

The potential value of some adipokines and cytokines as diagnostic biomarkers for prostate cancer

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ABSTRACT

Background: The role of Adipokines and proinflammatory cytokines is said to be crucial in the development of prostate cancer. Vaspin, Chemerin, Omentin, Interleukins IL-1 β , interleukin-8 (IL8), Colony-stimulating factor (GM-CSF) and CC chemokine ligand 18 (CCL18) have all been proven to take part in tumor growth and progression.

Aim of the study: The study aimed to explore circulating novel adipocytokines, such as serum of Vaspin, Chemerin and Omentin levels in patients with prostate cancer and to determine the level of selected proinflammatory cytokines (CCL18, IL-8, IL1, and GM-CSF).

Methods: Three groups were included in the current study: Group (1) :32 patients with metastatic prostate cancer who received chemotherapy, Group (2): 30 untreated patients with nonmetastatic prostate cancer, and Group (3): 30 healthy controls. ELISA technique was used to assess serum levels of Vaspin, Chemerin, Omentin, CCL18, IL-8, IL1, and GM-CSF).

Results: The Prostate cancer group exhibited higher serum levels of Vaspin, Chemerin, Omentin, CCL18, IL-8, IL1, and GM-CSF compared to the control group. Chemotherapy-treated patients exhibited significantly increased levels of the pro-inflammatory cytokines (IL-8) and Adipokines (Vaspin and Omentin) and decreased levels of the pro-inflammatory cytokines (IL-1) and Adipokines (Chemerin). The correlation analysis showed a significant positive correlation of serum Chemerin with Vaspin ($r = 0.957$, $p\text{-value} < 0.0001$), IL-8 ($r = 0.9475$, $p\text{-value} < 0.0001$) and IL-1 β ($r = 0.7771$, $p\text{-value} < 0.0029$). Omentin and GS-CSF levels showed a non-significant positive correlation with Chemerin level ($r = 0.1259$; $p = 0.6967$.) and ($r = 0.4247$; $p = 0.1688$), respectively. While significant negative correlation was found between (Chemerin) with CCL-18 ($r = -0.7916$, $p = 0.0022$), serum Vaspin was significantly and negatively correlated with the levels of CCL-18 ($r = -0.9349$, $p < 0.0001$), whereas there was a significant positive correlation between Vaspin level with IL-8 ($R = 0.9995$, $p < 0.0001$); IL-1 β ($r = 0.561$, $p = 0.0057$). The data demonstrated that Vaspin was positively and non-significantly correlated with the level of GS-CSF ($r = 0.1437$, $p = 0.656$); serum Omentin was significantly and negatively correlated with the levels of GS-CSF ($r = -0.8447$, $p = 0.0005$), and CCL-18 ($r = -0.7058$, $p = 0.0103$), whereas there was a non-significant positive correlation between Omentin level with IL-8 ($r = 0.4364$, $p = 0.1561$). The data demonstrated that Omentin was negatively and non-significantly correlated with the level of IL-1 β ($r = -0.5366$, $p = 0.0786$).

Conclusions: This study indicated increased levels of serum Vaspin, Chemerin, Omentin, Interleukins IL-1 β , interleukin-8 (IL8), Colony-stimulating factor (GM-CSF) and CC chemokine ligand 18 (CCL18) in patients with Prostate cancer. These findings suggest that the cytokines, and adipokines, whose levels were elevated in the chemotherapy-treated patients may be involved in the pathophysiology of prostate cancer. Vaspin, Chemerin and Omentin might play an important role in Prostate cancer progression through their association with Adipokines and proinflammatory cytokines. More studies are needed to investigate the possible role of Vaspin, Chemerin and Omentin as potential markers in the development of Prostate cancer.

Keywords: vaspin, chemerin, omentin, interleukins IL-1 β , interleukin-8 (IL8), colony-stimulating factor (GM-CSF), CC chemokine ligand 18 (CCL18), prostate cancer

Received: 19 July 2023; Accepted: 13 October 2023; Published: 19 October 2023

INTRODUCTION

Prostate cancer is the most prevalent non-skin cancer in men and a substantial cause of male cancer-related death. This disease is distinguished by its molecular, pathological, and genetic variability. Prostate carcinogenesis is a multi-step process that begins with the creation of low-grade prostatic intraepithelial neoplasia (PINs),

followed by castration-resistant prostate cancer (CRPC), metastatic prostate cancer plastic lesions, and chronic inflammation of the prostate [1]. Multiple reasons have been given for chronic prostate inflammation, which is one of the distinguishing hallmarks of cancer and plays a vital role in the genesis and evolution of human malignancies [2]. Both genetic and environmental factors contribute to the development of prostate cancer [3].

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Vaspin (Visceral Adipose tissue-derived Serine Protease Inhibitor) expression has been confirmed in many parts of the body like the hypothalamus, pancreas, thyroid gland, ovaries, placenta, and testes, where it may play a crucial role in osteogenesis, steroidogenesis, the formation of blood vessels, and food intake. In addition, there are many studies supporting an interaction between Vaspin and cell proliferation and apoptosis, which are crucial processes for maintaining homeostasis of the body [4]. Vaspin is a new adipokine that was initially found in 2005 in white AT of Otsuka Long-Evans Takashima Fatty (OLETF) rats. It is a 395-amino acid protein belonging to the serpin family, demonstrating 40% 1-anti-trypsin similarity and exerting *in vitro* insulin-sensitizing actions by inhibiting the activity of human kallikrein 7 to prevent insulin cleavage. Similar to other adipokines such as adiponectin, the concentration of plasma Vaspin is 2.5-fold greater in women than in males [5].

Numerous studies documented that Vaspin has antiapoptotic effects by activating PI3K/AKT and mitogen-activated protein kinase/ERK signaling pathways, so it may have a critical role in cell proliferation and cancer progression. Furthermore, it has been shown that Vaspin decreased the expression of the Bcl-2-associated x protein and increased the expression of Bcl-2 in human osteoblasts [6,7].

Chemerin is a multifunctional adipokine with established roles in inflammation, adipogenesis and glucose homeostasis. Increasing evidence suggests an important function of chemerin in cancer. Chemerin's main cellular receptors, chemokine-like receptor 1 (CMKLR1), G-protein coupled receptor 1 (GPR1) and C-C chemokine receptor-like 2 (CCRL2) are expressed in most normal and tumor tissues [8]. Chemerin's role in cancer is considered controversial since it is able to exert both anti-tumoral and tumor-promoting effects, which are mediated by different mechanisms like recruiting innate immune defences or activation of endothelial angiogenesis. Chemerin may exhibit varying degrees of bioactivity and elicit pro- or anti-inflammatory effects in different biological environments [9].

Omentin, also known as intelectin-1, intestinal lactoferrin receptor, or galactofuranose-binding lectin, is a new highly expressed adipokine that is mostly secreted from the visceral compared to the subcutaneous adipose tissue [10], the plasma concentration of which changes in prostate cancer, end-stage renal disease, insulin resistance-associated conditions, such as diabetes mellitus (DM), obesity, endothelial dysfunction, and atherosclerosis. Interleukins and other inflammatory cytokines are related to the development and progression of prostate cancer [11].

The transition to the androgen-insensitive stage known as castration-resistant prostate cancer (CRPC), the worst form of prostate cancer, is likely facilitated by inflammatory pathways. The nuclear factor κ B (NF κ B) pathway, which induces a complex immune response including upregulation of prosurvival antiapoptotic pathways and proinflammatory cytokines that recruit immune cells to areas of inflammation (e.g., Interleukins IL-1, interleukins IL-8 (IL8), Colony-stimulating factor (GM-CSF), CC chemokine ligand (CCL18), is a leading candidate in this process [12].

Interleukin (IL-1) is independently responsible for determining bone-metastatic behavior and has been found in both primary prostate cancer and bone-metastatic lesions in human tissues. The co-expression of IL-1 with the NEPC marker synaptophysin in prostate cells discovered in human skeletal lesions supports the notion that this cytokine contributes to the development of bone-metastatic tumors in ADT-treated prostate cancer patients.

Interleukin8 (IL8) is a proinflammatory cytokine generated by tumor cells, macrophages, and stromal cells, among others. Numerous stimuli, including NF κ B, TNF, IL1, environmental stresses, hypoxia, chemotherapeutic drugs, steroids (e.g. dexamethasone), androgens, and estrogens, enhance secretion [13].

A tumor microenvironment composed of TRegs, M2 macrophages, and immunosuppressive mediators such as CCL18 may promote tumor formation and progression. Greater infiltration of Tregs and M2 macrophages into prostate cancer tumor tissue has been related to a worse prognosis [14].

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a glycoprotein best recognized for its involvement in myelopoiesis and myeloid cell activity. GM-CSF is generated by lymphocytes, macrophages, fibroblasts, endothelial cells, chondrocytes, and cancer cells in response to immunogenic stimuli such as cytokines and TLR agonists. The beta chain is conserved by receptors for IL-3 and IL-5. Myeloid cells, B cells, and non-hematopoietic cells such as brain cells (neurons, astrocytes, and ependymal cells), endothelial cells, and alveolar cells express GM-CSFR. Similar to other class I cytokine receptors, activation of the GM-CSF receptor involves receptor dimerization and tyrosine transphosphorylation of its cytoplasmic domains. GM-CSFR lacks intrinsic tyrosine kinase activity, hence it binds to the Janus Kinase 2 (JAK2) tyrosine kinase [15]. This investigation's goal was to identify the serum levels of three novel adipokines (Vaspin, Chemerin, and Omentin), colony-stimulating factor (GM-CSF), and CC chemokine ligand 18 (CCL18) in men with prostate cancer and to

determine the influence of chemotherapy on the concentrations of serum adipokines and proinflammatory cytokines. Furthermore, the study aimed to find the correlation between adipokines (Vaspin, Chemerin, and Omentin) and the studied parameters.

METHODS

Study population and design

A total of 92 Iraqi males were enrolled in this study and were divided into three groups: 1) the control group (N=30), which consisted of normal healthy individuals who are volunteers, 2) the untreated group (N=30), which consisted of patients with non-metastatic prostate cancer who did not receive anticancer treatment (chemotherapy), 3) the chemotherapy group with pain (N=32), which consisted of patients with metastatic prostate cancer who received three or more cycles of chemotherapy. Patients with medical conditions that may result in alterations in cytokine levels were excluded, including patients with the following conditions: active infection, rheumatoid arthritis, chronic osteoarthritis, chronic liver disease, renal failure, diabetes mellitus, and chronic low back pain. Patients receiving hormones, anti-inflammatories, corticosteroids (for any reason other than premedication for chemotherapy), or who were on immune-suppressive medications were also excluded. Approval for the study was obtained from the Ethics Committee of the Hospital and informed consent has been obtained from the participants.

Collection of Blood Samples

Five to six ml venous blood samples were drawn for each case, which were placed in gold-top serum separator tubes (SST). The samples were then allowed to stand at room temperature for ten minutes before being centrifuged at 3000 rpm for fifteen minutes. The collected serum samples were immediately transferred to Eppendorf tubes that had already been pre-labeled and coded. For a given test, these samples were frozen at -20°C.

Immunological Assays

The concentrations of Vaspin, Chemerin, Omentin, Interleukins IL-1β, Interleukin-8 (IL8), Colony-stimulating Factor (GM-CSF), and (CC) Chemokine Ligand 18 (CCL18) in serum specimens were assessed through the utilisation of the sandwich enzyme-linked immunosorbent assay (ELISA) technique and kits manufactured by the Bio Vision Company (CN:SL1824Hu, SL0438Hu, SL1293Hu, SL0984Hu, SL1004Hu, SL0800Hu and SL3509H u), respectively.

Statistical analysis

Version 9 of GraphPad Prism was the software used in the study for statistical data analysis. The data were presented in the form of bar graphs, and statistical analysis was conducted to determine the mean SD. The evaluated parameters of the study groups were compared utilising the unpaired t-test (Man-Whitney U) between patients before and after chemotherapy.

RESULTS

Serum levels of Adipokines

Serum levels of Chemerin:

The study aimed to ascertain the serum levels of chemerin in both patients diagnosed with prostate cancer and healthy individuals serving as controls. The findings of the study indicate a statistically remarkable difference (p<0.0001) in the serum levels of chemerin between patients with prostate cancer (1736±67.55 pg/mL) and healthy individuals (122.7±8.297 pg/mL) as illustrated in Table 1.

Serum levels of Vaspin

The Vaspin level in the prostate cancer group was non-significantly (P=0.0591) higher (16.12±0.6780 pg/mL) when compared to the control group {(13.25±0.9135 pg/mL) as illustrated in {Table 1}.

Serum levels of Omentin

The findings presented in Table 1 demonstrate a statistically remarkable difference between the average Omen-

Table 1. Mean±SD values of adipokines and cytokines in sera samples of control and patient groups (without receiving chemotherapy)

Parameters	Healthy controls (Mean ± SD)	Prostate cancer patients (Mean ± SD)	p-Value
Vaspin (ng/mL)	13.25±0.9135	16.12±0.6780	0.0191
Omentin (pg/mL)	116.2±10.27	123.8±3.184	0. 6217
Chemerin (pg/mL)	122.7±8.297	1736±67.55	<0.0001
IL-1β (pg/mL)	60.03±4.121	89.72±2.322	<0.0001
IL8 (pg/mL)	47.95±6.719	143.8±10.69	<0.0001
GM-CSF (pg/mL)	0.5543±0.02190	0.6473±0.007038	0.0074
CCL18 (ng/mL)	0.4138±0.03172	0.5640±0.004207	0.0030

tin-1 levels in healthy individuals and those diagnosed with prostate cancer. Specifically, the mean Omentin-1 level was 123.8 ± 3.184 pg/ml in healthy controls and 143.9 ± 5.792 pg/ml in prostate cancer patients ($P = 0.0226$), as illustrated in Table 1.

Serum levels of Interleukin-8 (IL-8)

The Interleukin-8 level in the prostate cancer group was remarkably ($P < 0.0001$) higher (143.8 ± 10.69 pg/mL) when compared to the control group (47.95 ± 6.719 pg/mL) as illustrated in Table 1.

Serum levels of Interleukin IL-1 β

The IL-1 β level in the prostate cancer group was significantly ($P < 0.0001$) higher (89.72 ± 2.322 pg/mL) when compared to the control group (60.03 ± 4.121 pg/mL) (Table 1).

Serum levels of CC chemokine ligand 18 (CCL18)

The CCL18 level in the prostate cancer group was significantly ($P = 0.0030$) higher (0.5640 ± 0.004207 pg/mL) when compared to the control group (0.4138 ± 0.03172 pg/mL) as illustrated in Table 1.

Serum levels of Colony-stimulating factor (GM-CSF)

The CCL18 level in the prostate cancer group was significantly ($P = 0.0074$) higher (0.6473 ± 0.007038 pg/mL) when compared to the control group (0.5543 ± 0.02190 pg/mL) as illustrated in Table 1.

Comparison of serum levels of adipokines and cytokines in prostate cancer patients with and without receiving chemotherapy

Comparison of Serum levels of Adipokines and chemokines before and after cycles of chemotherapy

The results indicate that, based on Table 2, two out of the three adipokines analysed exhibited a statistically significant increase in mean levels among patients who underwent chemotherapy in comparison to patients who did not get therapy for prostate carcinoma (group 2). The present study has identified two adipokines, namely Vaspin ($P < 0.0001$) and Omentin ($P = 0.0226$), as

demonstrated in Table 2.

Comparison of the cytokine levels of the sera of prostate cancer patients before and after cycles of chemotherapy

The results indicate that, based on Table 2, only one out of the four cytokines analysed exhibited a statistically significant increase in mean levels among patients who underwent chemotherapy in comparison to patients who did not get therapy for prostate carcinoma (group 2). As shown in Table 2, the mean level of Interleukins IL-1 β preceding chemotherapy was 89.72 ± 2.322 pg/mL. Following six rounds of chemotherapy, the Interleukins IL-1 β level was increased to 166.3 ± 4.627 pg/mL ($p < 0.0001$).

Interrelationships of Chemerin with interrelated studied parameters

Table 3 presents the correlation between the concentration of Chemerin and the levels of adipokines and cytokines in prostate cancer. The results of the interrelationships analysis indicated a statistically significant positive correlation between serum levels of Chemerin and Vaspin ($r = 0.957$, $p\text{-value} < 0.0001$), IL-8 ($r = 0.9475$, $p\text{-value} < 0.0001$), and IL-1 β ($r = 0.7771$, $p\text{-value} < 0.0029$). The findings indicate that there was a non-significant positive interrelationship between the levels of Omentin and GS-CSF and the level of Chemerin ($r = 0.1259$; $p = 0.6967$) and ($r = 0.4247$; $p = 0.1688$), respectively. A noteworthy adverse correlation was observed between Chemerin and CCL-18, with a correlation coefficient of -0.7916 and a $p\text{-value}$ of 0.0022 .

Interrelationships of Vaspin with interrelated studied parameters

Table 4 presents a significant and negative correlation between serum Vaspin and CCL-18 levels ($r = -0.9349$, $p < 0.0001$). Conversely, a significant positive correlation was observed between Vaspin level and IL-8 ($Rr = 0.9995$, $p < 0.0001$), as well as IL-1 β ($r = 0.561$, $p = 0.0057$). The results of the study indicate that there exists a positive correlation between Vaspin and GS-CSF levels, although this correlation is not statistically significant ($r = 0.1437$, $p = 0.656$).

Table 2. Comparison of Serum levels of Adipokines and cytokines before and after chemotherapy - eight cycles of chemotherapy

Parameters	Patient before treatment (Mean $\pm$ SD)	Patient after treatment (Mean $\pm$ SD)	p-Value
Vaspin (ng/mL)	89.72 ± 2.322	164.6 ± 4.854	< 0.0001
Omentin (pg/mL)	123.8 ± 3.184	143.9 ± 5.792	0.0226
Chemerin (pg/mL)	1736 ± 67.55	1237 ± 84.56	0.0003
IL-1 β (pg/mL)	89.72 ± 2.322	166.3 ± 4.627	< 0.0001
IL8 (pg/mL)	143.8 ± 10.69	118.7 ± 8.475	0.2044
GM-CSF (pg/mL)	0.6473 ± 0.007038	0.5806 ± 0.02945	0.0797
CCL18 (ng/mL)	0.5640 ± 0.004207	0.5336 ± 0.01575	0.3934

Table 3. Correlation coefficient (r) and significant differences between Chemerin with interrelate studied parameters

Parameters	r	p-values
Chemerin vs Vaspin	0.9570	<0.0001
Chemerin vs Omentin	0.1259	0.6967
Chemerin vs GS-CSF	0.4247	0.1688
Chemerin vs CCL 18	-0.7916	0.0022
Chemerin vs IL-8	0.9475	<0.0001
Chemerin vs IL 1β	0.7771	0.0029

Table 4. Correlation coefficient (r) and significant differences between Vaspin with interrelated studied parameters

Parameters	r	p-values
Vaspin vs GS-CSF	0.1437	0.6560
Vaspin vs CCL 18	-0.9349	<0.0001
Vaspin vs IL-8	0.9995	<0.0001
Vaspin vs IL 1β	0.5610	0.0057

Interrelationships of Omentin with interrelate studied parameters

As shown in Table (5) serum Omentin was remarkably and negatively interrelated with the levels of GS-CSF ($r = -0.8447$, $p = 0.0005$), and CCL-18 ($r = -0.7058$, $p = 0.0103$), whereas there were non-remarkable positive interrelationships between Omentin level with IL-8 ($r = 0.4364$, $p = 0.1561$). The data demonstrated that Omentin was negatively and non-significantly interrelated with the level of IL-1β ($r = -0.5266$, $p = 0.0786$).

DISCUSSIONS

According to our knowledge, this study is the first to evaluate the diagnostic and prognosis value of serum chemerin levels in both healthy people and prostate cancer patients. Chemerin serum levels were discovered to be increased in patients with prostate cancer. Chemerin is an emerging adipokine that plays a key role in adipocyte differentiation and the chemotaxis of innate immune cells [16]. The adipokine known as Chemerin and its primary receptor, CMKLR1, exhibit expression within white fatty tissue. In instances of obesity and metabolic syndrome, there is an observed elevation in the levels of this circulating adipokine. Chemerin, being a proinflam-

matory cytokine, has the ability to attract and stimulate immune cells, thereby inducing inflammation. Its function is to encourage macrophage adhesion to VCAM-1, a vascular cell adhesion molecule and fibronectin suggests a potential association between obesity and inflammation [17]. The relationship between Chemerin and malignancy is not yet completely recognized. Chemerin facilitates angiogenesis by inducing the secretion and activity of matrix metalloproteinase. Consequently, it is believed that elevated levels of Chemerin may play an initiating role in a subsequent process: carcinogenesis, followed by metastasis [18]. Furthermore, it has been demonstrated that chemerin possesses the capability to attract cytotoxic T cells, which are hypothesised to exert a significant influence on the body's immune response to neoplastic growths.

The precise understanding of the connection between prostate cancer and the modification of adipokines in the bloodstream remains incomplete. Adipose tissue dysfunction is closely correlated with obesity, and it is hypothesised that inflammation resulting from obesity plays a pivotal role in the association between being overweight and colorectal cancer [19]. Chemerin is an emerging adipokine that exerts regulatory control over a range of physiological processes, including angiogenesis, inflammation, cellular migration and proliferation, chemotaxis, homeostasis of glucose, and metabolism of lipids [20]. Although there have been reports of dysregulated Chemerin expression in tumour tissues, the findings have been inconclusive. The apparent contradictions could be explained by the fact that the expression of Chemerin may exhibit heterogeneity across various cancer types, a common phenomenon in the field of tumour biology. The study findings indicate that the circulating level of chemerin was higher in patients with prostate carcinoma as compared to the control group. Comparable outcomes were observed [21,22]. According to Erdogan et al. [21] have revealed that an increased risk of colon cancer is associated with increased levels of serum chemerin, CRP, fibrinogen, and nESR values. According to the research, the role of inflammation in the development of cancer is significant, and chemerin has the potential to serve as an inflammatory biomarker.

The current investigation aims to elucidate the importance of Vaspin in the context of prostate cancer. Vaspin has been identified as a suppressor of apoptosis through the activation of the phosphatidylinositol-3-kinase/protein kinase B pathway, which has been implicated in the pathogenesis of colorectal cancer. The prevention of programmed cell death in cells that possess the capability to transform into malignant neoplasms facilitates the development of tumours. Based on the findings of the investigation, a cumulative

Table 5. Correlation coefficient (r) and significant differences between Omentin with interrelated studied parameters

Parameters	r	p-values
Omentin vs GS-CSF	-0.8447	0.0005
Omentin vs CCL 18	-0.7058	0.0103
Omentin vs IL-8	0.4364	0.1561
Omentin vs IL 1β	-0.5266	0.0786

of three research endeavours attempted to exhibit the correlation between Vaspin and cancer. The study conducted by Fazeli and colleagues involved the comparison of Vaspin levels between a group of 39 patients with biopsy-confirmed colorectal cancer and a control group of healthy individuals. The researchers observed a significant increase in Vaspin concentrations among individuals diagnosed with colorectal cancer [23].

The absence of programmed cell death, also known as apoptosis, in malignant cells may impede their demise. There exist multiple mechanisms through which malignant cells may attain a state of resistance to apoptosis. The phenomenon may arise due to an inequilibrium between pro- and anti-apoptotic proteins or due to the involvement of the caspase enzyme family, which confers cellular morphology and restrains cell death signalling during apoptosis [24]. Vaspin may contribute to tumour formation by blocking programmed cell death through cellular mechanisms. In turn, it can enhance the proliferation of potentially cancerous cells. Nonetheless, Vaspin also seems to exhibit anti-inflammatory impacts through comparable cellular signalling pathways [25].

In recent years, significant associations between Omentin and various cancers, particularly colorectal cancer, have been established [26]. In mesothelioma, Omentin levels were also reported to be elevated [27]. The majority of investigations have documented that elevated Omentin concentrations in gastric and pancreatic cancer are independent of BMI, glucose, and lipid parameters [28]. Elevated omentin concentrations in cases of pancreatic cancer have been reported [29]. Fryczkowski et al. [30] performed a case-control investigation on a group of forty patients confirmed with prostate cancer (PC) and forty patients confirmed with benign prostatic hyperplasia (BPH). The study findings indicated that the levels of Omentin were significantly higher in patients with PC compared to those with BPH. The researchers suggest that this particular adipocytokine has the potential to function as a noninvasive biomarker for pancreatic cancer, with a probable correlation to oncogenic impacts [30].

The exact role of Omentin in the progression of cancer remains unclear, and the reasons behind the increased levels of Omentin in malignant conditions are not fully comprehended. The varying outcomes observed in *in vitro* and *in vivo* studies indicate that Omentin may serve as an inhibitor of tumour growth. Zhang et al., 2013 observed that Omentin elicited an inhibitory effect on cellular proliferation and triggered programmed cell death in HepG2 and HuH-7 cells of human liver cancer. This was achieved through the activation of the JNK signalling pathway and the promotion of p53 expression [31]. Ji et

al. reported that Omentin demonstrated the ability to impede the proliferation of colon cancer stem cells and facilitate apoptosis [32]. Based on the aforementioned results, it can be inferred that Omentin possesses anti-cancer properties, and its increased levels may serve as a compensatory mechanism. Other academics have compiled a variety of findings regarding Omentin's effect on the growth of carcinoma cells, which suggests that Omentin acts as a catalyst for the development of cancer. The study performed by Zhang et al., 2020 revealed that Omentin is expressed and secreted by colorectal carcinoma cells in nearby tissues. The hypothesis put forth by the authors posits that the adipocytokine in question facilitates the development of cancer through autocrine, paracrine, and endocrine pathways [33]. The potential carcinogenic impact of Omentin on PR may be contingent upon its ability to augment glucose uptake. The activation of PI3K/Akt signalling represents an additional feasible mechanism underlying the proliferative impact of Omentin on cells [34]. Evidence has shown that the activated PI3K/Akt/mTOR pathway plays a significant impact in the initiation of prostate cancer [35].

Prostate cancer risk and aggressiveness are associated with SNPs in cytokine genes, and inflammatory cytokines may drive inflammation-related prostate carcinogenesis. Monocytes, neutrophils, endothelium, and epithelial cells all release the proinflammatory chemokine IL8, which is expressed by cancer cells. IL8 may be influenced by inflammatory signals like IL1b, stress from chemicals and the environment, and steroid hormones like androgens. As a chemoattractant and neutrophil activator, IL8 may encourage cell division, invasion, survival, and chemoresistance. Men with prostate cancer had higher blood levels of IL-8, which is linked to worse outcomes. Additionally, it has been claimed that stroma around prostate tumours has higher levels of IL8 protein expression than stroma surrounding the prostate epithelium, which seems to be normal [36].

As the initial line of defence for the body against inflammatory stimuli like infections, prostate epithelial cells may become chronically inflamed as a result of repeated assaults from these pathogens. In research on people who had their prostates biopsied, 20% of those who had persistent prostate inflammation had their PCa identified after a 5-year follow-up. On the other hand, IL-6 and IL-8, which are implicated in the onset, continuance, and development of inflammation, are only a few of the cytokines that PCa cells produce, according to studies. IL-8 is a crucial proinflammatory cytokine that is released by a range of healthy and malignant cells from many organs, including the prostate [37]. The ability of PCa cells to spread metastatically is correlated with their ability to secrete IL-8, which is higher in androgen-

independent metastatic cells. The autocrine IL-8 production and signalling in PCa cells produce partial or total deletion of the tumour suppressor gene PTEN were less viable when IL-8 signalling was attenuated. Overall, our findings imply that IL-8 may play a key regulatory role within the tumour microenvironment and may be connected to improved angiogenesis, tumour development, and resistance to chemotherapy and androgen deprivation. However, it is uncertain what role IL-8 release by healthy prostate cells has in prostate cancer development and aggressiveness [38].

Epithelial cells release chemoattractant and proinflammatory cytokines, particularly IL-8, due to inflammation brought on by infections and other factors. Previous research looked at the relationship between PCa aggressiveness and the basal level of IL-8 production from unstimulated levels of normal prostate epithelial cells in culture. Since IL-8 is recognized to serve as an early warning system and to promote the recruitment of immune and inflammatory cells, this is extremely important that may create oxidative chemicals, possibly producing precancerous lesions by destroying cell components including DNA and cell walls. The optimal conditions for the onset and development of cancer are also created by the fact that IL-8 is a potent angiogenic agent. Others have also noted variations in the blood levels of IL-8 and other cytokine production [39] in a small panel of prostate tissues, and in situ. Numerous biological processes, such as cell signalling pathways, transcriptional and posttranscriptional regulation, and regulatory mechanisms, control IL-8 production. Deregulation of one of these biological mechanisms, resulting in elevated IL-8 secretion, may promote carcinogenesis or the spread of cancer.

The pathogenesis of prostate cancer has been attributed to the significant involvement of immune and inflammatory responses mediated by cytokines. The cytokine interleukin-1 β (IL1B) is a constituent of the interleukin-1 family, with a molecular weight of 17 kDa. Its functions are associated with the control of immunity and inflammation. The aforementioned substance is generated by various types of cells, including B-lymphocytes, macrophages, endothelial cells, fibroblasts, and dendritic cells. The gene known as IL1B is situated on chromosome 2q14 and has been observed to exhibit a correlation with several types of cancer through its expression. The presence of IL1B polymorphisms has been linked to a rise in IL1B production in comparison to the wild-type gene, as reported in a study [40].

Interleukin (IL)1-specific cytokines are produced when inflammatory cells, like monocytes and macrophages, are activated. These cytokines are essential for starting, maintaining, and increasing the inflammatory response.

Interleukin-1 (IL-1) is a prominent cytokine involved in the regulation of inflammation, playing crucial roles in tumour invasiveness and metastasis. In addition, it has been previously documented that certain genetic variants, specifically single nucleotide polymorphisms (SNPs), play a remarkable role in the susceptibility to prostate carcinoma (PCa) [41]. Single nucleotide polymorphisms (SNPs) within the gene encoding Interleukin-1 β (IL-1 β) have been associated with cytokine generation in various malignancies, including lung cancer, hepatocellular carcinoma, and gastric cancer [42]. Moreover, IL1- β polymorphisms have been found to be associated with elevated IL1- β production in breast cancer and cervical cancer as compared to individuals with the wild-type gene [43].

As a novel defined member of CC chemokines, CC chemokine ligand 18 (CCL18) was originally discovered as pulmonary and activation-regulated chemokine (PARC), dendritic cell- (DC-) chemokine 1 (DC-CK1), alternative macrophage activation-associated CC chemokine-1 (AMAC-1), and macrophage inflammatory protein-4 (MIP-4). It is predominantly produced by monocyte-derived cells with M2 phenotype. CCL18 contains an open-reading frame encoding a polypeptide of 89 amino acids. Excessive production of CCL18 in M2-macrophages was demonstrated in various chronic inflammations and fibrotic diseases.

Besides these, CCL18 has been demonstrated to promote the invasiveness of cancer cells by triggering integrin clustering and enhancing their adherence to the extracellular matrix (ECM). It is conceivable that CCL18 can act in a paracrine fashion during tumor initiation/establishment. In gastric cancer, CCL18 overexpression has been reported to be associated with better survival in patients. In opposition to gastric cancer, CCL18 could promote the tumor-malignant progression of breast cancer, ovarian cancer, and bladder cancer [44].

The mechanism of the pro-tumor activity of CCL18 can be divided into two aspects. First, it has a direct effect on the cancer cell, in particular through the PITPNM3 receptor. As a result, the migration of neoplastic cells is induced. The second aspect is the effect on non-cancerous cells, which cooperate with the neoplastic cells in the tumor. The greatest amounts of CCL18 are produced by TAMs, with CAFs producing smaller amounts. This chemokine acts on these cells in an autocrine manner. For this reason, CCL18 is essential in the interdependence of TAMs and CAFs, as well as in the influence of these cells on regulatory T cells (Treg) and tumor-associated dendritic cells (TADCs) [45].

CCL18 may have an influence on the proliferation of cancer cells. However, this effect is dependent on the type of tumor. In non-small cell lung cancer cells, CCL18

reduces proliferation. It also reduces the proliferation of pre-B acute lymphocytic leukemia cells. This effect depends on the activation of GPER1/GPR30, which leads to the disruption of the function of CXCR4. In breast cancer [46] and ovarian cancer [47], the chemokine increases the proliferation of cancer cells. Moreover, CCL18 does not affect the proliferation of gastric cancer [48] and pancreatic ductal adenocarcinoma cells [49]. At least in osteosarcoma cells, CCL18 causes an increase in the expression of the urothelial carcinoma-associated 1(UCA1), which results in the activation of the catenin pathway [50]. This in turn results in an increased proliferation and migration of these cells. It has also been shown that CCL18 can increase the expression of stem cell markers in the cells of tumors such as oral squamous cell carcinoma and squamous cell carcinoma of the head and neck [51].

Increased levels of CCL18 in the serum or the tumor are also associated with a worse prognosis for patients of cancers such as breast cancer, cutaneous T-cell lymphoma, laryngeal squamous cell carcinoma, lung cancer, oral squamous cell carcinoma, ovarian cancer, osteosarcoma, pancreatic ductal adenocarcinoma, and esophageal squamous cell carcinoma. An increased level of CCL18 in colorectal cancer and gastric adenocarcinoma is associated with a better prognosis. In non-small cell lung cancer, a greater infiltration of CCL18-producing cells is associated with a better prognosis [52], although the level of this chemokine in the plasma of patients with this type of cancer is associated with a worse prognosis. Since CCL18 has been demonstrated to be released by TAMs which play important roles in malignant diseases, CCL18 has been increasingly considered to be involved in the pathogenesis and progress of various cancers. It has been demonstrated that TAMs may enhance the growth of PCa cells and release CCL18, which brought us to the hypothesis that CCL18 might function as a tumor promoter for PCa [53].

The primary function of granulocyte-macrophage colony-stimulating factor (GM-CSF), also referred to as CSF-2, is widely recognised for its crucial involvement in immune modulation and hematopoiesis. A substantial body of experimental evidence suggests that GM-CSF, a cytokine that is commonly overexpressed in various human malignancies, serves as an effective means of immunogenic labelling for cancer cells. Within this particular framework, the majority of research endeavours have primarily concentrated on the role of this entity as an immunomodulator. Specifically, its capacity to induce the maturation of dendritic cells (DCs) and enhance the activity of monocytes and macrophages has been the primary focus of investigation. Nevertheless, recent research has indicated that GM-CSF may ad-

ditionally facilitate tumour progression in an immune-independent manner by providing support to tumour microenvironments and inducing tumour growth and metastasis. While certain studies have proposed that GM-CSF exhibits inhibitory effects on the growth and spread of tumours, a larger body of research indicates that GM-CSF actually promotes tumour progression. It is noteworthy that the granulocyte-macrophage colony-stimulating factor has also been identified as a factor that promotes tumour growth in different cancer models through autocrine or paracrine mechanisms. The phenomenon of constitutive secretion of granulocyte-macrophage colony-stimulating factor, often accompanied by the presence of the granulocyte-macrophage colony-stimulating factor receptor, has been observed in various tumour models, such as small-cell lung carcinomas and meningiomas skin carcinoma, gliomas and head and neck squamous cell carcinomas. In several experimental studies, the administration of granulocyte-macrophage colony-stimulating factor was found to induce migration of cancer cells in vitro and in vivo as well as their proliferation, irrespective of immune response, across various types of cancer, such as lung cancer cells, head and neck squamous cell carcinomas, gliomas, and skin carcinoma [54].

In brief, numerous prior investigations have demonstrated the tumour-promoting impact of granulocyte-macrophage colony-stimulating factor across various cancer types, thereby generating intriguing inquiries regarding the underlying mechanisms responsible for GM-CSF-induced cancer advancement and metastasis. Granulocyte-macrophage colony-stimulating factor (GM-CSF), which can increase the expression of matrix metalloproteinases (MMPs), makes it easier for cancer cells to grow and move, and it induces keratinocyte growth, thereby accelerating wound healing [55].

Due to the aforementioned effects, granulocyte-macrophage colony-stimulating factor has been employed in the context of adjuvant tumour therapies. Nevertheless, the significance of GM-CSF remains a subject of intense debate due to its varied impact on tumour advancement, contingent upon the specific tumour type or cancer model under consideration.

A substantial body of empirical evidence suggests that granulocyte-macrophage colony-stimulating factor has the potential to function as a factor derived from tumours, which could potentially facilitate the growth and advancement of tumours. Constitutive expression and secretion of the granulocyte-macrophage colony-stimulating factor protein have been consistently observed in various cancer models, often accompanied by the presence of its associated receptors. [56]

Elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) in the bloodstream are regarded as a potential diagnostic and prognostic indicator, suggesting an unfavourable prognosis among individuals diagnosed with colorectal cancer. The study demonstrated a remarkable interrelationship between elevated levels of the granulocyte-macrophage colony-stimulating factor protein, along with vascular endothelial growth factor and platelet-derived growth factor (PDGF), and the occurrence of invasion and an unfavourable prognosis in individuals diagnosed with head and neck cancers. In accordance with this discovery, prior research has indicated that GM-CSF facilitates the proliferation and migration of cancer cells in diverse solid tumours and cancer cell lines. The results of this investigation reveal that, apart from its role in stimulating the immune system, GM-CSF may also exert a direct influence on the advancement and infiltration of tumours. Hence, this review aims to present a comprehensive analysis of the available empirical evidence, outlining the merits and drawbacks associated with the increasing impact of GM-CSF on the process of tumorigenesis. The objective is to offer guidance for prospective investigations in this field [57].

The study found a statistically significant decrease in serum Chemerin levels among patients who received chemotherapy compared to those who did not receive any treatment for their cancer.

Fatty tissue is a significant endocrine organ that secretes multiple protein hormones that exert an impact on energy metabolism. Additionally, adipose tissue possesses various other biological properties. The bi-directional nature of the correlation between adipose tissue and cancer, as well as chemotherapy, is evident. The efficacy of chemotherapy may be influenced by the chemical configuration of Fatty tissue. In patients with breast cancer, higher levels of fatty acids, specifically docosahexaenoic acid (DHA), in adipose breast tissue have been found to enhance the extent of shrinkage of tumour following primary chemotherapy. Furthermore, certain hormones, specifically oestrogens, employed in the treatment of specific cancers have the potential to influence the concentrations of adipocytokines. Even though there is more and more evidence that adipokines may be important in different types of cancer, we don't know much about whether or not they are present and active in the serum of patients with disseminated colon cancer who are getting palliative chemotherapy.

The primary outcomes of the current investigation indicate that the administration of 5-fluorouracil and oxaliplatin in combination with 5-fluorouracil-based chemotherapy to patients with prostate cancer result-

ed in elevated levels of Vaspin and Omentin in the serum while concurrently reducing the concentration of Chemerin.

The present study did not provide a comprehensive explanation for the specific mechanism by which chemotherapy affects the production and release of adipokines. The direct or indirect influence of adipose cells remains unknown. In their study, Melichar et al. found that patients with metastatic colorectal carcinoma who were treated with a combination of bevacizumab, oxaliplatin, 5-fluorouracil, and leucovorin had a significant drop in their total cholesterol (TC) and low-density lipoprotein cholesterol (LDL) levels throughout the treatment. Interestingly, the researchers also noted a significant increase in serum retinol levels during the second and third months of the chemotherapy. The impact of treatment extends to both fatty tissue and the serum lipid profile. However, additional research is necessary to elucidate the underlying mechanisms responsible for this phenomenon.

The findings of this study hold significance as they validate the impact of chemotherapy on prostate cancer patients, not only in terms of its clinical benefits on disease progression but also in terms of its positive influence on cytokine production and release. Specifically, chemotherapy has been observed to increase the levels of Vaspin and Omentin, which possess anti-angiogenic properties and inhibit cancer cell proliferation, while simultaneously decreasing the levels of Chemerin, a proangiogenic factor. The re-establishment of proper function of adipose tissue is imperative for patients to attain a favourable prognosis for survival.

Patients non-responders to treatment had more increased levels of adipokines in their plasma than subjects who were classified as partial responders (PR). This is an important finding from the current study. This distinction was observed both prior to and following chemotherapy. The findings suggest that the adipokines leptin, resistin, and visfatin could potentially serve as prognostic indicators for chemotherapy response. However, it is important to note that the limited number of cases in the PD group may somewhat diminish the robustness of this conclusion. Zemanova et al. recently conducted a study examining the potential of adipokines to serve as prognostic indicators for assessing the effectiveness of cancer therapy [58]. The researchers discovered that a considerable baseline concentration of serum adiponectin was linked to a reduction in the overall survival rate among individuals diagnosed with squamous cell esophageal cancer who underwent a multimodal treatment approach involving concurrent neoadjuvant chemoradiotherapy followed by surgical intervention.

The researchers discovered that a considerable baseline concentration of serum adiponectin was linked to a reduction in the overall survival rate among individuals diagnosed with squamous cell esophageal cancer who underwent a multimodal treatment approach involving concurrent neoadjuvant chemoradiotherapy followed by surgical intervention.

As depicted in Table 2, the average concentration of Interleukins GM-CSF prior to chemotherapy was determined to be 0.6473 ± 0.007038 pg/mL. Following the completion of six treatment courses, it was observed that the level of granulocyte-macrophage colony-stimulating factor (GM-CSF) exhibited a decrease to a mean value of 0.5806 ± 0.02945 pg/mL. ($P = 0.0797$).

As shown in Table 2, the average concentration of interleukins in GM-CSF prior to chemotherapy was determined to be 0.5640 ± 0.004207 pg/mL. Following the administration of six courses of treatment, the concentration of granulocyte-macrophage colony-stimulating factor (GM-CSF) exhibited a decrease to a mean value of 0.5336 ± 0.01575 pg/mL ($P = 0.0797$).

Despite being a common cancer treatment, chemotherapy has the potential to create a protumorigenic milieu by inducing the production of proinflammatory mediators. Chemotherapy is the standard cancer treatment, and it has an impact on a patient's immune system [59].

Despite being the cornerstones of cancer treatment, chemotherapy, targeted therapy, or radiation, tumour cells destroyed by the therapy (also known as "tumour cell debris") may play a crucial function in the tumour microenvironment to support the proliferation of lingering surviving cancer cells [60]. Chemotherapy stimulates tumour growth, angiogenesis, and metastasis by inducing macrophage chemotaxis and proinflammatory cytokines from dying tumour cells [61,62]. Cytotoxic cancer therapy is therefore a double-edged sword since, by creating a protumorigenic milieu, the exact treatment intended to stop cancer simultaneously aids in its survival and growth. Notably, paclitaxel or carboplatin, the chemotherapeutic drugs most often used to treat ovarian cancer, increase metastases in mice after a single dosage. The processes of chemotherapy-induced tumour growth, however, are still poorly understood, making it difficult to create efficient therapies [63]. The induction secretion of various protumorigenic factors, such as proangiogenic growth factors, inflammatory cytokines, chemokines, and alarmins are a negative side effect of chemotherapy. These factors work together to create a prometastatic environment that causes apoptotic tumour cells to activate macrophages to release proinflammatory lipids, such as S1P, and to up-regulate cy-

cloxygenase-2 (COX-2). Since COX-2 expression is linked to chemoresistance and a bad prognosis for patients, it is a possible therapeutic goal in ovarian cancer. Thus, mediators brought on by chemotherapy, such as cytokines and bioactive lipids, produce a protumor-genetic milieu via a variety of mechanisms [64].

The possible reason for the differences in cytokine levels we saw between the groups in our study is that immune responses change and grow over time as prostate cancer gets worse and as chemotherapy is given. The theory posits that breast cancer cells employ immunosuppressive mechanisms to evade immune cell-mediated cytotoxicity, primarily through the activation of the programmed cell death protein 1 (PD-1) pathway. This phenomenon may also contribute to the pathogenesis of breast cancer [65].

Studies have shown immunosuppression after therapy and Immunostimulation in the early stages of malignancy [66,67]. Chemotherapy-treated prostate cancer patients showed reduced inflammation, confirming the idea that cancer treatment affects the immune system. The course of depression among our participants also agrees with the research's conclusions. In the current retrospective analysis, we predicted that chemotherapy for patients with prostate cancer would cause the upregulation of various types of inflammatory cytokines. The levels of adipokines and cytokines are favourably linked with the levels of Chemerin, according to the findings of our research. The findings might be explained by the fact that both proteins are proinflammatory cytokines and participate in the development and spread of tumours.

CONCLUSIONS

In summary, our results highlight the role of serum cytokines and adipokines as potential prognostic biomarkers in prostate cancer patients, which could contribute to tumour growth and progression. These results suggest that cytokines and adipokines might represent candidate PC biomarkers.

It is concluded that the administration of palliative chemotherapy to patients with prostate cancer not only yields clinical advantages but also exerts a positive influence on the production and release of cytokines and adipokines in these individuals. In our study, it was observed that the administration of palliative chemotherapy resulted in elevated serum concentrations of Vaspin, Omentin, and IL-1 β , while causing a decrease in serum levels of Chemerin, GM-CSF, CCL18, and IL-8. These molecules have been previously identified as factors that facilitate angiogenesis and the proliferation of cancer cells in individuals diagnosed with prostate carcinoma.

Furthermore, it is worth noting that the initial levels of Chemerin, GM-CSF, CCL18, and IL8 could potentially function as prognostic markers for predicting an unfavourable reaction to chemotherapy. The findings of this investigation revealed that the cytokines, chemokines, and adipokines that exhibited increased levels in patients undergoing chemotherapy may play a role in the pathophysiology of prostate carcinoma.

ABBREVIATIONS

PCa – Prostate Cancer

PINs- Prostatic intraepithelial neoplasia

IL-1 β -Interleukins1 β

interleukin-8 (IL8),

GM-CSF-Colony-stimulating factor

CCL18-CC chemokine ligand 18

ELISA – Enzyme-linked immunosorbent assay

ACKNOWLEDGMENT

Authors are grateful to the Rzgary Hospital (Oncology unit) and Nanakaly Hospital for blood disease and cancer for providing valuable support during the collection of the data and research work.

AUTHORS' CONTRIBUTION

P. A. I. was involved in analysis of the results, data interpretation, operational completion of the study. P. A. Y. was involved in protocol development, gaining ethical approval and patient recruitment, and implementation of the study. All authors critically reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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REFERENCES

- Sharma S, Zapatero-Rodriguez J, O'Kennedy R. Prostate cancer diagnostics: Clinical challenges and the ongoing need for disruptive and effective diagnostic tools. *Biotechnology Advances*. 2017;35(2):135-49. DOI: 10.1016/j.biotechadv.2016.11.009
- Hanahan D. Hallmarks of cancer: new dimensions. *Cancer discovery*. 2022;12(1):31-46. DOI: 10.1158/2159-8290.CD-21-1059
- Sfanos KS, De Marzo AM. Prostate cancer and inflammation: the evidence. *Histopathology*. 2012;60(1):199-215. DOI: 10.1111/j.1365-2559.2011.04033.x
- Kurowska P, Mlyczyńska E, Dawid M, Jurek M, Klimczyk D, Dupont J, et al. Vaspin (SERPINA12) expression and function in endocrine cells. *Cells*. 2021;10(7):1710. DOI: 10.3390/cells10071710
- Zhang P, Wang G, Gui Y, Guo Z, Ren R, Sun Y, et al. Serum vaspin as a predictor of severity and prognosis in acute ischemic stroke patients. *Nutritional Neuroscience*. 2022;25(4):737-45. DOI: 10.1080/1028415X.2020.1806191
- Agarwal S, Desai S. Vaspin and its relation to cancer. *World Academy of Sciences Journal*. 2021;3(6):1-6. DOI: 10.3892/wasj.2021.129
- Si H, Zhang Y, Song Y, Li L. Overexpression of adrenomedullin protects mesenchymal stem cells against hypoxia and serum deprivation-induced apoptosis via the Akt/GSK3 β and Bcl2 signaling pathways. *International journal of molecular medicine*. 2018;41(6):3342-52. DOI: 10.3892/ijmm.2018.3533
- Treeck O, Buechler C, Ortmann O. Chemerin and cancer. *International journal of molecular sciences*. 2019;20(15):3750. DOI: 10.3390/ijms20153750
- Groblewska M, Litman-Zawadzka A, Mroczko B. The role of selected chemokines and their receptors in the development of gliomas. *International journal of molecular sciences*. 2020;21(10):3704. DOI: 10.3390/ijms21103704
- Jaikanth C, Gurumurthy P, Cherian K, Indhumathi T. Emergence of omentin as a pleiotropic adipocytokine. *Experimental and clinical endocrinology & diabetes*. 2013;121(07):377-83. DOI: 10.1055/s-0033-1345123
- Uyeturk U, Sarici H, Kin Tekce B, Eroglu M, Kemahli E, Uyeturk U, et al. Serum omentin level in patients with prostate cancer. *Medical oncology*. 2014;31:1-5. DOI: 10.1007/s12032-014-0923-6
- Li B. Effects of NF κ B Inhibition on Macrophage-adipocytes-prostate Cancer Cell Crosstalk: University of Sheffield; 2021.
- Wang W, Nag SA, Zhang R. Targeting the NF κ B signaling pathways for breast cancer prevention and therapy. *Current medicinal chemistry*. 2015;22(2):264-89. DOI: 10.2174/0929867321666141106124315
- Davidsson S, Carlsson J, Greenberg L, Wijkander J, Söderquist B, Erlandsson A. Cutibacterium acnes induces the expression of immunosuppressive genes in macrophages and is associated with an increase of regulatory T-cells in prostate cancer. *Microbiology spectrum*. 2021;9(3):e01497-21. DOI: 10.1128/spectrum.01497-21
- Kumar A, Khani AT, Ortiz AS, Swaminathan S. GM-CSF: A double-edged sword in cancer immunotherapy. *Frontiers in Immunology*. 2022;13. DOI: 10.3389/fimmu.2022.901277
- Rourke J, Dranse H, Sinal C. Towards an integrative approach to understanding the role of chemerin in human health and disease. *Obesity Reviews*. 2013;14(3):245-62. DOI: 10.1111/obr.12009
- Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. *Nature reviews immunology*. 2011;11(2):85-97. DOI: 10.1038/nri2921

18. Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. *Biochemical and biophysical research communications*. 2010;391(4):1762-8. DOI: 10.1016/j.bbrc.2009.12.150
19. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, et al. Insulin, insulin-like growth factor-I, endogenous estradiol, and risk of colorectal cancer in postmenopausal women. *Cancer research*. 2008;68(1):329-37. DOI: 10.1158/0008-5472.CAN-07-2946
20. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. *Hormone molecular biology and clinical investigation*. 2015;21(1):57-74. DOI: 10.1515/hmbci-2014-0037
21. Erdogan S, Yilmaz FM, Yazici O, Yozgat A, Sezer S, Ozdemir N, et al. Inflammation and chemerin in colorectal cancer. *Tumor Biology*. 2016;37:6337-42. DOI: 10.1007/s13277-015-4483-y
22. Wang C, Wu WK, Liu X, To K-F, Chen GG, Yu J, et al. Increased serum chemerin level promotes cellular invasiveness in gastric cancer: a clinical and experimental study. *Peptides*. 2014;51:131-8. DOI: 10.1016/j.peptides.2013.10.009
23. Fazeli MS, Dashti H, Akbarzadeh S, Assadi M, Aminian A, Keramati MR, et al. Circulating levels of novel adipocytokines in patients with colorectal cancer. *Cytokine*. 2013;62(1):81-5. DOI: 10.1016/j.cyto.2013.02.012
24. Wong RS. Apoptosis in cancer: from pathogenesis to treatment. *Journal of experimental & clinical cancer research*. 2011;30(1):1-14. DOI: 10.1186/1756-9966-30-87
25. Danielsen SA, Eide PW, Nesbakken A, Guren T, Leithe E, Lothe RA. Portrait of the PI3K/AKT pathway in colorectal cancer. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer*. 2015;1855(1):104-21. DOI: 10.1016/j.bbcan.2014.09.008
26. Zhao X, Zhang Y, Deng L, Wang Y, Li Y, Chen M. The association between Chinese patients' elevated omentin-1 levels, their clinicopathological features, and the risk of colorectal cancer. *International journal of clinical and experimental pathology*. 2019;12(6):2264.
27. Washimi K, Yokose T, Yamashita M, Kageyama T, Suzuki K, Yoshihara M, et al. Specific expression of human intelectin-1 in malignant pleural mesothelioma and gastrointestinal goblet cells. *PLoS One*. 2012;7(7):e39889. DOI: 10.1371/journal.pone.0039889
28. Karabulut S, Afsar CU, Karabulut M, Alis H, Bozkurt MA, Aydogan F, et al. Clinical significance of serum omentin-1 levels in patients with pancreatic adenocarcinoma. *BBA clinical*. 2016;6:138-42. DOI: 10.1016/j.bbcli.2016.10.002
29. Zhou L, He W, Wang W, Zhou D. Altered circulating levels of adipokine omentin-1 in patients with prostate cancer. *OncoTargets and therapy*. 2019;12:3313. DOI: 10.2147/OTT.S197507
30. Fryczkowski M, Bułdak R, Hejmo T, Kukla M, Żwirski-Korczala K. Circulating levels of omentin, leptin, VEGF, and HGF and their clinical relevance with PSA marker in prostate cancer. *Disease markers*. 2018;2018. DOI: 10.1155/2018/3852401
31. Zhang Y-Y, Zhou L-M. Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. *European journal of pharmacology*. 2013;698(1-3):137-44. DOI: 10.1016/j.ejphar.2012.11.016
32. Ji H, Wan L, Zhang Q, Chen M, Zhao X. The effect of omentin-1 on the proliferation and apoptosis of colon cancer stem cells and the potential mechanism. *J buon*. 2019;24(1):91-8.
33. Zhang Y, Zhao X, Chen M. Autocrine action of adipokine omentin1 in the SW480 colon cancer cell line. *Oncology Letters*. 2020;19(1):892-8. DOI: 10.3892/ol.2019.11131
34. Borowski A, Siemińska L. Serum omentin levels in patients with prostate cancer and associations with sex steroids and metabolic syndrome. *Journal of Clinical Medicine*. 2020;9(4):1179. DOI: 10.3390/jcm9041179
35. Lin S, Li X, Zhang J, Zhang Y. Omentin-1: Protective impact on ischemic stroke via ameliorating atherosclerosis. *Clinica Chimica Acta*. 2021;517:31-40. DOI: 10.1016/j.cca.2021.02.004
36. Pin E, Stratton S, Belluco C, Liotta L, Nagle R, Hodge KA, et al. A pilot study exploring the molecular architecture of the tumor microenvironment in human prostate cancer using laser capture microdissection and reverse phase protein microarray. *Molecular Oncology*. 2016;10(10):1585-94. DOI: 10.1016/j.molonc.2016.09.007
37. Neveu B, Moreel X, Deschênes-Rompré M-P, Bergeron A, LaRue H, Ayari C, et al. IL-8 secretion in primary cultures of prostate cells is associated with prostate cancer aggressiveness. *Research and reports in urology*. 2014;27-34. DOI: 10.2147/RRU.S58643
38. Chaiswing L, Weiss HL, Jayswal RD, Clair DKS, Kyprianou N. Profiles of radioresistance mechanisms in prostate cancer. *Critical Reviews™ in Oncogenesis*. 2018;23(1-2). DOI: 10.1615/CritRevOncog.2018025946
39. Touvier M, Fezeu L, Ahluwalia N, Julia C, Charnaux N, Sutton A, et al. Association between prediagnostic biomarkers of inflammation and endothelial function and cancer risk: a nested case-control study. *American journal of epidemiology*. 2013;177(1):3-13. DOI: 10.1093/aje/kws359
40. Yencilek F, Yildirim A, Yilmaz SG, Altinkilic EM, Dalan AB, Bastug Y, et al. Investigation of interleukin-1 β polymorphisms in prostate cancer. *Anticancer Research*. 2015;35(11):6057-61.
41. Thibodeau S, French A, McDonnell S, Cheville J, Middha S, Tillmans L, et al. Identification of candidate genes for prostate cancer-risk SNPs utilizing a normal prostate tissue eQTL data set. *Nature communications*. 2015;6(1):8653. DOI: 10.1038/ncomms9653
42. Park M-J, Hyun M-H, Yang J-P, Yoon J-M, Park S. Effects of the interleukin-1 β -511 C/T gene polymorphism on the risk of gastric cancer in the context of the relationship between race and H. pylori infection: a meta-analysis of 20,000 subjects. *Molecular biology reports*. 2015;42:119-34. DOI: 10.1007/s11033-014-3748-7
43. Wang J, Shi Y, Wang G, Dong S, Yang D, Zuo X. The association between interleukin-1 polymorphisms and their protein expression in Chinese Han patients with breast cancer. *Molecular Genetics & Genomic Medicine*. 2019;7(8):e804. DOI: 10.1002/mgg3.804
44. Urquidí V, Kim J, Chang M, Dai Y, Rosser CJ, Goodison S. CCL18 in a multiplex urine-based assay for the detection of bladder cancer. *PLoS One*. 2012;7(5):e37797. DOI: 10.1371/journal.pone.0037797
45. Sun Z, Du C, Xu P, Miao C. Surgical trauma-induced CCL18

- promotes recruitment of regulatory T cells and colon cancer progression. *Journal of cellular physiology*. 2019;234(4):4608-16. DOI: 10.1002/jcp.27245
46. Wang L, Wang Y-x, Zhang D-z, Fang X-j, Sun P-s, Xue H-c. Let-7a mimic attenuates CCL18 induced breast cancer cell metastasis through Lin 28 pathway. *Biomedicine & Pharmacotherapy*. 2016;78:301-7. DOI: 10.1016/j.biopha.2016.01.028
 47. Wang Q, Tang Y, Yu H, Yin Q, Li M, Shi L, et al. CCL18 from tumor-cells promotes epithelial ovarian cancer metastasis via mTOR signaling pathway. *Molecular Carcinogenesis*. 2016;55(11):1688-99.. DOI: 10.1002/mc.22419
 48. Hou X, Zhang Y, Qiao H. CCL18 promotes the invasion and migration of gastric cancer cells via ERK1/2/NF- κ B signaling pathway. *Tumor Biology*. 2016;37:641-51. DOI: 10.1007/s13277-015-3825-0
 49. Meng F, Li W, Li C, Gao Z, Guo K, Song S. CCL18 promotes epithelial-mesenchymal transition, invasion and migration of pancreatic cancer cells in pancreatic ductal adenocarcinoma. *International journal of oncology*. 2015;46(3):1109-20. DOI: 10.3892/ijo.2014.2794
 50. Su Y, Zhou Y, Sun Y-j, Wang Y-L, Yin J-y, Huang Y-j, et al. Macrophage-derived CCL18 promotes osteosarcoma proliferation and migration by upregulating the expression of UCA1. *Journal of Molecular Medicine*. 2019;97:49-61. DOI: 10.1007/s00109-018-1711-0
 51. She L, Qin Y, Wang J, Liu C, Zhu G, Li G, et al. Tumor-associated macrophages derived CCL18 promotes metastasis in squamous cell carcinoma of the head and neck. *Cancer cell international*. 2018;18(1):1-14. DOI: 10.1186/s12935-018-0620-1
 52. Schmid S, Csanadi A, Kozhuharov N, Tchudjin M, Kayser C, Rawluk J, et al. CC-chemokine ligand 18 is an independent prognostic marker in lymph node-positive non-small cell lung cancer. *Anticancer Research*. 2018;38(7):3913-8. DOI: 10.21873/anticancer.12676
 53. Chen G, Liang Y-x, Zhu J-g, Fu X, Chen Y-f, Mo R-j, et al. CC chemokine ligand 18 correlates with malignant progression of prostate cancer. *BioMed research international*. 2014;2014. . DOI: 10.1155/2014/230183
 54. Hong I-S. Stimulatory versus suppressive effects of GM-CSF on tumor progression in multiple cancer types. *Experimental & molecular medicine*. 2016;48(7):e242-e. DOI: 10.1038/emmm.2016.64
 55. Rho CR, Park M-y, Kang S. Effects of granulocyte-macrophage colony-stimulating (GM-CSF) factor on corneal epithelial cells in corneal wound healing model. *PLoS One*. 2015;10(9):e0138020. DOI: 10.1371/journal.pone.0138020
 56. Urduingio RG, Fernandez AF, Moncada-Pazos A, Huidobro C, Rodriguez RM, Ferrero C, et al. Immune-Dependent and Independent Antitumor Activity of GM-CSF Aberrantly Expressed by Mouse and Human Colorectal TumorsAntitumor Activity of GM-CSF in Colorectal Tumors. *Cancer research*. 2013;73(1):395-405. DOI: 10.1158/0008-5472.CAN-12-0806
 57. Ardekani MTF, Malekzadeh M, Hosseini SV, Bordbar E, Doroudchi M, Ghaderi A. Evaluation of pre-treatment serum levels of IL-7 and GM-CSF in colorectal cancer patients. *International journal of molecular and cellular medicine*. 2014;3(1):27.
 58. Zemanová M, Staňková B, Ušiaková Z, Tvrzická E, Pazdro A, Petruželka L, et al. Serum adiponectin relates to shortened overall survival in men with squamous cell esophageal cancer treated with preoperative concurrent chemoradiotherapy: A pilot study. *Medical Science Monitor: International Medical Journal of Experimental and Clinical Research*. 2014;20:2351. DOI: 10.12659/MSM.891088
 59. Gartung A, Yang J, Sukhatme VP, Bielenberg DR, Fernandes D, Chang J, et al. Suppression of chemotherapy-induced cytokine/lipid mediator surge and ovarian cancer by a dual COX-2/sEH inhibitor. *Proceedings of the National Academy of Sciences*. 2019;116(5):1698-703. DOI: 10.1073/pnas.1803999116
 60. Haak VM, Huang S, Panigrahy D. Debris-stimulated tumor growth: a Pandora's box? *Cancer and Metastasis Reviews*. 2021;1-11. DOI: 10.1007/s10555-021-09998-8
 61. Mendoza-Reinoso V, Baek DY, Kurutz A, Rubin JR, Koh AJ, McCauley LK, et al. Unique pro-inflammatory response of macrophages during apoptotic cancer cell clearance. *Cells*. 2020;9(2):429. DOI: 10.3390/cells9020429
 62. Morana O, Wood W, Gregory CD. The apoptosis paradox in cancer. *International Journal of Molecular Sciences*. 2022;23(3):1328. DOI: 10.3390/ijms23031328
 63. Middleton JD, Fehlman J, Sivakumar S, Stover DG, Hai T. Stress-inducible gene Atf3 dictates a dichotomous macrophage activity in chemotherapy-enhanced lung colonization. *International journal of molecular sciences*. 2021;22(14):7356. DOI: 10.3390/ijms22147356
 64. Peng S, Fu Y. FYN: emerging biological roles and potential therapeutic targets in cancer. *Journal of Translational Medicine*. 2023;21(1):84. DOI: 10.1186/s12967-023-03930-0
 65. Kaplanov I, Carmi Y, Kornetsky R, Shemesh A, Shurin GV, Shurin MR, et al. Blocking IL-1 β reverses the immunosuppression in mouse breast cancer and synergizes with anti-PD-1 for tumor abrogation. *Proceedings of the National Academy of Sciences*. 2019;116(4):1361-9. DOI: 10.1073/pnas.1812266115
 66. Ghahartars M, Abtahi S, Zeinali Z, Fattahi MJ, Ghaderi A. Investigation of TNF- α and IL-6 levels in the sera of non-melanoma skin cancer patients. *Iranian biomedical journal*. 2021;25(2):88. DOI: 10.29252/ibj.25.2.88
 67. Fletcher R, Tong J, Risnik D, Leibowitz BJ, Wang Y-J, Concha-Benavente F, et al. Non-steroidal anti-inflammatory drugs induce immunogenic cell death in suppressing colorectal tumorigenesis. *Oncogene*. 2021;40(11):2035-50. DOI: 10.1038/s41388-021-01687-8

