Chapter

Obesity as a Promoter of Cancer Development and Progression

Nicole Bonan and Katie DeCicco-Skinner

Abstract

The incidence of obesity is growing worldwide. In the United States, it is now estimated that one in three adults is categorized as obese. Obesity is a risk factor for multiple forms of cancer, and obese individuals have a higher risk of death. This chapter will share insight into how obesity is associated with cancer development, progression, and drug resistance by looking at the interplay between adipocytes (fat cells) and cancer cells. In particular, we will focus on alterations that occur in an obese state and biological mechanisms such as inflammation, oxidative stress, and hormonal imbalances that contribute to increased cancer risk.

Keywords: adipocyte, adipokine, adiponectin, adipose, cancer, estrogen, HIF, hormone, hyperinsulinemia, hypoxia, IFNγ, inflammation, insulin, leptin, MAPK, obesity, resistance, T cell

1. Introduction

Obesity has reached epidemic levels in the United States, and it is a growing health concern worldwide. It is estimated that one in three adults in the US is obese, while another one in three is overweight [1]. Worldwide, obesity has close to tripled since 1975. In 2016, 13% of adults were categorized as obese and 39% as overweight [2]. Obesity is a risk factor for multiple diseases, including heart disease, stroke, type 2 diabetes, and cancer, and obese individuals have a higher risk of death [1–3]. In the US, quality-adjusted life years lost to obesity are now higher than those lost to smoking [4].

"Obesity" is most often defined by body mass index (BMI), a calculation based on a ratio of one's height and weight (kg/m^2). "Obese" refers to a BMI of 30 or more, while "overweight" is categorized as a BMI between 25–30 and "normal weight" is defined as a BMI of 18.5–25.

Cancer describes the uncontrolled growth of cells which can metastasize, or spread, to other parts of the body. It can occur in any tissue and can be caused by a variety of environmental and genetic factors. About 15–20% of all cancers are estimated to be caused by being obese or overweight [5, 6]. Obese patients diagnosed with many types of cancers tend to have a worse prognosis, increased risk of metastatic cancers, and a shorter remission period than normal weight individuals [4, 7]. However, some cancers are more strongly associated with obesity than others [4, 7], and the correlation is dependent mainly on tissue type and patient cohort [5]. Cancers that are most closely correlated with obesity include: kidney [8], endometrial [9], ovarian [8], liver [10], pancreatic [11], gastrointestinal [8], colorectal [12], prostate [13], and postmenopausal breast cancer [14]; and multiple myeloma [7, 8, 15, 16]. Postmenopausal women are an

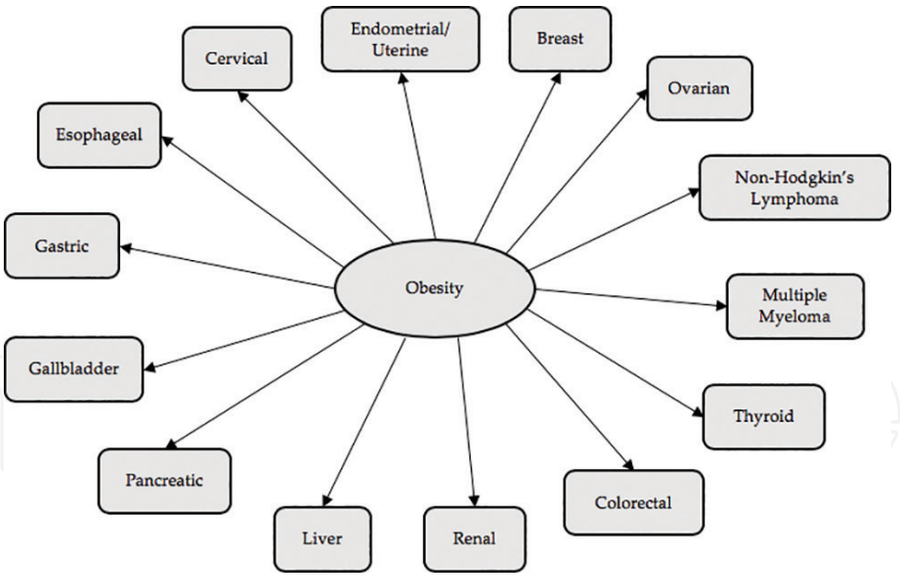

Figure 1.
Obesity can increase the risk of many cancers, including: cervical, endometrial, uterine, breast, ovarian, thyroid, colorectal, renal, liver, pancreatic, gallbladder, gastric, and esophageal cancer; non-Hodgkin's lymphoma; and multiple myeloma.

especially susceptible patient cohort, as half of all cancers in this group are caused by obesity [5]. The most common cancers caused by obesity in post-menopausal women are breast, endometrial, and ovarian cancers (**Figure 1**).

Besides storing lipids, adipose tissue is increasingly being recognized as the largest endocrine organ in the body. The adipose tissue itself is comprised of multiple cell types, including adipocytes, immune cells, and endothelial cells, among others [17]. Adipocytes themselves can secrete a variety of adipokines, hormones, and inflammatory factors [17]. As such, adipocytes are involved in signaling pathways with neighboring cells. Signaling mechanisms in the adipose tissue are altered by obesity and can contribute to cancer development, progression, and drug resistance. Cancers that are in direct contact with adipocytes, such as breast cancer, and even cancers that are in close proximity to adipocytes, such as colon cancer and endometrial cancer, are most susceptible to increased aggression stimulated by adipocyte signaling [17]. This chapter will focus on a few of the mechanisms through which adipocytes affect the tumor microenvironment (TME), including insulin resistance and hyperinsulinemia, sex steroid hormone signaling, changes in the adipokine profile, and chronic inflammation and hypoxia.

2. Adipose tissue

Generally, adipose tissue is divided into two main groups: visceral adipose tissue (VAT), which surrounds internal organs, and subcutaneous adipose tissue (SAT), which is located just under the skin. These two types of adipose tissue show large differences in metabolic activity and influence on disease risk [18]. Generally, both SAT and VAT increase in volume in obesity. However, too much VAT is associated with more negative health effects than SAT.

Visceral obesity, rather than subcutaneous obesity, increases the risk of multiple diseases including cancer [18]. This phenomenon is manly a result of the differing physiological roles of VAT and SAT. VAT acts as an endocrine organ and can signal other parts of the body via adipokine and cytokine secretion [18]. It also contains more immune cells and is more highly vascularized than SAT [19]. VAT adipocytes

are generally more metabolically active than SAT adipocytes [19], and as such, most of the changes that occur to adipose tissue during obesity occur in VAT rather than in SAT [19]. Overall, VAT is a stronger predictor of mortality due to obesity than SAT [19], especially when the VAT surrounding abdominal organs is high [18].

SAT acts as more of a storage tissue than VAT, as SAT adipocytes absorb free fatty acids and store them as triglycerides [19]. Increased SAT is generally not strongly associated with obesity-related cancers [18], with the exception of abdominal SAT. Multiple studies have shown that increased abdominal SAT can promote cancer growth progression, sometimes independently of overall adiposity [15, 20]. SAT (excluding abdominal SAT) has actually shown a somewhat protective role in cancer. Patients with more SAT generally have increased survival rates after treatment than those with less SAT [21].

This paper will focus on VAT, as this tissue type is most strongly correlated with cancer risk. Thus, references made to obesity and adipocytes throughout the rest of this paper refer to VAT.

3. Insulin resistance and hyperinsulinemia

Insulin is a hormone that is primarily responsible for stimulating glucose uptake and storage, but it is involved in multiple evolutionarily conserved pathways involving cell growth and proliferation [22, 23]. This pluripotency is not unusual. Signaling pathways related to nutrient availability and growth are closely related, as uptake of nutrients is essential for supporting growth on both a systemic and intracellular level in the body [24].

Obesity, which is characterized by an excess of nutrient availability, stimulates the body to increase insulin secretion and continually activate growth pathways. In this way, obesity can change the balance of inter- and intracellular signaling that controls cycle progression, growth, proliferation, and angiogenesis. Any of these effects in excess can contribute to neoplastic transformation, and since these pathways are highly conserved and interconnected, any alterations to one pathway risk overcompensation through another [24]. Thus, the increase in insulin secretion and growth activation caused by obesity can directly contribute to tumor development and progression.

3.1 Insulin and insulin-like growth factors

Insulin is secreted by pancreatic beta cells when serum glucose levels are elevated. The insulin then enters the bloodstream and binds insulin receptors (IR) on the plasma membrane of target cells. IRs are a type of receptor tyrosine kinase (RTK). Thus, binding of the ligand causes autophosphorylation of the tyrosine residues on the cytoplasmic tails of IRs, activating signaling pathways related to cell growth, proliferation, and glucose metabolism [5, 24, 25] (**Figure 2**).

There are two isoforms of IRs that are created by alternative splicing of the insulin receptor (INSR) gene: IR-B and IR-A. IR-B is expressed at high levels in adipocytes, hepatocytes, and muscle cells, as it is the isoform that regulates glucose metabolism [26]. IR-A is usually expressed at low levels in most normal cells compared to IR-B, but it is the isoform that is often over-expressed in cancer cells [26].

Insulin-like growth factors (IGFs) are endocrine hormones that are homologous to and have a similar mechanism of action as insulin [24, 27]. While insulin is primarily involved in glucose metabolism via IR/PI3K signaling, IGFs are directly responsible for stimulating cell growth and proliferation via IGF-1 receptor

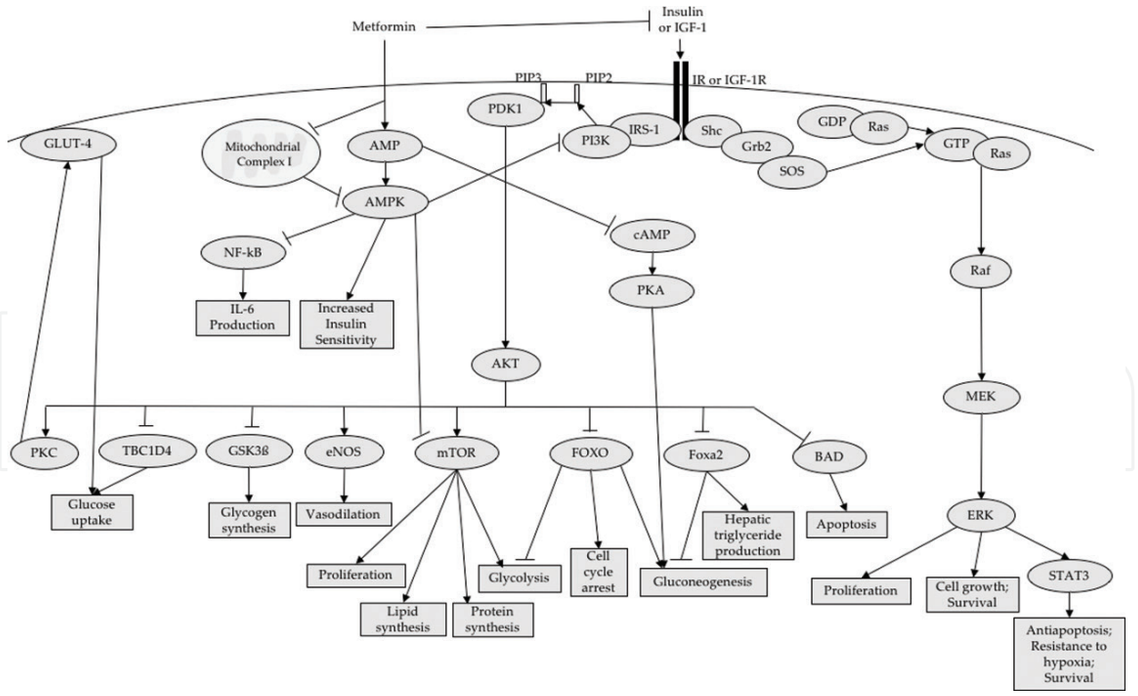

Figure 2.
IR and IGF-1R can activate the same signaling pathways. In normal cells, stimulation of either receptor activates pathways related to cell growth and proliferation. IR is also responsible for regulating glucose metabolism, while IGF-1R activates signaling pathways related to evasion of apoptosis, metastasis, and angiogenesis. In obesity, this specificity is lost. Treatment with metformin activates AMPK signaling, which blocks many of the pathways activated by AKT and can decrease tumor growth and progression.

(IGF-1R)/mitogen activated protein kinase (MAPK) signaling (**Figure 2**). However, IR and IGF-1R signaling overlap to a large extent, and the exact conditions that determine their specificity are not well understood [23].

There are two main types of IGFs, IGF-I and IGF-II, both of which are secreted by the liver in response to other growth hormones [5, 24]. Once in the tissue and bloodstream, IGFs are generally bound by IGF binding proteins (IGFBP), which both increase the half-life of IGFs [27] and prevent them from binding receptors [24, 27]. When serum glucose levels are elevated, IGFs dissociate from their binding proteins. IGF-1 can then bind IGF-1 receptor (IGF-1R), an RTK that is similar to IR [24], or, with lower affinity, IR-A [23]. Binding of IGF-1 to its receptor can activate MAPK signaling, inhibit p53, or stimulate hypoxia-inducible factor 1 alpha (HIF-1α) expression. The result of these pathways are cell growth and proliferation, evasion of apoptosis and metastasis, and angiogenesis, respectively [5]. IGF-II can bind both IGF-1R and IR-A with high affinity [5] and IR-B with low affinity [23].

Insulin and IGF signaling pathways are highly conserved, as they are essential for normal development [24, 27]. As such, disruptions in the balance of signaling through these pathways, such as changes in metabolism associated with obesity, can lead to cancer development and progression.

3.2 Insulin resistance, hyperinsulinemia, and cancer

In obese individuals, glucose is constantly produced in the liver in response to nutrient excess, and adipose tissue over-secretes insulin in response. However, chronic over-secretion of insulin can lead to insulin resistance. This condition occurs when the body only minimally responds to insulin and thus cannot metabolize glucose. To compensate, beta cells secrete even more insulin, causing hyperinsulinemia [5]. The high serum insulin levels caused by hyperinsulinemia have multiple physiological effects that can contribute to cancer progression.

High serum insulin levels can increase production of IGF-1, which, as discussed earlier, activates signaling pathways related to growth, proliferation, evasion of apoptosis and metastasis, and angiogenesis [5]. Cancer cells can then use these pathways to meet their high metabolic demands [24]. Insulin can stimulate production of growth hormone receptor (GHR), which, when bound to its ligand, stimulates hepatic synthesis of IGF-1 [5]. Insulin can also decrease production of IGFBP-1 and 2. This decrease leads to an increase in free IGF-1 in the serum [5].

Increased insulin and IGF-1 serum levels can cause overproduction and overstimulation of IR-A and IGF-1R, which is a phenomenon that is commonly observed in cancer cells [23]. The signaling pathways activated by IR and IGF-1R overlap, so overstimulation of both receptors leads to amplification of shared pathways such as mTOR and MAPK. As a result, excessive cell growth and proliferation can be stimulated [23]. The specific functions of insulin, IGFs, IR, and IGF-1R also often become convoluted in the context of cancer. In normal cells, IR is mainly responsible for controlling metabolism, while IGF-1R is more involved in regulating cell growth [23]. However, because IR and IGF-1R are highly homologous, a hybrid of the two receptors can form when they are both overexpressed. The hybrid has a higher affinity for IGF-1 than for insulin, which amplifies IGF signaling and thus contributes to cell growth, proliferation, and evasion of apoptosis. This hybrid can be expressed in normal cells, but it tends to be expressed more highly in cancer cells, especially of the breast and thyroid [5].

Some cancer treatments target IGF-1R, as this receptor is more historically known for its role in regulating cell growth. However, while preclinical studies targeting this receptor were promising, clinical studies were widely unsuccessful, and many were terminated [23, 28]. Moreover, sensitivity to IGF-1R inhibition varies widely among tumors even though most have an overexpression of IGF-1R [23, 28, 29]. Current studies are focusing on finding biomarkers that can predict sensitivity to IGF-1R inhibition [28]. Other studies aim to determine whether combination therapy might make IGF-1R inhibition more viable, such as IGF-1R inhibitors given with mTOR or IR inhibitors [28]. Since the functions of IGF-1R and IR overlap in the context of cancer, signaling through IR may be a mechanism of resistance to IGF-1R inhibitors. Some studies are researching whether targeting both IGF-1R and IR can prevent resistance from developing to IGF-1R inhibitors [23].

Other studies aim to determine whether common drugs used to treat diabetes, such as metformin, can have anti-cancer effects. So far, these studies have shown promising results. Metformin is used to decrease serum levels of insulin and hepatic glucose production in diabetic patients. However, metformin has been found to also increase AMPK production via inhibition of mitochondrial complex I. AMPK can then increase in insulin sensitivity and inhibit the mTOR/AKT pathway, which decreases glycolysis and lipid synthesis [30] (**Figure 2**). Both animal and clinical studies thus far have shown that metformin can decrease the risk of tumor development and progression, though the exact mechanisms of action of the drug have yet to be elucidated [23]. The main side effect of the drug is gastrointestinal disturbance, which occurs in about 30% of patients [30].

In summary, hyperinsulinemia is a common condition in obesity that is characterized by over-secretion of insulin and IGF-1. Both of these factors can contribute to overexpression of IR, IGF-1R, and the IR-A/IGF-1R hybrid, which can dysregulate growth and metabolism and have tumor-promoting effects.

4. Sex steroid hormones

It is already well-established that obesity can directly increase the concentration of circulating sex steroid hormones (SSH), especially estrogen. As such, obesity is a known

risk factor for cancers that can be caused in part by increased levels of these hormones, such as breast, endometrial, uterine, ovarian, and prostate cancers [5, 6, 24].

Estrogen is formed from the aromatization of androgens such as testosterone and androstenedione [24]. In premenopausal women, this aromatization takes place mainly in the ovaries [24], but it shifts to the adipose tissue and epidermis in postmenopausal women [17]. Estrogen production occurs primarily in the testes of men [31]. Once in circulation, estrogen can have multiple physiological effects.

Estrogen can bind ERs on cells to stimulate cell division [4], cell cycle progression [32], and increase proliferation and angiogenesis [24]. ER activation is a major contributor to cancer progression in ER+ breast cancers. ER+ breast cancers account for approximately 70% of human breast cancers overall [33], and obesity is known to increase the risk of these cancers in postmenopausal women [34]. In these cancers, overactive ER signaling can cause DNA damage by dysregulating genes that control cell cycle, such as Cyclin D1. Overactive ER signaling can also increase the formation of R-loops in genes that are activated by estrogen. R-loops are formed when newly-synthesized RNA binds its DNA template, and they can regulate certain aspects of transcription. However, in the context of ER overstimulation, an excess of R-loops can lead to double-stranded breaks in genes activated by estrogen, contributing to genome instability and dysregulation of cell growth and proliferation [32, 35]. Hormone therapy is often given post-surgery in ER+ breast cancers, which has been shown to improve survival and decrease the risk of relapse [33], illustrating the large extent to which ER signaling contributes to cancer progression.

The increased levels of estrogen caused by obesity can also increase IR-A expression and amplify IGF signaling in breast cancer. These factors can contribute to IGF-1R inhibitor resistance and inhibition of apoptosis, respectively, as discussed in the previous section [4, 5]. In addition, estrogen can act as a mitogen, activating MAPK pathways and RTKs that, like ER, lead to cell cycle progression, proliferation, and survival [5].

There are a few mechanisms that control the increase in circulating SSH caused by obesity. Adipose tissue can produce aromatase, and increased adiposity is correlated with an increased production of the enzyme. Aromatase stimulates the conversion of androgens to estrogens in both men and postmenopausal women. In excess, the enzyme can increase circulating concentrations of the estrogen estradiol, which can cause DNA damage as discussed [4]. This signaling mechanism is a likely explanation for why breast cancer risk increases with BMI in postmenopausal women that do not receive hormone replacement therapy [24]. Adipose tissue can also decrease production of globulins, which would otherwise bind and inhibit the activity of hormones such as estradiol [24], contributing to DNA damage.

Severe obesity can also modulate other molecules that can contribute to cancer risk and progression. The concentration of circulating glucocorticoids, hormones that act to negatively regulate cell cycle and decrease inflammation, can be downregulated [24]. Severe obesity can also stimulate an increase in serum concentrations of IGF-1 and the pro-inflammatory cytokine IL-6. Both of these molecules can activate the androgen receptor and contribute to survival and proliferation in prostate cancer [24].

5. Adipokines

Adipokines are cytokines that are secreted by adipose tissue. These adipokines can play important roles in metabolism, endocrine activities, satiety, and inflammation [5, 17, 24]. However, adipokines can also both contribute to and suppress tumorigenesis. Obesity is generally correlated with a decrease in tumor-suppressing and an increase in

tumor-promoting adipokines. There are multiple types of adipokines, but the most well-researched and abundant adipokines in the human body are leptin and adiponectin [5].

5.1 Leptin

Leptin is the most well-known adipokine, and its main function is to suppress appetite [24]. It is secreted by adipose tissue in response to nutrient availability, and it binds leptin receptors on cells such as neurons, skeletal muscle cells, adipocytes, and epithelial cells [26]. This binding signals a decrease in appetite and creates a negative feedback loop between adipose tissue and the central nervous system [24].

Leptin production increases proportionally with body fat. However, leptin resistance often develops in the context of obesity. This resistance occurs because the adipose tissue in obese patients produces excessive amounts of leptin, which overstimulates leptin receptors. The receptors then become less sensitive to the adipokine, and in response, the adipose tissue secretes even more leptin [26, 36]. As a result, obese patients often experience a dysregulation in appetite where they do not feel satiated even when their body has taken in all necessary nutrients because their bodies do not respond to leptin.

Leptin has other important physiological functions besides appetite suppression. When bound to their ligand, leptin receptors can activate the PI3K, MAPK, and JAK/STAT signaling pathways. All of these pathways lead to either inflammation, cell growth and proliferation, angiogenesis, or prevention of apoptosis [5, 24]. Since leptin is often over-secreted in obesity, this adipokine is known to contribute to the systemic inflammation observed in many obese patients [17, 24, 26], which will be discussed in later sections of this chapter.

Leptin is also a likely link between obesity and cancer. Most studies researching leptin and cancer have been done in a breast cancer model. These studies have found that leptin increases aromatase expression, which upregulates estrogen production and ER signaling [5]. As discussed previously, ER signaling stimulates cell division, proliferation, and angiogenesis, and it prevents apoptosis [4, 24], all of which can contribute to tumorigenesis and cancer progression. Other studies have found that leptin may activate proliferation and survival of cancer cells in *in vitro* models of prostate, endometrium, and colon cancer [24].

5.2 Adiponectin

Adiponectin is the most abundant cytokine in the body, and it is the main hormone produced by adipose tissue [7]. The major roles of adiponectin are to increase sensitivity to insulin [7] and increase energy expenditure [26]. By increasing insulin sensitivity, adiponectin can help prevent the development of insulin resistance and thus can help control glucose metabolism and growth [37]. Adiponectin can also inhibit angiogenesis and migration [37], stimulate apoptosis [24], and downregulate vascular endothelial adhesion molecules and decrease inflammation [37].

Adiponectin has a protective role in carcinogenesis [37], but serum levels of adiponectin tend to decrease with increased BMI and visceral adiposity [26]. Adiponectin activates the AMPK pathway, which can inhibit mTOR and cause cell cycle arrest [37]. It also inactivates MAPK1/3 and ERK1/2 and can stimulate apoptosis by inducing expression of p53 and Bax and decreasing expression of Bcl-2 [5]. However, estrogen and insulin both can suppress adiponectin secretion [5]. Thus, there is a complex balance of sex hormones, insulin, and adipokines that contribute to both obesity and cancer.

Current studies have shown the beneficial effects of adiponectin in cancer. Breast cancer risk is lower when serum levels of adiponectin are elevated in both pre and postmenopausal women [5]. Similarly, increased levels of adiponectin are associated

with decreased risk of endometrial, colon, and prostate cancers [4]. Adiponectin has also been shown to inhibit growth in *in vivo* models of all of these cancers [24]. Lower levels of adiponectin in men are correlated with a higher risk of colon cancer [5], and adiponectin has been shown to suppress the formation of colon polyps in mouse models of colon cancer [26]. In general, increased levels of adiponectin are correlated with a decrease in both the occurrence and severity of multiple cancers [5].

Other adipokines besides leptin and adiponectin exist. Resistin may be involved in promoting inflammation and angiogenesis, which can contribute to tumorigenesis [4]. Plasminogen activator inhibitor type 1 (PAI-1) is generally used as an indicator of poor prognosis in breast cancer, especially in obese women [5]. High levels of PAI-1 often indicate low peroxisome proliferator-activated receptor gamma (PPARγ) function, which is a receptor that induces apoptosis and decreases proliferation. However, PPARγ expression is often downregulated in obesity. PAI-1 can also inhibit apoptosis and induce inflammation, neutrophil recruitment, proliferation of smooth muscle cells, cell adhesion, and migration, all of which can contribute to tumorigenesis [5]. Growth-regulated oncogene alpha (GRO-α), tissue inhibitor of metalloproteinases 1 (TIMP-1), and thrombopoietin (TPO) are adipokines that tend to be over-secreted in obesity and are believed to promote carcinogenesis. GRO-α can promote inflammation and tumorigenesis; GRO-α and TIMP-1 can promote cell proliferation, angiogenesis, and prevent apoptosis; and TPO can stimulate cell proliferation and differentiation of megakaryocytes [5].

6. Inflammation and hypoxia

The chronic nutrient overload that is characteristic of obesity contributes to inflammation and hypoxia both in adipose tissue and systemically. These effects can impact the tumor microenvironment (TME) to promote tumorigenesis and cancer progression through a variety of mechanisms.

In general, chronic nutrient overload leads to chronic inflammation of the adipose tissue, which is characterized by a sustained increase in inflammatory cytokines and infiltration of macrophages. Levels of adiponectin decrease, while leptin levels increase [26]. The inflammation can also induce hypoxia in the tissue, which can in turn induce more inflammation. Hypoxia is a state of low oxygen. One of the hallmarks of hypoxia is an increase in production of reactive oxygen species (ROS), which can mutate the DNA of nearby cells. These mutations can give cells a potentially cancerous phenotype. In these ways, chronic inflammation and hypoxia can contribute to tumorigenesis and cancer progression [17].

The TME describes the cellular environment that surrounds and feeds a tumor. Once a tumor is established, cells in the TME begin to behave in ways that promote the growth of the cancer. Normal mechanisms for blocking inflammation and encouraging immune surveillance are lost, and metabolic signaling is altered in order to promote the increased energy demand of rapidly-dividing cancer cells. This section will briefly outline the role of obesity-induced inflammation and hypoxia in carcinogenesis and in the TME overall.

6.1 The role of leptin in inflammation and hypoxia

The most notable effect of chronic inflammation in adipose tissue is an over-secretion of leptin, an adipokine that was discussed previously in this chapter. Leptin can in turn induce more inflammation and hypoxia.

Leptin can stimulate cells in the TME to increase transcription of signaling molecules such as nitric oxide (NO) and cyclooxygenase-2 (COX-2) [17]. NO is

synthesized by nitric oxide synthases (NOS). The main role of NO is to respond to infection by causing inflammation and tissue damage. In excess, NO destroys enough tissue to induce a state of hypoxia, which is most often the case in the TME and in obesity. This tissue destruction stimulates more inflammation as a result of innate immune cell activation, further exacerbating the cycle. COX-2 upregulates production of prostaglandins, which are precursors for inflammation, proliferation, and survival. It is downstream of NF-kB, which can be activated by the proinflammatory cytokine IL-1β. Overexpression of COX-2 has been observed in cancers including those of the prostate, colon, breast, lung, cervix, pancreas, skin, intestine, and stomach [38], and increased IL-1β expression in tumor cells is correlated with poor prognosis [17].

Leptin can also stimulate innate immune cells in the TME to secrete proinflammatory cytokines including IL-1, IL-6, TNFα, and IFNγ. IL-1 and IL-6 are used as markers for poor prognosis in many obesity-related cancers. IL-1 can activate NF-kB signaling to stimulate cytokine production and cell survival. IL-1 signaling through NF-kB also upregulates expression of hypoxia inducible factor 1 (HIF-1) in the context of obesity-induced inflammation, which induces hypoxia in the adipose tissue and supports angiogenesis, inflammation, and increased energy metabolism [26]. HIF-1 is correlated with increased metastatic spread and poor prognosis of cancer [5].

IL-6 expression is known to be elevated in obese patients [26]. It induces hypoxia in the adipose tissue, and it also stimulates angiogenesis, proliferation, and survival via the JAK/STAT signaling pathway [17]. Like IL-6, TNFα is commonly over-expressed in obese patients. However, TNFα is involved in all stages of tumorigenesis including cell proliferation, transformation, angiogenesis, invasion, and metastasis of cancer cells. TNFα may also stimulate an increase in ROS, which, as discussed, can cause potentially carcinogenic mutations in nearby cells [26].

The role of IFNγ is closely intertwined with T cell signaling in the adipose tissue. IFNγ stimulates naïve CD4+ T cells to differentiate into the type 1 subset (Th1), and it blocks differentiation into other subsets such as type 2 and type 17 helper T cells (Th2 and Th17, respectively). Th1 cells are effector T cells that stimulate macrophages to phagocytose foreign microbes in the body, and they both secrete and are stimulated by IFNγ [39]. Thus, a positive feedback loop occurs in obesity where over-secretion of leptin promotes IFNγ secretion, which stimulates Th1 differentiation, which increases IFNγ secretion. IFNγ can then induce polarization of adipose tissue macrophages (ATMs) to the classical, or M1, phenotype. ATMs are innate immune cells that reside in the adipose tissue, and they are mainly responsible for clearing dead cells and debris [40]. Under normal conditions, the M1 phenotype generally induces an anti-microbial response [41]. It predominates in obese patients, and when activated, M1 ATMs secrete proinflammatory cytokines such as TNFα and IL-6. These cytokines can increase NO concentration in the adipose tissue and contribute to adipose tissue hypoxia. The overall result of M1 ATMs in obese patients is insulin resistance, inflammation, and hypoxia-induced tissue damage [26] (**Figure 3**).

The alternative, or M2, phenotype of ATMs generally induces immune tolerance and tissue remodeling under normal conditions [41]. It predominates in lean patients. These ATMs repair damaged tissue, prevent inflammation from starting, and inhibit insulin resistance. M2 ATMs are activated by anti-inflammatory cytokines secreted by CD4+ type 2 helper T cells (Th2), which include IL-4, IL-10, and IL-13 [26] (**Figure 3**). Since M2 polarization is blocked by IFNγ, levels of M2 ATMs tend to be reduced in obese patients [17].

6.2 The role of adipocytes in the tumor microenvironment (TME)

Cells and signaling pathways in the TME are altered by the tumor itself in order to promote cancer growth. Generally, the TME is characterized by an increase in

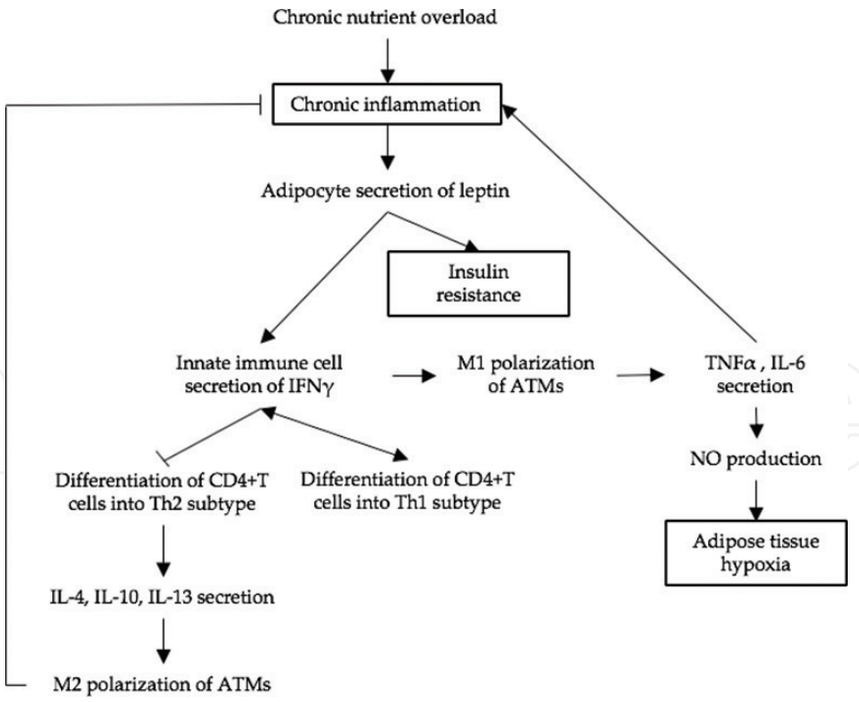

Figure 3.
Chronic nutrient overload, which is characteristic of obesity, can lead to chronic inflammation in the adipose tissue. This inflammation upregulates leptin secretion by adipocytes, which stimulates insulin resistance and IFNγ secretion by innate immune cells. IFNγ blocks differentiation of CD4+ T cells into the Th2 subtype, which would otherwise secrete anti-inflammatory cytokines, induce M2 polarization of ATMs, and block chronic inflammation. Instead, IFNγ stimulates differentiation of CD4+ T cells into the Th1 subtype, which secretes more IFNγ and induces M1 polarization of ATMs. These ATMs secrete more TNFα and IL-6, which contributes to adipose tissue hypoxia, chronic inflammation, and insulin resistance.

inflammation and a decrease in immune surveillance. Adipocytes play a central role in these processes as they are on the interface of cell metabolism and the body's immune response to the tumor. However, the role of adipocytes in the TME is still poorly understood as adipocytes were only recently recognized to have functions besides energy storage.

In direct contrast to the macrophage profile seen in obese patients, M2 macrophages in the TME exist in much higher numbers than their M1 counterparts. Tumor associated adipocytes (TAA), which are adipocytes that are in close proximity to and signal tumor cells, can induce M2 polarization [41]. The macrophages can also be repolarized, or the tumor can recruit M2 macrophages. In the TME, M2 macrophages promote tumor progression via angiogenesis, tissue repair, and secretion of anti-inflammatory cytokines. These cytokines can induce differentiation of T cells into regulatory T cells (Tregs), which prevent the host from mounting an immune response to the tumor. M1 macrophages inhibit tumorigenesis as they can recognize tumor cells as they would a foreign microbe. The M1 macrophages can then phagocytose the tumor cells or release toxins to destroy them. Thus, while M1 macrophages predominate in the adipose tissue of obese patients, the TME induces an increase in M2 polarization. In this way, the ATM profile in obesity may contribute to the inflammation needed to promote the early stages of tumor formation. In later stages, the TME flips the M1:M2 ratio in order to suppress the host's immune response [41].

One of the characteristics of obesity is increased adipocyte death. If this increase in adipocyte cell death occurs in close proximity to a tumor, it can help fuel the growing cancer. The presence of dying adipocytes recruits M1 macrophages, which form crown-like structures (CLSs) around the cells to eliminate them [41]. The CLSs cause a release of DNA from the dying adipocytes into the tissue, which is recognized by toll-like receptor 9 (TLR-9) on macrophages. The macrophages

mount a response, recruiting more monocytes to the site of the CLS and inducing more inflammation. The action of CLSs on adipocytes also causes a release of free fatty acids (FFA) into the tissue, which the tumor cells can use for fuel [41].

The "Warburg Effect" describes the change in metabolism from oxidative phosphorylation (OXPHOS) to glycolysis that cancer cells exhibit, and this change may explain some of the immunosuppressive effects of the TME. It is known that the TME has only a small number of effector T cells, which would otherwise detect and eliminate cancer cells. Most cells in the body use OXPHOS for ATP production, but activated CD8+ T cells tend to use glycolysis. Cancer cells also use glycolysis to produce ATP. As a result, cancer cells and effector T cells in the TME compete for the same nutrients. The cancer cells ultimately win, preventing the T cells from meeting their metabolic demands and halting their proliferation near the tumor [42]. Many oncogenes involve activation of glycolytic pathways, while many tumor suppressor genes induce OXPHOS. CD4+ T cells tend to be less affected by the Warburg Effect, however, as they can utilize both glycolysis and OXPHOS to produce ATP. Unstimulated T cells, which do not rapidly divide, use OXPHOS [42].

There are also other mechanisms that contribute to immune suppression in the TME. Tumor cells can stimulate macrophages to produce arginase 1 and the anti-inflammatory cytokines IL-4 and TGFβ. All three factors recruit monocytes to the tumor microenvironment, which in turn recruit tumor-associated macrophages (TAMs). TAMs have multiple effects. They secrete vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which induce angiogenesis and metastasis, respectively. TAMs also block activation of most CD8+ T cells and some CD4+ T cells, which decreases immune surveillance similarly to the Warburg Effect. At the same time, TAMs recruit Tregs to the TME and secrete TGFβ and IL-10, which induce Treg differentiation. The TGFβ can also recruit more monocytes, beginning the cycle again [17].

The presence of Tregs and the decrease in activated T cells play an important role in the ability of the cancer to develop. Tregs are immunosuppressive, and in the context of the tumor microenvironment, they prevent the host from mounting an immune response against the tumor. Interestingly, leptin can both induce and prevent differentiation of T cells into Tregs. IFNγ secretion, stimulated by leptin, can directly block Treg differentiation. However, the proinflammatory cytokines secreted by Th1 T cells, whose differentiation can be induced by leptin, can stimulate tumor cells to secrete C-C motif chemokine 22 (CCL22). This chemokine recruits Tregs to the TME [17, 42, 43]. It is important to note that while Tregs act to suppress the immune system in most cancers, there are some exceptions. Tregs can help slow tumor growth in colorectal cancers, as the Tregs can act to decrease the inflammation needed by the cancer to grow. However, this effect is likely caused by the gut microbiota [44].

The TME can also control adipose-derived stem cell (ASC) activity and fate in order to support cancer growth. ASCs are multipotent stem cells in the adipose tissue. In the context of the TME, ASCs can be induced to secrete matrix metalloproteinases (MMPs). MMPs degrade the extracellular matrix and allow cancer cells access to blood vessels to metastasize to other parts of the body. ASCs can also induce Treg differentiation in a similar manner as TAMs: via TGFβ and IL-10 secretion. Alternatively, the TME can induce ASC differentiation into cancer-associated fibroblast (CAFs) [17], which can then secrete chemokines and growth factors that activate pathways related to cell growth and survival [45].

The TME can also induce hypoxia via anaerobic respiration, even in the presence of oxygen [46]. Under hypoxic conditions, ASCs are recruited to the tissue and are stimulated to secrete VEGF. This allows formation of blood vessels and angiogenesis [17]. Adipocytes can also contribute to angiogenesis in the TME. Adipocytes

in obese patients have a higher expression of HIF-1α, which is largely because the adipocytes are rapidly expanding and proliferating in response to nutrient excess. This HIF-1α simulates VEGF secretion. Hypoxia in the adipose tissue also induces IL-6 secretion, which can promote insulin secretion [46].

HIF-1α is a transcription factor that activates hypoxia response elements. In normal conditions, it is hydrolyzed by prolyl hydroxylase domain proteins (PHDs) and ubiquitinated by Von Hippel-Lindau (VHL), which prevents the transcription factor from activating its targets. In hypoxia, however, PHDs and VHL are inhibited. HIF-1α can then bind and activate genes that induce macrophage infiltration and inflammation [46].

HIF-1α can also regulate expression of glycolytic enzymes. This effect is especially important during the metabolic reprogramming that occurs as a result of the Warburg Effect. Most notably, lactate dehydrogenase alpha (LDHα) is transactivated exclusively by HIF-1α. LDHα is responsible for converting pyruvate to lactate during glycolysis in cancer cells [46].

In addition to activating glycolytic pathways, HIF-1α can also block OXPHOS. One of the genes that HIF-1α activates is miR-210, a type of miRNA that is overexpressed in hypoxia in many cancer cells. miRNAs are small stretches of RNA that can bind an inhibit expression of target genes. As such, miR-210 is used as a biomarker for tumor hypoxia and is generally correlated with a worse prognosis. miRNAs bind mRNA to block their transcription, and miR-201 binds mRNAs that are needed for mitochondrial activity. miR-210 can also stabilize HIF-1α, which allows the transcription factor to bind and activate hypoxia-inducing genes. In this way, miR-210 can also contribute to increase hypoxia [46].

7. Conclusion

Obesity can contribute to cancer progression through a variety of mechanisms. However, the main effects of obesity in the context of cancer are activation of pathways that lead to drug resistance, inflammation, and dysregulation of sex hormones and adipokines. The adipokine leptin plays a central role in the contribution of obesity to cancer progression, as it is over-expressed in obesity and contributes to insulin secretion and inflammation. Estrogen, IGF-1, and inflammatory factors also play pivotal roles cancer progression in the context obesity. However, the mechanisms discussed in this chapter are by no means an exhaustive list of what is known, and more research must still be done to completely understand the interplay between adipose tissue and the tumor microenvironment.

IntechOpen

IntechOpen

Author details

Nicole Bonan and Katie DeCicco-Skinner*
Department of Biology, American University, Washington, DC, United States

*Address all correspondence to: decicco@american.edu

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Centers for Disease Control and Prevention. Adult Obesity Facts [Internet]. 2017. Available from: https://www.cdc.gov/obesity/data/adult.html [Accessed: Jun 8, 2018]

[2] World Health Organization. Obesity and Overweight Fact Sheet [Internet]. 2018. Available from: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight [Accessed: Jul 13, 2018]

[3] Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: Two diseases with obesity as a common risk factor. Diabetes, Obesity, and Metabolism. 2014;**16**:97-110. DOI: 10.1111/dom.12124

[4] Basen-Engquist K, Chang M. Obesity and cancer risk: Recent review and evidence. Current Oncology Reports. 2011;**13**:71-76. DOI: 10.1007/s11912-010-0139-7

[5] De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. Journal of Obesity. 2013;**2013**:1-11. DOI: 10.1155/2013/291546

[6] Ligibel JA, Alfano CM, Courneya KS, Demark-Wahnefried W, Burger RA, et al. American Society of Clinical Oncology statement on obesity and cancer. Journal of Clinical Oncology. 2014;**32**:3568-3574. DOI: 10.1200/JCO.2014.58.4680

[7] O'Flanagan CH, Bowers LW, Hursting SD. A weighty problem: Metabolic perturbations and the obesity-cancer link. Hormone Molecular Biology and Clinical Investigation. 2016;**23**:47-57. DOI: 10.1515/hmbci-2015-0022

[8] Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer—Mechanisms underlying tumor progression and recurrence. Nature Reviews Endocrinology. 2015;**10**:455-465. DOI: 10.1038/nrendo.2014.94

[9] Onstad MA, Schmandt RE, Lu KH. Addressing the role of obesity in endometrial cancer risk, prevention, and treatment. Journal of Clinical Oncology. 2016;**34**:4225-4230. DOI: 10.1200/JCO.2016.69.4638

[10] Aleksandrova K, Stelmach-Mardas M, Schlesinger S. Obesity and liver cancer. Recent Results in Cancer Research. 2014;**10**:455-465. DOI: 10.1038/nrendo.2014.94

[11] Preziosi G, Oben JA, Fusai G. Obesity and pancreatic cancer. Surgical Oncology. 2014;**23**:61-71. DOI: 10.1016/j.suronc.2014.02.003

[12] Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut. 2013;**62**:933-947. DOI: 10.1136/gutjnl-2013-304701

[13] Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL Jr, Freedland SJ. Obesity increases the risk for high-grade prostate cancer: Results from the REDUCE study. Cancer Epidemiology, Biomarkers and Prevention. 2014;**23**:2936-2942. DOI: 10.1158/1055-9965.EPI-14-0795

[14] Chan DC, Norat T. Obesity and breast cancer: Not only a risk factor. Current Treatment Options in Oncology. 2015;**16**:22. DOI: 10.1007/s11864-015-0341-9

[15] Bullwinkle EM, Parker MD, Bonan NF, Falkenberg LG, Davison SP, DeCicco-Skinner KL. Adipocytes contribute to the growth and progression of multiple myeloma: Unraveling obesity related differences in adipocyte signaling. Cancer Letters. 2016;**380**:114-121. DOI: 10.1016/j.canlet.2016.06.101

[16] National Cancer Institute at the National Institutes of Health. Cancers Associated with Overweight and Obesity [Internet]. Available from: https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/overweight-cancers-infographic [Accessed: Jun 8, 2018]

[17] Deng T, Lyon CJ, Bergin S, Caligiuri MA, Hsueh WA. Obesity, inflammation, and cancer. Annual Review of Pathology: Mechanisms of Disease. 2016;**11**:421-449. DOI: 10.1146/annurev-pathol-012615-044359

[18] Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: A clinical review of methods for visceral adipose tissue analysis. The British Journal of Radiology. 2012;**85**:1-10. DOI: 10.1259/bjr/38447238

[19] Ibrahim MM. Subutaneous and visceral adipose tissue: Structural and functional differences. Obesity Reviews. 2010;**11**:11-18. DOI: 10.1111/j.1467-789X.2009.00623.x

[20] Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB. Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: Sixteen years of follow-up in US women. Circulation. 2008;**117**:1656-1667. DOI: 10.1161/CIRCULATIONHA.107.739714

[21] Ebadi M, Martin L, Ghosh S, Field CJ, Lehner R, Baracos VE, Mazurak VC. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. British Journal of Cancer. 2017;**117**:148-155. DOI: 10.1038/bjc.2017.149

[22] De Meyts P. The insulin receptor and its signal transduction network. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext. South Dartmouth: MDText.com, Inc.; 2016

[23] Malaguarnera R, Belfiore A. The insulin receptor: A new target for cancer therapy. Frontiers in Endocrinology. 2011;**2**:93. DOI: 10.3389/fendo.2011.00093

[24] Hopkins BD, Goncalves MD, Cantley LC. Obesity and cancer mechanisms: Cancer metabolism. Journal of Clinical Oncology. 2016;**34**:4277-4283. DOI: 10.1200/JCO.2016.67.9712

[25] Haeusler RA, McGraw TE, Accili D. Biochemical and cellular properties of insulin receptor signaling. Nature Reviews. 2017;**19**:31-44. DOI: 10.1038/nrm.2017.89

[26] Tarasiuk A, Mosinska P, Fichna J. The mechanisms linking obesity to colon cancer: An overview. Obesity Research and Clinical Practice. 2018. DOI: 10.1016/j.orcp.2018.01.005

[27] Allard JB, Duan C. IGF-binding proteins: Why do they exist and why are there so many? Frontiers in Endocrinology. 2018;**9**:1-12. DOI: 10.3389/ fendo.2018.00117

[28] King H, Aleksic T, Haluska P, Macaulay VM. Can we unlock the potential of IGF-1R inhibition in cancer therapy? Cancer Treatment Reviews. 2014;**40**:1096-1105. DOI: 10.1016/j.ctrv.2014.07.004

[29] Davaadelger B, Duna L, Perez R, Gitelis S, Maki CG. Crosstalk between the IFD-1R/AKT/mTORC1 pathway and the tumor suppressors p53 and p27 determines cisplatin sensitivity and limits the effectiveness of an IGF-1R pathway inhibitor. Oncotarget. 2016;**7**:27511-27526. DOI: 10.18632/oncotarget.8484

[30] Pernicova I, Korbonits M. Metformin—Mode of action and clinical implications for diabetes and cancer. Nature Reviews Endocrinology. 2014;**10**:143-156. DOI: 10.1038/nrendo.2013.256

[31] Schulster M, Bernie AM, Ramasamy R. The role of estradiol in male reproductive function. Asian Journal of Andrology. 2016;**18**:435-440. DOI: 10.4103/1008-682X.173932

[32] Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. Cell. 2017;**168**:644-656. DOI: 10.1016/j.cell.2017.01.002

[33] Lumachi F, Brunello A, Maruzzo A, Basso U, Basso SM. Treatment of estrogen receptor-positive breast cancer. Current Medicinal Chemistry. 2013;**20**:596-604. DOI: 10.2174/092986713804999303

[34] Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA: A Cancer Journal for Clinicians. 2017;**67**:378-397. DOI: 10.3322/caac.21405

[35] Stork CT, Bocek M, Crossley MP, Sollier J, Sanz LA, Chedin F, Swigut T, Cimprich KA. Co-transcriptional R-loops are the main cause of estrogen-induced DNA damage. eLIFE Sciences. 2016;**5**:1-21. e17548. DOI: 10.7554/eLife.17548

[36] Newman G, Gonzalez-Perez RR. Leptin-cytokine crosstalk in breast cancer. Molecular and Cellular Endocrinology. 2014;**382**:570-582. DOI: 10.1016/j.mce.2013.03.025

[37] Dalamaga M, Diakopoulos KN, Mantzoros CS. The role of adiponectin in cancer: A review of current evidence. Endocrine Reviews. 2012;**33**:547-594. DOI: 10.1210/er.2011-1015

[38] DeCicco-Skinner KL, Nolan SJ, Deshpande MM, Trovato EL, Dempsey TA, Wiest JS. Altered prostanoid signaling contributes to increased skin tumorigenesis in Tpl2 knockout mice. PLoS One. 2013;**8**:e56212. DOI: 10.1371/journal.pone.0056212

[39] Abbas AK, Lichtman AH, Pillai S. Differentiation and functions of CD4+ effector T cells. In: Cellular and Molecular Immunology. 8th ed. Philadelphia: Elsevier Saunders; 2015. pp. 213-230

[40] Gerriets VA, MacIver NJ. Role of T cells in malnutrition and obesity. Frontiers in Immunoloy. 2014;**5**:379. DOI: 10.3389/fimmu.2014.00379

[41] Corrêa LH, Corrêa R, Farinasso CM, de Sant'Ana Dourado LP, Magalhães KG. Adipocytes and macrophages interplay in the orchestration of tumor microenvironment: New implications in cancer research. Frontiers in Immunology. 2017;**8**:1129. DOI: 10.3389/fimmu.201701129

[42] Kouidhi S, Noman MZ, Kieda C, Elgaaied AB, Chouaib S. Intrinsic and tumor microenvironment-induced metabolism adaptations of T cells and impact on their differentiation and function. Frontiers in Immunology. 2016;**7**:114. DOI: 10.3389/fummu.2016.00114

[43] Pucino V, De Rosa V, Procaccini C, Matarese G. Regulatory T cells, leptin, and angiogenesis. In: Marone G, Granat F, editors. Angiogenesis, Lymphangiogenesis and Clinical Implications. Basel: Karger; 2016. pp. 155-169. DOI: 10.1159/000353557

[44] Ladoire S, Martin F, Ghiringhelli F. Prognostic role of FOXP3+ regulatory T cells infiltrating human carcinomas: The paradox of colorectal cancer. Cancer Immunology, Immunotherapy. 2011;**60**:909-918. DOI: 10.1007/s00262-011-1046-y

[45] Rothenberger NJ, Somasundaram A, Stabile LP. The role of the estrogen

pathway in the tumor microenvironment. International Journal of Molecular Sciences. 2018;**19**: 1-16. DOI: 10.3390/ijms19020611

[46] Diedrich J, Gusky HC, Podgorski I. Adipose tissue dysfunction and its effects on tumor metabolism. Hormone Molecular Biology and Clinical Investigation. 2015;**21**:17-41. DOI: 10.1515/hmbci-2014-0045

IntechOpen

IntechOpen