblats cells to secrete pro-tumorigenic cytokines such as IL-8 and IL-6 in the PCa stromal microenvironment, especially under an obese state. These upregulated functional cytokines directly and/or indirectly stimulated PCa cell proliferation, invasion, and metastasis.(18)

Furthermore, the enhanced free fatty acid release in periprostatic adipocytes significantly stimulated the expression and secretion of MIC-1 in PCa cells following direct co-culture with periprostatic adipocytes. Similarly, data also showed that MIC-1 is expressed and secreted with a much higher level from PCa cells than stromal cells.(18)

In addition, the binding of MIC-1 with glial-derived neurotrophic factor receptor α-like (GFRAL), its functional receptor, can activate many intracellular signaling cascades, such as AKT and anti-extracellular signal-regulated kinase (ERK) ½.(18) Multiple studies propose, that GFRAL was expressed in PCa cells and surrounding stromal fibroblasts, and the expression of GFRAL was linked with the effect of cancer neoadjuvant chemotherapy.(18) These findings strongly suggest that MIC-1/GFRAL signaling could indirectly stimulate PCa progression by promoting the expression and secretion of pro-tumorigenic cytokines from cancer stromal cells in the TME and enhance the PCa progression through the direct and/or indirect signaling cascade.(18)

3.3 Obesity, Adipokines and Prostate Cancer

Adipocytes 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.(25) Adipokines are cytokines, hormone-like polypeptides, that can exert their biological actions on target cells via endocrine, paracrine, and autocrine pathways.(13) Several of these molecules have been recognized to have multiple effects on PCa cells.

3.3.1 Leptin

Leptin is a polypeptide hormone that is mainly produced by adipocytes. In adipose tissue, the secretion levels of leptin are strictly controlled and maintain a balance to ensure adequate regulation of food intake and energy expenditure under physiological conditions.(6,25) Contrary to adiponectin, leptin levels are increased in obese individuals.(6,25) It also participates in lipogenesis and β-oxidation metabolism, which can enhance oxidative stress and, as a result, inflammation.(4) At the same time, high leptin levels attract more inflammatory cells and promote monocyte to macrophage differentiation, maintaining the obesity-associated state of chronic inflammation.(6)

Leptin has an important role in the development of a large variety of malignancies, predominantly acting through the JAK/STAT pathway, which modulates phosphatidylinositol 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) 1/2 signaling pathways increasing the expression of anti-apoptotic proteins,

inflammatory markers (TNF-α, IL-6), angiogenic factors (VEGF), and HIF-1α, thus promoting cancer cell survival, proliferation, and migration.(6)

Besides, it is essential to remark, the levels of leptin in plasma are correlated with the percentage of body fat, even though epidemiological findings are controversial regarding the association between serum leptin levels and PCa risk.(25)

Circulating leptin has been shown to be two-fold higher in PCa patients compared to healthy people and, moreover, leptin receptor expression on PCa cells has been associated with an adverse prognosis.(13) Additional, recent studies demonstrated administration of a leptin receptor antagonist decreased tumor growth and delayed progression to castration-resistant disease, in mice.(13)

Simultaneously, long-term exposure to leptin enhanced proliferation, invasion, and migration of PCa cells suggesting the participation of leptin in cell cycle progression.(25)

3.3.2 Adiponectin

Adiponectin is a protein displaying structural similarities to collagen and TNF-α.(6) It is mainly secreted by adipocytes and regulates glucose and lipid metabolism, vascular remodeling, and bone homeostasis.(6) Adiponectin promotes an increased fatty acid oxidation and glucose uptake in the liver and skeletal muscle as well as a decreased hepatic gluconeogenesis.(6) These biological effects are mediated by two transmembrane adiponectin receptors, AdipoR1 and AdipoR2, which are expressed in many tissues and activate the downstream targets AMPK, PPAR-α, and p38 MAPK.(6)

Importantly, in humans, plasma concentrations of adiponectin are significantly lower in obesity and insulin-resistant states.(6,25) Reduced adiponectin levels in the obese state lead to the development of insulin resistance and compensatory chronic hyperinsulinemia.(6) Increased insulin levels lead to reduced liver synthesis and secretion of insulin-like growth factor-binding protein (IGFBP)-1 and -2, resulting in increased levels of bioavailable insulin-like growth factor (IGF)-1. Insulin and IGF-1 promote cellular proliferation and inhibit apoptosis in many tissue types, leading to carcinogenesis.(6)

Several studies have shown adiponectin may possess anticancer properties, due to the decreased expression of adiponectin receptors in PCa tissues compared to normal prostate and is also decreased in aggressive PCa compared to indolent disease.(13)

Therefore, it has been suggested it may play an essential role in suppressing PCa cells growth through inhibition of VEGF-A-mediated cancer neovascularization.(13)

3.3.3 Visfatin

Visfatin also known as pre-B cell colony enhancing factor (PBEF) or nicotinamide phosphoribosyltransferase (NAMPT) is a protein with apparently insulin-mimetic actions and increased plasma concentrations in patients with obesity.(6,24) It stimulates glucose-induced insulin secretion in β-pancreatic cells and has been further identified in inflammatory cells with its levels being reportedly increased in various inflammatory conditions(6,24). Furthermore, it is a rate-limiting enzyme involved in the regeneration of nicotinamide adenine dinucleotide (NAD+) from nicotinamide, hence, it has an important role in many cellular functions.(24)

Visfatin has proinflammatory properties and has been shown to stimulate endothelial proliferation and capillary tube formation via the upregulation of VEGF and matrix metalloproteinases (MMP-2 and MMP-9) mediated by MAPK/PI3K-Akt/VEGF signaling pathways.(24)

Visfatin, is over-expressed in human PCa which increases PCa cell resistance to oxidative stress.(24) Conversely, its inhibition was shown to significantly suppress PCa cell growth, colony formation, and invasion, leading to apoptosis.(24)

3.3.4 BMP

Bone morphogenic proteins (BMPs) are extracellular signaling proteins with an important presence in bone and cartilage, where they regulate the neoformation and regeneration of these supporting tissues.(26) Additionally, recent studies state BMP also contributes to the modulation of cell lineage commitment, morphogenesis, differentiation, proliferation, and apoptosis.(24)

The actions of BMP are mediated through two types of transmembrane serine/threonine kinase receptor (type I and type II), and intracellular downstream signaling is through BMP-specific SMAD proteins.(24)

It should be emphasized that several studies have been conducted in order to establish the intrinsic relationship of this molecule with bone metastases in PCa. However, up to this moment, the findings have been conflicting.(24,26) BMP2, BMP4, and BMP7 are predominantly expressed in normal prostatic tissue and their expressions tend to decline

with disease progression. In contrast, BMP6 is more likely to be expressed in metastatic PCa but not in non-metastatic or benign prostate tissue.(24,26)

3.4 Obesity, IGF and Prostate Cancer

Obesity is also associated with greater circulating IGF-1 and decreased IGF-Binding Protein (IGFBP) thus, obesity establishes a physiological environment conducive toward mitogenic signaling.(15) Similar to insulin, IGF-1 is a single-chain peptide composed of 70 amino acids and shares 50% homology with insulin.(27) It is a potent mitogenic factor and mediator of JNK, p38 MAPK, and PI3K/AKT/mTOR signaling pathways which promote cell survival, growth, and proliferation.(4,15,16) Consequently, erratic regulation of the IGF-1 signaling axis may promote PCa onset or disease progression.

IGFBP3 is the most abundant circulating IGFBP, and it competitively binds to IGF-1 against the IGF-1 receptor. Consequently, IGFBP3 may inhibit cell proliferation and survival, and the loss of IGFBP3 expression may contribute to drug resistance.(24)

Circulating insulin levels correlate positively with increasing BMI.(25) These molecules are fundamental to maintain body homeostasis as well as to allow the development of any type of organ, including the normal functional prostate. Nevertheless, dysregulations on the expression of this factor may lead to irreversible phenomena that trigger tumorigenesis.(4) Concurrently, IL-6 signaling trans-activates the endocrine IGF signaling axis in cancer cells.(16)

Epidemiological data suggest that high levels of circulating IGF-1 are associated with an increased risk of PCa development, and IGF-1 signaling is elevated in PCa compared to prostate epithelium and is associated with tumor progression. In addition, overexpression of the IGF-1 receptor has been shown in PCa and higher serum IGF-1 concentrations and downregulated circulating IGFBP3 levels are correlated with an increased risk of developing PCa.(25,28)

3.5 Current developments in targeted therapy

Recent investigations have resulted in the identification of a large number of potential targets for PCa therapy. Although most established therapies target the androgen receptor (AR) or elements of the AR signaling pathway, it is clear, as mentioned earlier, that several molecules present in the TME such as cytokines contribute to growth at different stages of the prostate carcinogenesis process and may also play a role as therapeutical tools.(29)

3.5.1 IL-6 targeted therapy – Siltuximab

Therapeutic approaches in PCa could be focused on IL-6, which signaling is mediated primarily through JAK/STAT3 pathway. Therefore, intricate investigations were conducted in order to establish the monoclonal antibody siltuximab as a potential anti-IL-6 agent with therapeutical properties in the management of PCa and to establish its feasibility in combination with classical chemotherapeutic agents, such as docetaxel.(29,30) This particular combination showed preliminary evidence of clinical efficacy, subsequently further studies of this possible therapeutical combination were proposed in randomized trials.(29,30)

Although these primary results of preclinical studies with siltuximab suggested that IL-6 and downstream signaling pathways should be targeted in PCa, translation of these findings into clinical context have been associated with difficulties, such as the availability of biomarkers that may allow the selection of patients who may benefit from these therapies. These biomarkers are still not extensively available making the appropriate selection of patients a challenging task.(29)

We should also emphasize the outcome of these therapies depends on interactions with other cellular pathways as well as on drug pharmacokinetics and pharmacodynamics.(29)

3.5.2 Anti–IGF-1R targeted therapy – a possible breakthrough

IGF-1/IGF-1Receptor (IGF-1R) inhibitory agents have been established to prevent cancer development and improve survival, including a variety of human neutralizing antibodies, such as cixutumumab, a recombinant human monoclonal antibody directed at IGF-1R that induces IGF-IR internalization, leads to apoptosis and cell-cycle arrest.(27,31,32) A portion of these agents has been tested in clinical trials alone or in combination with conventional therapies in PCa to determine its efficacy and safety in recent years.(27) However, the results have been somewhat mixed due to the different disease stages and combination drugs used in different trials.(27)

We postulated cixutumumab would potentiate the antitumor activity, however, in contrast to the strong scientific rationale, this therapy showed limited antitumor activity with no objective responses or PSA value modifications in phase I studies, with a higher than anticipated incidence of adverse effects including low-grade pneumonitis and hyperglycemia, resulting in dose modifications and treatment discontinuation for some

patients.(32) Considering the reported findings, some authors state it is unlikely that another large randomized controlled trial with cixutumumab or another similar IGF-IR monoclonal antibody will be explored for PCa.(31) However, considering the heterogeneous and conflicting findings of these clinical trials, we consider there is a rationale for further investigations, particularly exploring other combinations with cixutumumab, such as docetaxel, in order to determine with certainty the efficacy, safety and feasibility of cixutumumab targeted therapies.(27)

3.6 Breast cancer targeted therapy: a possible role model for PCa

3.6.1 TNF-alfa – Infliximab

The TME that hosts breast cancer (BC) epithelial cells includes many different cell types, among which are TAMs, B lymphocytes and other immune cells, cancer-associated fibroblasts (CAFs), mesenchymal stem cells, adipocytes, myoepithelial cells, pericytes and endothelial cells are the most frequent ones.(33) Accordingly, we recognize the significant similarity in the TME of BC and PCa, hence it is plausible to correlate important insights gained from the study of targeted therapies for BC.

Furthermore, several therapeutic approaches have been studied in order to design a TNF-α-related treatment regimen in BC, either through the administration of exogenous TNF-α, as a single agent or as adjuvant therapy, or through neutralization of endogenous TNF-α by TNF antagonists.(33) Therefore, when tested in combination with doxorubicin, a standard first-line chemotherapeutic agent in BC, it improved the treatment efficacy by reducing the tumor size, in comparison to doxorubicin alone.(33) This combinatory treatment showed better results due to both the cytotoxic effects exhibited by TNF-α on the tumor cells and the increased doxorubicin concentrations found in the tumor tissues when TNF-α was added to the therapeutic regimen.(33) Consequently, TNF-α administration seems to be a useful adjuvant in combination with standard chemotherapy regimens in BC.(33) Nevertheless, we should acknowledge that, in the studies aforementioned, TNF-α was administered by intra-tumoral injection, thereby circumventing the major problem encountered in all previous clinical trials, which was systemic TNF-α toxicity.(33) Some reported symptoms in such patients include fever, chills, hypotension, fatigue, anorexia, headaches, reduced hippocampal volume, verbal memory difficulties and impaired metabolism of triglycerides.(33–35)

A particular example of the previously mentioned process is infliximab, a chimeric murine monoclonal antibody, that specifically targets TNF-α by inhibiting TNF-α mediated molecular pathways through its high affinity binding with both soluble and membrane-bound forms of this cytokine.(33,35) TNF-α administration may hold promise for future therapeutic strategies, by being capable of improving both chemotherapy and radiotherapy outcomes in BC.(33)

Consequently, as previously stated, the similarities in the tumor microenvironments of PCa and BC provide a solid basis for considering the incorporation of TNF-α antagonists in forthcoming clinical trials for PCa. The existing preclinical trials firmly endorse this proposition, whereas there is a notable scarcity of clinical research in this domain. Comprehensive clinical investigation is needed in order to reveal the precise scenarios in which TNF-α antagonists could prove beneficial as an effective targeted therapy for patients with PCa, once it proves to be an extremely promising weapon.

4. Conclusion

The current research overwhelmingly implies that obesity fosters an environment favorable to PCa development and progression.(4) The TME is a highly complex network comprised of extracellular matrix, fibroblasts, and a variety of nonmalignant cell types, including immune system cells, CAFs, myofibroblasts, vascular cells, and mesenchymal stromal cells.(12)

Numerous studies advocate obesity also promotes more aggressive and severe carcinomas, and higher BMI values contribute to that mechanism.(4) When these risk factors are combined with epigenetics, the circumstances for PCa development are generated. As a result, it's vital to understand the disease's molecular pathways, as well as how they affect metabolism in general. The modified pathways not only cause the activation of malignant mechanisms, such as increased proliferation but also cause the cell to adapt to the cancer microenvironment.(4)

As outlined in this review, research has uncovered several mechanisms by which these disease-promoting factors contribute to and facilitate several cancer hallmarks, including angiogenesis, invasion, and metastasis, sustained proliferative signaling, evasion of immune destruction, modification of cellular energetics, tumor-fueling inflammation, and destabilizing genomic structure.(15) Thus, a detailed understanding of these intrinsic and complex processes will enable us to comprehend the mechanisms by which PCa develops, as well as evades currently administered therapies.

While early research in cancer biology principally focused on the cancer cell compartment and driver mutations, we now recognize that cancer cells are only one component of the "tumor organ" in which cancer cells are one part of a complicated ecosystem. In the TME, very early peripheral immune cells, fibroblasts, cytokines, vessels, and adipocytes are recruited by the tumor to promote tumor growth.(8) Once cells are transformed, they reprogram the complicated paracrine and autocrine communication system that allows tissue homeostasis in healthy individuals, resulting in carcinogenesis.(8) A comprehensive, structured, and detailed understanding of all the participants in this carcinogenesis process, would allow for the development of new targeted and personalized therapies for the treatment of PCa.

5. Future Perspectives

The complex microenvironment that comprises PCa is more than just cancer epithelial cells. Some of the main non-cancer cells present, such as fibroblasts, adipocytes, TAMs, and CAA in the TME play a crucial role in the initiation and progression of PCa via the secretion of proinflammatory cytokines and other inflammatory mediators.

Consequently, future research should aim to clarify and distinguish the metabolic and physiological processes of all participants in this TME, which mediate and amplify the process of prostatic carcinogenesis. Moreover, investigating the circulating factors associated with this metabolic disorder, along with understanding their influence on tumor cells, holds significant relevance and may unveil innovative therapeutic strategies. It is conceivable, in a near future, that the therapy for PCa may involve the addition of agents targeted to the tumor microenvironment in addiction with the already established and conventional treatments.

6 . References

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