

Multifaceted oncogenic role of adipocytes in the tumour microenvironment

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Abstract

Obesity has for decades been recognised as one of the major health concerns. Recently accumulated evidence has established that obesity or being overweight is strongly linked to an increased risk of cancer. However, it is still not completely clear how adipose tissue (fat), along with other stromal connective tissues and cells, contribute to tumour initiation and progression. In the tumour microenvironment, the adipose tissue cells, in particular the adipocytes, secrete a number of adipokines, including growth factors, hormones, collagens, fatty acids, and other metabolites as well as extracellular vesicles to shape and condition the tumour and its microenvironment. In fact, the adipocytes, through releasing these factors and materials, can directly and indirectly facilitate cancer cell proliferation, apoptosis, metabolism, angiogenesis, metastasis and even chemotherapy resistance. In this chapter, the multidimensional role played by adipocytes, a major and functional component of the adipose tissue, in promoting cancer development and progression within the tumour microenvironment will be discussed.

1 Introduction

1.1 Obesity and cancer

Changes in the environmental factors, diets, eating habits and daily lifestyles can cause an accumulation of adipose tissue in the body. This can ultimately lead to over-weight and the development of obesity, which has multiple detrimental health impacts. It is now evident that the accumulation of adipose tissue-fat, is strongly correlated with many diseases, including cancer (Zhang and Scherer, 2018). This has put obesity as one of the major health concerns, particularly with the steady rise in number of obese individuals (Calle and Kaaks, 2004).

Obesity is a pathological condition where there is excessive deposition of fat due to an imbalance between the dietary intake and energy output. The excessive energy is converted into lipids and stored primarily in the adipose tissue, ultimately leading to an increase in the mass of the individual. The expansion of this energy-rich storage is predominantly due to an increase in volume (hypertrophy) of adipocytes (fat cells) rather than an increase in number (hyperplasia) of adipocytes (Sun et al., 2011). With increased levels of fat deposition, individuals with excessive body weight are known to have elevated risks of cancers, including breast, prostate, colon and ovarian cancer. Moreover, cancer survival outcomes are also influenced by obesity. Although these observations are informative, the whole picture by which adipocytes in obese individuals contribute to cancer development is only beginning to unveil. In this chapter, we will discuss the potential mechanisms by which adipocytes can provide a favourable microenvironment for cancer initiation, progression and drug resistance.

1.2 The tumour microenvironment

Cancers are heterogeneous tissues made up of multiple components which include tumour cells and the stromal cells in the microenvironment. The stroma itself consists of connective tissues of different cell types, which function together to provide support for organs in our body. Recently, significant attention has been directed towards the interactions between the stromal and the cancer cells in the tumour microenvironment. The properties of stromal cells are known to be modified in cancer. On the other hand, these altered and sometimes deregulated stromal cells can also influence cancer progression in a positive feedforward mechanism (Hoy et al., 2017).

1.3 Adipose tissue

In our body, adipose tissues can broadly be classified into two main categories, the white adipose tissue (WAT) and the brown adipose tissue (BAT). The WAT is found predominantly at the subcutaneous, visceral organ and female mammary glands. Its main role is to store energy and regulate weight control. The BAT is found in supraclavicular regions and paracervical to control body temperature in response to the dietary intakes and the changes in the environmental temperature. In these adipose tissues, adipocytes are considered to be the major functional components (Duong et al., 2017) and account for over 20% of the adipose tissue cells (Suga et al., 2008). In humans, adipose tissues (fat) are found under the skin (subcutaneous fat), around internal organs (visceral fat), in bone marrow (yellow bone marrow), in muscles (muscle fat) and in the breast tissue (breast fat). This allows the adipocytes to be close to and crosstalk with many organs, such as the breast, prostate, colon and ovaries. For example, normal breast tissue is made up of mammary glands which are embedded in a stroma enriched with connective tissues (Hovey et al., 1999).

1.4 Adipocytes

The stromal adipose tissues consist predominantly of adipocytes, but they also contain cells including preadipocytes, fibroblasts, vascular endothelial cells and immune cells, such as macrophages. These stromal adipocytes can contribute to the cancer cell development in a variety of ways. Apart from being an energy provider, adipocytes also release into the tumour microenvironment various factors, such as adipokines, growth factors, hormones, collagens, fatty acids, extracellular vesicles and other metabolites, all of which can contribute to the cancer initiation, progression and therapeutic resistance (Park et al., 2011, Park et al., 2013).

1.5 Cancer-associated adipocytes (CAAs)

In normal breast tissue, the stroma separates the mammary glands from the adipocytes. However, during tumour development, the breast tissue undergoes extracellular matrix remodelling, resulting in the adipocytes being in closer proximity to the mammary glands (Wang et al., 1975). Similar processes are also detected during the development of other solid tumours, including that of the ovarian and prostate cancer (Finley et al., 2009, Kristin et al., 2011). This close proximity between the adipocytes and the cancer cells has profound impacts on the adipocyte development (Dirat et al., 2011). In fact, adipocytes are transformed by proximal cancer cells into cancer-associated adipocytes (CAAs) to acquire an activated phenotype that contributes to cancer invasion and progression (Dirat et al., 2011). For instance, adipocytes cultivated with breast cancer cells exhibit an activated phenotype characterized by the overexpression of proteases, such as matrix metalloproteinase-11, and proinflammatory cytokines, including interleukin (IL)-6 and IL-1 β . In agreement, histological studies also showed that adipocytes situated close to the larger tumours and/or with enhanced local invasion express higher levels of the proinflammatory cytokine IL-6 (Dirat et al., 2011). Another study using an ovarian cancer and adipocyte co-culture system as well as a mouse model also showed that adipocytes promote homing, migration and invasion of ovarian cancer cells, through overexpressing adipokines, including interleukin-8 (IL-8) (Kristin et al., 2011). The study also revealed that co-culturing with adipocytes induce the ovarian cancer cells to express the fatty acid transporter FABP4, which has a key role in promoting ovarian cancer metastasis (Kristin et al., 2011).

To date, many studies have focused on determining the role of adipose tissues, in particular adipocytes, in cancer initiation and progression. However, this was only started recently in 1992, when co-transplantation studies using murine models showed that mammary carcinoma cells grow better with fat fragments. This finding suggests that adipose tissue plays an integral part in cancer development (Elliott et al., 1992). Later in 2003, another study revealed that only mature adipocytes could facilitate tumour growth in estrogen receptor positive (ER+) breast cancer cell lines using a collagen gel matrix culture system. This differentiates the mature adipocytes from pre-adipocytes in their contributions to the cancer progression, and highlights adipocytes as a key cancer promoting component in the tumour

microenvironment (Manabe et al., 2003). Consistent with this finding, a further study in 2011 demonstrated that human adipocytes can promote the growth of ovarian cancer cells both *in vivo* and *in vitro* (Kristin et al., 2011). This finding narrows down further the mechanisms by which adipose tissue affects cancer growth. Likewise, similar observations were documented in the colon and prostate cancer and demonstrated a role for adipocytes (Tokuda et al., 2003, Aoki et al., 2007). Furthermore, another study also showed that CAAs contribute to breast cancer invasion (Dirat et al., 2011). However, recently in 2015, an *in vivo* study using breast tumours revealed that the estrogen receptor negative (ER-) breast tumours in close proximity to the adipose tissues have a low mitotic index (Han Suk et al., 2015). This observation is at odds with the results from other findings which suggested that CAAs contribute to cancer progression (Dirat et al., 2011, Kristin et al., 2011, Tokuda et al., 2003, Aoki et al., 2007). Nevertheless, the general role of the adipocytes in the cancer progression can be influenced by the tumour-type and other factors in the microenvironment.

These added layers of complexity indicate that despite plenty of evidence showing that tumour growth can be promoted by the presence of adipocytes, the complete picture of the relationships between adipocytes and cancer cells in the tumour is only beginning to be revealed.

2 Role of adipocytes and their secreted factors in cancer development

For years, adipocytes have been thought of as passive energy storage depots. However, more recent research has revealed that adipocytes also act as the sources for endocrine and paracrine factors (Darimont et al., 1994, Amri et al., 1994). These secreted factors are also known as adipokines and they consist of cytokines, chemokines, hormones and other growth factors. Other adipocyte-derived materials include fatty acids and other metabolites, which play important parts in facilitate metabolic crosstalks between adipocytes and the cancer cells (Figure 1). These factors function both locally and systemically to play distinct roles in the cancer proliferation, growth, invasion, angiogenesis and metabolism as well as therapeutic resistance (Duong et al., 2017).

2.1 Leptin

Leptin is a hormone *that* helps to control energy intake and the body weight (Zhang et al., 2005)Zhang, 1997 #234}. It is produced mainly by the adipocytes, released into the bloodstream, and received by the hypothalamus in the brain. High leptin levels cause a reduction in energy/food intake, while low levels stimulate an increase in energy/food intake and fat storage. In obese individuals, the secretion of leptin is elevated due to the increase in adipose tissues, but the brain becomes insensitive to high leptin levels. This high levels of leptin have also been found to be accompanied by the overexpression of leptin receptors in many cancer cells, such as breast and ovarian cancer (Ishikawa et al., 2004, Uddin et al., 2009).

Leptin has also been shown to function as a growth factor for cancer cells (Endo et al., 2011). Consistent with this idea, the elevated levels of leptin have been found to promote cancer cell proliferation through the activation of the extracellular signal-regulated kinase1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK) signalling pathways (Garofalo and Surmacz, 2006). This concept is further supported by three-dimensional collagen gel co-culture studies using colon cancer cells and adipocytes from leptin-deficient mice, showing that the trophic effects induced by adipocytes are abolished in leptin-deleted mice (Aoki et al., 2007). In concordance, the mammary and colorectal tumour growth is retarded in obese mice-deficient for leptin or its receptor (Endo et al., 2011, Qiao et al., 2011). Similarly, the prostate tumours induced in leptin receptor-deficient mice are significantly smaller (Ribeiro et al., 2010). However, the prostate tumours induced in the leptin-deleted mice were significantly larger. This discrepancy may be attributed to the differences in the local tumour microenvironment and the fact that leptin is also a critical regulator of the development and activation of natural killer (NK) cells (Tian et al., 1959), which have the ability to detect and kill tumour cells (Wu and Lanier, 2003).

Nonetheless, in breast cancer cells, leptin has been shown to promote cancer cell proliferation in the tumour microenvironment via activating the phosphoinositide 3-kinase (PI3K)-Akt signalling pathway and pyruvate kinase M2 expression, which are important for cell proliferation and epithelial-mesenchymal transition (EMT) (Wei et al., 2016, Qiao et al., 2011). Consistently, the elevated proliferative effects of adipocytes on cancer cells are lowered when leptin expression is depleted using short hairpin (sh) RNA (Amy et al., 2015). Collectively, these findings show leptin produced by adipocytes play a critical role in stimulating cancer cell proliferation

2.2 Adiponectin

Contrary to leptin, adiponectin is an adipokine whose plasma concentrations are significantly lower in obese individuals than in non-obese subjects (Arita et al., 1999), Exposure of cancer cells to adiponectin also causes the cancer cells to cease proliferation and undergo apoptosis, suggesting an anti-tumour role in adiponectin (Kang et al., 2005, Dieudonne et al., 2006, Ishikawa et al., 2007). In agreement, adiponectin depletion was shown to promote human breast cancer growth in nude mouse xenograft models, through activating the glycogen synthase kinase-3 β / β -catenin signalling pathway (Wang et al., 2006). Subsequently, it was discovered that adiponectin also restricts cancer cell growth through activating the 5' AMP-activated protein kinase (AMPK) as well as inhibiting the AKT, ERK1/2, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) and Wnt pathways (Dalamaga et al., 2012). Interestingly, adipocytes from the tumour microenvironment are less differentiated and secrete significantly lower amounts of adiponectin than adipocytes from normal microenvironment (Fletcher et al., 2017). As both leptin and adiponectin are antagonistic adipokines secreted by the adipocytes, the ratio of these adipokines may influence the progression of the cancers. Indeed, the balance between leptin and adiponectin is often shifted in obese individuals (Al-Hamodi et al., 2014). These observations are further supported by clinical studies showing a positive correlation between leptin/adiponectin ratio and cancer risk (Ashizawa et al., 2010).

2.3 Insulin-like growth factor 1 (IGF-1)

Another key cytokine secreted by adipocytes is insulin-like growth factor 1 (IGF-1). IGF-1 is strongly associated with cell proliferation and survival. As it is produced by adipocytes, the level of free IGF-1 is appropriately strongly associated with obesity (Nam et al., 1997). IGF-1 is an important regulator of energy metabolism and growth (Pollak, 2008). The binding of the IGF-1 to its receptors activates primarily the PI3K-AKT and Mitogen-activated protein kinases (MAPK) pathways to promote cancer cell growth and progression (Pollak, 2008). The concentration of circulating IGF-1 has also been linked to increased cancer risk (Shanmugalingam et al., 2016). Conversely, inhibition of IGF-1 receptor kinase activity limits the growth-promoting effect of adipocytes on cancer cells (D'Esposito et al., 2012). Thus, in summary, the secretion of IGF-1 by adipocytes has a direct role in stimulating the proliferation and survival of cancer cells in the tumour microenvironment and will have direct impact on cancer initiation and progression.

2.4 Vascular endothelial growth factor (VEGF) and cancer angiogenesis

When a tumour grows beyond 1-2 mm, it requires extra blood vessels to supply nutrients, oxygen and growth factors for continuous proliferation and survival. In the absence of new blood vessel formation, the expanding tumours may become starved of oxygen (a condition termed hypoxia), nutrients and growth factors and undergo necrosis or even apoptosis (Muz et al., 2015). Thus, the formation of the new blood vessels, a phenomenon known as angiogenesis, is crucial for tumour expansion (Nishida et al., 2006). Angiogenesis is tightly regulated in the microenvironment by both the cancer and the stromal cells. The adipocytes can promote new vessels formation by secreting adipokines (Cao, 2013). VEGF is a vital mediator of angiogenesis (the formation of new blood vessels) in cancer (Figure 2) (Nishida et al., 2006), and it binds VEGF receptors which are expressed on the surface of vascular endothelial cells. In response to insulin, adipocytes secrete vascular endothelial growth factor

A (VEGFA) to promote angiogenesis (Mick et al., 2002). Furthermore, leptin released by adipocytes also drives endothelial cell differentiation and proliferation (Gonzalez-Perez et al. 2013). Previous studies also showed that VEGF can also be upregulated by leptin in breast cancer cells through the transcription factors HIF-1 and NF- κ B (Gonzalez-Perez et al., 2010). However, unlike leptin, the effects of adiponectin in angiogenesis are not clear-cut. Some studies showed adiponectin as a pro-angiogenesis factor, while other studies demonstrated that it has the opposite effect (Rei et al., 2004, Man et al., 2010).

2.5 Free fatty acids, metabolites and the Warburg effect

Cancer cells reprogramme their energy metabolism to promote their growth, survival, proliferation, and self-renewal. The hallmark of this altered cancer metabolism (also called Warburg effect) to yield the extra energy needed is to increase glucose uptake and generate energy through glucose to lactate fermentation in anaerobic glycolysis, even in the presence of sufficient oxygen (Warburg, 1956). In other words, cancer cells prefer to produce adenosine triphosphate (ATP) via glycolysis instead of oxidative phosphorylation (OXPHO). The cancer-associated adipocytes have been shown to have increased secretion of inflammatory cytokines, such as TNF α , IL6 and IL-1 β , and matrix metalloproteinase 11 (MMP11), which play a key part in cancer energy metabolism by promoting metabolic switch in tumours (Ribeiro et al., 2012, Dali-Youcef et al., 2016, Dirat et al., 2011). In the tumour microenvironment, lactate and amino acids are the alternative external sources of energy available for cancer cells (Duong et al., 2017). Lately, the reverse Warburg effect has also been proposed, in which the cancer cells induce the CAFs to undergo aerobic glycolysis to produce the metabolic by-products, such as lactate and pyruvate, for the consumption of cancer cells. This induction also applies to the other stromal cells, including adipocytes, found in the tumour microenvironment (Pavlidis et al., 2009). Specifically, under hypoxic conditions, lactate is secreted by these stromal cells through monocarboxylate transporters (MCTs) into the tumour microenvironment (Gonzalez-Perez et al., 2010). The secreted lactate is then imported and metabolised by the cancer cells to produce energy and other essential metabolites (Pavlidis et al., 2009).

Nevertheless, many studies have now confirmed that fatty acids (FFAs) are in fact the primary source of energy for cancer cells delivered from adipocytes. In terms of lipid and energy metabolism, the principal function of adipocytes is to store triglyceride and release fatty acids for other cells and tissues when needed. *In vitro* and *in vivo* studies have shown that cancer cells can induce lipolysis and free fatty acid production in adipocytes. A recent study showed that CAAs have enhanced potentials to increase their lipid synthesis capacity and to breakdown the lipids by hydrolysis to release fatty acids, a process termed lipolysis (Balaban et al., 2017). Subsequently, the cancer cells will import the secreted FFAs from their microenvironment and use them for energy production or store them as triglycerides in lipid droplets (Young and Zechner, 2013). Notably, the majority of the FFAs secreted by the adipocytes and imported by the cancer cells have been found to be long chain fatty acids, such as palmitic acid (Kwan et al., 2014). Interestingly, the fatty acid transfer to cancer cells is further enhanced in "obese" adipocytes compared with normal adipocytes (Balaban et al., 2017). In addition to supplying the FFAs, the adipocytes can stimulate the cancer cells to express higher levels of carnitine palmitoyltransferase 1A (CPT1A) and electron transport chain proteins to elevate their rates of fatty acid β -oxidation (Figure 2) (Balaban et al., 2017). Furthermore, the adipocytes also induce the cancer cells to release the stored FFAs from their lipid droplets intracellularly through the adipose triglyceride lipase (ATGL)-dependent lipolytic pathway for fatty acid β -oxidation (Wang et al., 2017b).

In ovarian cancer, the uptake of FFAs is associated with an increased rate of fatty acid β -oxidation (FAO) to generate a large amount of energy in the form of adenosine triphosphate (ATP) (Kristin et al., 2011). Similarly, FFAs imported have been shown to be used for fatty acid β -oxidation to generate energy to promote cell proliferation and migration in breast cancer (Balaban et al., 2017). However, recent breast cancer studies reported that the import of FFAs do not lead to the ATP production via fatty acid β -oxidation and cell proliferation or survival

but cancer cell invasion (Wang et al., 2017b). In concordance with this, free fatty acids have been shown to enhance breast cancer cell migration through inducing the expression of plasminogen activator inhibitor-1 via SMAD4 (Byon et al., 2009). Moreover, a study following FA transfer from bone marrow adipocytes to metastatic prostate cancer cells also showed a shift in intracellular energy production from fatty acid β -oxidation to lactate production (Diedrich et al., 2016). The study also revealed that this shift to Warburg phenotype is mediated by the hypoxia-inducible factor 1 α (HIF-1 α)(Diedrich et al., 2016). Nevertheless, these findings collectively suggest that FFAs secreted by adipocytes into the tumour microenvironment could provide distinct effects under different conditions, but ultimately they all function to promote cancer progression and metabolism (Diedrich et al., 2016).

2.6 FABP4 (A-FABP)

Fatty acid binding protein 4 (FABP4) is a member of the FABP family of proteins involved in fatty-acid import, storage and export as well as cholesterol and phospholipid metabolism (Chmurzynska, 2006, Furuhashi and Hotamisligil, 2008). FABP4 expression itself is induced by high-fat diet (HFD) or obesity in adipocytes in the tumour microenvironment (Huang et al., 2017). Moreover, co-culture experiments also showed that adipocytes can also induce cancer cells to upregulate FABP4 expression (Kristin et al., 2011). FABP4 has many roles in cancer progression. FABP4 can enhance cancer progression by upregulating matrix metalloproteinases and stromal cell cytokine production (Huang et al., 2017). FABP4 also promotes cancer proliferation through inducing the expression of Forkhead box transcription M1 (FOXM1), a key transcription factor involved in driving cancer progression and drug resistance (Yao et al., 2018, Guaita-Esteruelas et al., 2017). The role of FABP4 in promoting cancer proliferation and migrating appears to be associated with its ability to facilitate fatty acid (FA) metabolism in both adipocytes and cancer cells. A study showed that pharmaceutical inhibition of FABP4 in ovarian cancer cells lowered their lipid droplet accumulation and their metastatic and growth potentials. Likewise, FABP4-deletion in mice also impairs the metastatic tumour growth, indicating that FABP4 has a key role in cancer metastasis (Kristin et al., 2011). Moreover, FFAs secreted by adipocytes can elevate prostate cancer invasion, which can be reduced by pharmaceutical inhibition of the fatty acid transporter FABP4 (Herroon et al., 2013). FABP4 also enhances prostate cancer progression and invasiveness by upregulating matrix metalloproteinases and cytokine production in the cancer microenvironment, especially under HFD or obesity (Huang et al., 2017). A most recent study revealed that FABP4 also has a key role in mediating lipolysis (Hua et al., 2019). Besides FABP4, current research also showed that CAAs can also enhance lipid metabolism in breast cancer and melanoma cells by inducing the expression of another fatty acid transporter FATP1 (Lopes-Coelho et al., 2018, Zhang et al., 2018). Thus, in addition to being an energy source to fuel the Warburg effect in cancer, the adipocyte-derived fatty acids also function as a signalling molecule to drive the phenotypic changes in cancer to drive cancer progression within the tumour environment (Furuhashi and Hotamisligil, 2008).

2.7 Matrix metalloproteinases (MMPs)-extracellular matrix remodelling

Apart from cancer growth and energy metabolism, adipocytes also support tumour progression by remodelling the extracellular matrix in the tumour microenvironment to facilitate cancer cell invasion and metastasis. Cancer cells can induce the adipocytes to secrete collagen VI which in turn promote cancer cell survival in a paracrine positive feedback fashion (Petricoin Iii et al., 2005). Notably, a cleaved product of collagen VI, known as endotrophin, has also been shown to stimulate EMT and cell metastasis. To remodel the extracellular matrix, adipocytes also release degradation enzymes known as matrix metalloproteinases (MMPs) to facilitate cancer cell invasion and metastasis (Figure 2) (Carine et al., 2003). Cancer cells can also induce the adipocytes to produce MMP-11 to facilitate the extracellular matrix remodelling and this enhances their invasion of the adipose tissue, highlighting the importance of MMP-11 in extracellular matrix remodelling and cancer invasion. In support of this finding, small interfering ribonucleic acid (siRNA) mediated MMP-11 depletion causes a reduction in cancer metastasis (Jia et al., 2007). siRNA targeted against matrix

metalloproteinase 11 can restrict the of cancer cells to invade and metastasize to local lymph nodes. Indeed, high levels of MMP-11 expression are associated with cancer cell invasion and poor prognosis (Rouyer et al., 1994). Apart from secreting MMPs directly, adipocytes also release leptin to enhance the release of MMPs by the cancer cells to facilitate cancer invasion (Yeh et al., 2009).

After the local invasion, adipocytes also support cancer cells migration and seeding at the distant site. In fact, the adipose tissue is a preferential site for many metastatic cancers. This is true as adipocytes secrete many cytokines, including IL-8 in favour of the cancer cell survival (Kristin et al., 2011). An *in vitro* experiment using mice showed that inhibition of IL-8 receptors, particularly CXCR1 could reduce the homing of ovarian cancer cells towards adipocytes (Kristin et al., 2011). Similar observations were also found in the acute lymphoblastic leukaemia (ALL). For leukaemic cell migration, SDF-1 has been identified as a chemoattractant released by adipocytes. This leukaemic migration towards adipocytes could be blocked when SDF-1 receptors on the leukaemia cells were inhibited (Pramanik et al., 2012).

2.8 Inflammatory cytokines-cancer metastasis

Metastasis is the spread and establishment of secondary cancer growths at a distal site from the primary cancer and the major cause of cancer deaths. The locations of future metastasis are predetermined microenvironments called 'pre-metastatic niches' (PMNs), and adipocytes also play an essential role in the homing of these metastasizing cancer cells (Peinado et al., 2017). Indeed, primary human omental adipocytes promote the homing, migration and invasion of metastasizing ovarian cancer cells, through releasing adipokines including IL-6 and IL-8 (Kristin et al., 2011). The lipids, predominantly FFAs, released by resident adipocytes also serve as a source of energy to promote the growth and proliferation of the homing cancer cells (Kristin et al., 2011).

In terms of metastasis, adipocytes can induce the cancer cells an incomplete epithelial-mesenchymal transition (EMT), a crucial process involved in the development of an invasive and metastatic cell phenotype. In adipocyte-breast cancer co-culture studies, the cancer cells displayed reduced expression of the epithelial marker, E-cadherin, without a significant increase in mesenchymal marker expression (Dirat et al., 2011). However, subsequent experiments revealed that conditioned media from CAAs alone are enough to increase cancer cell invasiveness (Dirat et al., 2011). Experiments using the co-culture system or conditioned media with breast cancer cells also demonstrated that adipocytes have an ability to enhance the cancer cell proliferation, invasion and migration through Jak/STAT3 signalling pathway (Lapeire et al., 2014). Similar outcomes are also observed when the experiments are performed using xenograft models and 3D culture systems (Laetitia et al., 2013, Brian et al., 2014). Consistent findings were observed between adipocytes and prostate cancer cells (Abel, 2012). To promote cancer invasion, adipocytes have been demonstrated to release the pro-inflammatory cytokine IL-6 into the tumour microenvironment. This level of IL-6 is directly correlated with the cancer aggressiveness, and its inhibition using an IL-6 antibody could suppress the invasiveness of the cancer cells (Dirat et al., 2011). Moreover, the secreted IL-6 can also lead to the local inflammation and activation of immune cells in the tumour microenvironment (Wright and Simone, 2016). The IL-6-activated macrophages can further produce and secrete more the inflammatory cytokines to promote further cancer metastasis (McNelis and Olefsky, 2014). Apart from IL-6, leptin has also been identified as a promoter for breast cancer cell invasion. In fact, breast cancer-associated adipocytes also secrete proinflammatory cytokines, including IL6, IL8, IFN γ -inducible protein-10 (IP10, also called CXCL10), CCL2 (MCP1), and CCL5 (RANTES), to drive tumour-initiating cell abundance and metastatic progression (Picon-Ruiz et al., 2016).

2.8 Extracellular vesicles

Tumour cells communicate with their microenvironment not only via soluble and secreted factors but also through extracellular vesicles (EVs). These EVs, which can be released by both cancer and stromal cells, are further classified into exosomes, microvesicles (MVs), and apoptotic bodies (ABs). There is a key function of extracellular vesicles in the establishment and maintenance of the tumour microenvironment (Han et al., 2019, Han et al., 2017). These EVs facilitate bioactive cargo transfer between cancer and stromal cells in the tumour microenvironment and play essential roles in maintaining cell proliferation, evading growth suppression, resisting cell death, acquiring genomic instability and reprogramming stromal cell lineages and cancer cells, together contributing to the generation of a remodelled TME. For example, EVs secreted by cancer cells are involved in the transfer of IL-6 to activate the STAT3 signalling pathway to induce lipolysis and the generation of FFAs in adipocytes in lung cancer-adipocyte co-culture models (Hu et al., 2019). Conversely, Circular RNAs (circRNAs) secreted in exosomes by adipocytes promote the tumour growth by inhibiting deubiquitination in hepatocellular carcinoma (HCC) (Zhang et al., 2019).

3.1 Adipocytes crosstalk with other stromal cells in the tumour environment

Cancer-associated fibroblasts (CAFs) are known to play a vital role in cancer development and progression through the release of growth factors and chemokines and by involving in the remodelling of the extracellular matrix (Orimo et al., 2005, Buchsbaum and Oh, 2016, Bochet et al., 2013). In the tumour microenvironment, the proximal localization of cancer cells to adipocytes can cause the adipocytes to undergo phenotypical changes to generate fibroblast-like cells termed adipocyte-derived fibroblasts (ADFs). These ADFs exhibit CAF-like phenotypes, including augmented fibronectin and collagen I secretion, enhanced migratory/invasive abilities, and enhanced expression of the CAF marker FSP-1 (Bochet et al., 2013). This may ultimately contribute to the number and the function of cancer-associated fibroblasts (CAFs) in the tumour environment. In addition, obese individuals also have more pre-adipocytes, macrophages and monocytes deposited in the adipose tissue. These changes to the microenvironment of obese individuals may promote cancer development (Wang et al., 2017a, Wang et al., 2017b). Adipose stem cells (ASCs) are known to alter the microenvironment and promote cancer progression. Accordingly, ASCs induce local inflammation through TGF-beta signalling pathway to recruit immune cells (Razmkhah et al., 2011). Moreover, ASCs can also promote angiogenesis by the platelet-derived growth factor BB/platelet-derived growth factor receptor- β (PDGF-BB/PDGFR- β) signalling pathway (Gehmert et al., 2010). Apart from the induction of inflammation and angiogenesis, co-culture and conditioned medium experiments revealed that ASCs also enhance epithelial-mesenchymal transition (EMT) (Zimmerlin et al., 2011). In addition, ASCs can be differentiated into proliferation-promoting fibroblasts in a variety of cancers, including those of the breast, ovarian and lung, to accelerate cancer progression (Jotzu et al., 2010).

3.2 Therapeutic resistance

Drug resistance is a major obstacle to effective cancer chemotherapy and is directly associated with limited therapeutic options and poor prognosis in cancer patients. Reduced or lack of drug responses are observed in obese cancer patients (Chen et al., 2012, Horowitz and Wright, 2015), and there are plenty of examples to suggest that the cancer-associated adipocytes are involved in conferring resistance to therapeutic treatments. For instance, adipocytes secrete adipokines such as leptin and growth differentiation factor 15 (GDF15) to block the growth inhibitory action of trastuzumab in HER2-positive cancers (Griner et al., 2013). Adipocytes also produce leptin to promote melanoma drug resistance through the upregulation of pro-survival PI3K/Akt and MEK/ERK signalling pathways (Chi et al., 2014). A similar chemoprotective effect by adipocytes through leptin was also observed in colon cancer (Bartucci et al., 2010). Adipocytes impair the cytotoxic effects of the drug vincristine through elevating pro-survival signals such as Bcl-2 and Pim-2 in the leukaemic cells (Behan et al., 2009). Moreover, obesity-associated adipocytes also promote breast cancer chemotherapy resistance through releasing major vault protein (MVP), a suppressor of NF- κ B signalling (Lehuede et al., 2019). L-asparaginase (ASNase) is a first-line therapy for acute lymphoblastic

leukaemia (ALL) that breaks down the essential metabolic substrates asparagine and glutamine, which drive cancer metastasis (Luo et al., 2018); in this respect, adipocytes can release glutamine to the cancer microenvironment and provide the essential amino acid to the cancer cells directly to sustain proliferation and protein synthesis and lessen the cytotoxic effects of asparagine and glutamine shortage (Ehsanipour et al., 2013). Furthermore, another study reported that hypoxia conditions enhance the adipocyte-protection on breast cancer cells from chemotherapeutic toxicity (Rausch et al., 2017). Adipocytes in the bone marrow microenvironment can protect myeloma cells against chemotherapy through releasing adipokines, such as leptin and adiponectin, to promote autophagy and therefore chemoresistance in the myeloma cells (Liu et al., 2015). In summary, the cancer-associated adipocytes can enhance cancer therapeutic resistance through upregulating the survival signalling pathways and DNA-repair activity in the cancer cells and by providing metabolic substrates to boost cancer proliferation and survival.

3.3 Targeting adipocyte signalling and other therapeutic perspectives

Recent data has shown that the mechanisms of energy metabolism are dysregulated in cancer. Because of the need to meet the high energy demands, tumour cells shift to the Warburg phenotype and preferentially import an excess of glucose and convert it to lactate for energy (ATP) production. At the same time, unlike their normal counterparts, the cancer cells are also less able to use lipids, like FAs, to generate (ATP) production via fatty acid β -oxidation (Diedrich et al., 2016, Wang et al., 2017b) because of the lower levels of fatty acid metabolic enzymes in mitochondria of the cancer cells (Vidali et al., 1983). The low-carbohydrate, high-fat ketogenic diet is an example where our knowledge of cancer energy metabolism has been successfully translated into treatment strategies. The ketogenic diet has been designed to mimic the effects of glucose starvation and is based on the fact that cancer cells fail to adapt to glucose shortage and use lipids/fatty acids as alternative energy sources. On this diet, the cancer cells will rapidly consume intracellular energy reserves through glycolysis because of the Warburg effect. Therefore, the ketogenic diet has the potential to be an effective cancer diet therapy. In support, experiments with animal models showed that the ketogenic diet significantly reduced the growth of tumours and that the diet prolonged animal survival (Raphael Johannes et al., 2015, Kennedy et al., 2007). These findings are also well correlated with a reduction in the plasma glucose concentrations and cancer cellular proliferation markers in animal models (Martuscello et al., 2016). While the ketogenic diet works relatively well in the short term, the long term health effects of the diet remain to be determined, as there is plenty of evidence to suggest that an accumulation of adipose tissue (fat) in the tumour microenvironment will accelerate cancer progression. Specifically, the cancer-associated adipocytes can modify the cancer cell phenotype to utilise alternative energetic nutrients to replace glucose, as well as essential metabolites, like FAs and glutamate, as energy sources to sustain cancer cell proliferation, survival and progression. In consequence, another potential strategy is to target the crosstalks between adipocytes and the cancer cells, in particular the fatty acid transporters, such as FABP4 which plays a pivotal role in fatty acid metabolism and transport in both the adipocytes and the cancer cells. Indeed, the highly specific FABP4 inhibitor, BMS309403, has been shown to be able decreased tumour cell proliferation and migration by downregulating HIF1 pathway in hepatocellular carcinoma (HCC) and reduce tumour growth in heterotopic and orthotopic xenografted mice models (Laouirem et al., 2019). In addition, prostate stromal cells can augment cancer cell invasiveness by secreting IL-8 and IL-6, which can be also abrogated by BMS309403. Thus, targeting the crosstalks between adipocytes and the cancer cells or vulnerabilities arisen as a result may provide novel strategies of cancer treatment and for overcoming drug resistance. Moreover, FABP4 expression is frequently elevated in breast cancer and has been shown to be a potential good diagnostic and prognostic marker in patients with breast cancer (Cui et al., 2019).

4 Conclusion and future perspectives

Tumorigenesis and cancer progression require the interaction of tumour cells with the surrounding tissues in the tumour microenvironment. The contribution of adipose tissue, in particular adipocytes to the development of cancer has help us to establish a link between obesity and cancer. The proximal location of the cancer cells can dramatically modifies the adipocytes to a pro-cancer phenotype. Over the past few decades the rates of obesity have risen at a dramatic rate globally. Obesity and being over-weight further condition the function of the cancer-associated adipocytes. Thus, targeting the crosstalks between adipocytes and the cancer cells or vulnerabilities arisen as a result of these interactions may provide novel strategies of cancer treatment and for overcoming drug resistance. Nevertheless, further work will be required to obtain a more complete understanding of the mechanisms by which adipocytes, in conjunction with other stomal cells, promote cancer initiation, progression and drug resistance (Table 1). This information will allow us to identify biomarkers for early cancer risk prediction and diagnosis as well as targets and opportunities for therapeutic intervention.

6. References

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Figure and Table Legends

Figure 1. Crosstalks between adipocytes and cancer cells.

Adipocytes secrete various adipokines and other factors to promote cancer progression. Specifically, the ratio of leptin and adiponectin plays an important role to the survival of cancer cells. At the same time, cancer cells drive adipocytes lipolysis to generate free fatty acids for themselves.

Figure 2. Adipocytes and tumour microenvironment.

Cancer cells import adipocyte-secreted free fatty acids which resulting in larger lipid droplets and fat reservoir. In addition, adipocytes secrete VEGFA and MMPs to promote angiogenesis and cancer invasion respectively to enhance cancer progression.

Table 1. Summary of Cancer-Associated Adipocyte Secretosome

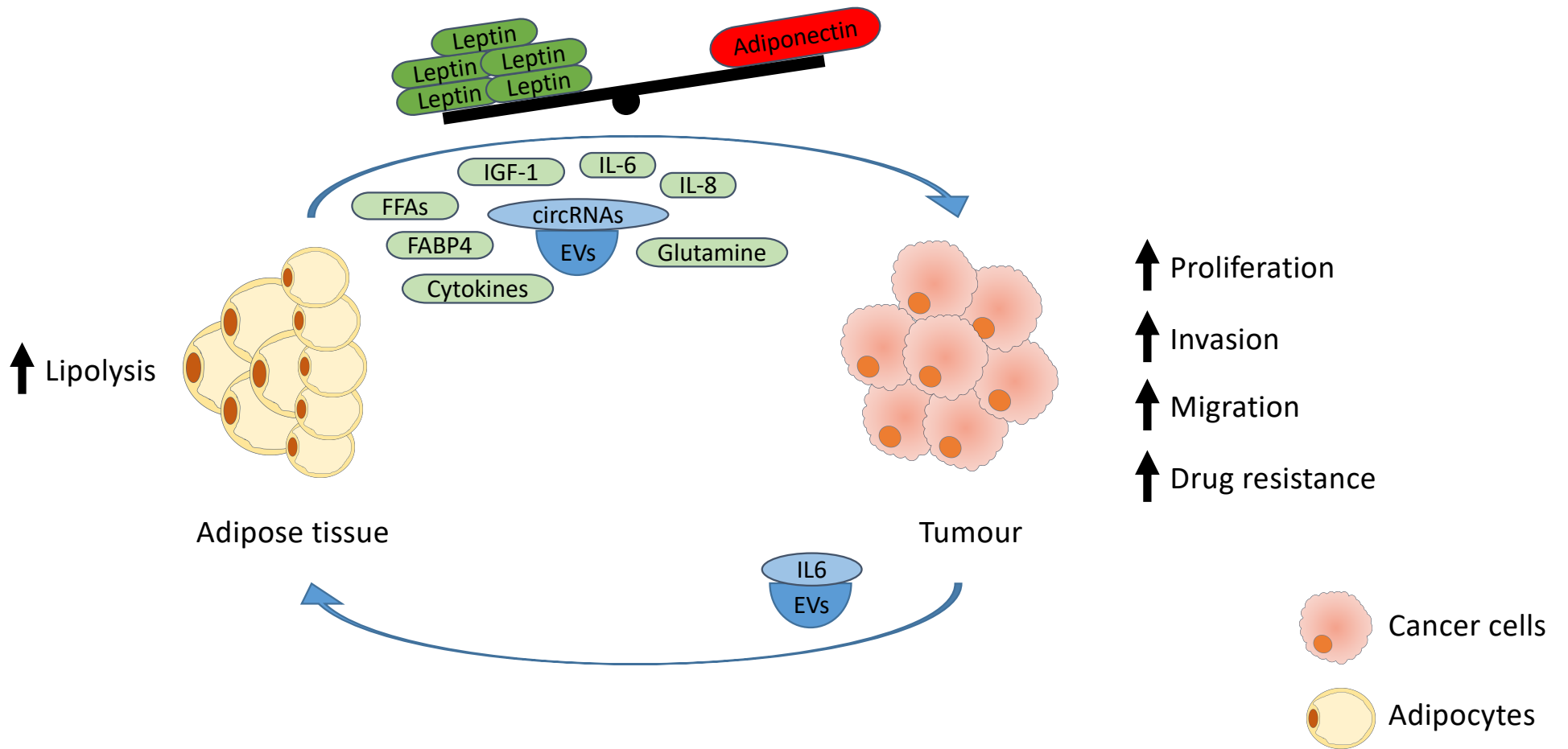


Figure 1.

Table 1. Summary of Cancer-Associated Adipocyte Secretosome

Secretome	Targets	Descriptions
Leptin	ERK1/2 JNK PI3K/AKT	Cell proliferation Epithelial-mesenchymal transition Angiogenesis Chemotherapeutic resistance
Adiponectin	GSK3 β / β -catenin AMPK	Apoptosis Restrict cell growth
Insulin-like growth factor (IGF)	PI3K/AKT MAPK	Cell growth
Vascular endothelial growth factor (VEGF)	VEGFR	Angiogenesis
Free fatty acids (FFAs)	Lipid droplets SMAD4	Source of energy Cell proliferation Migration Invasion
Fatty acid binding protein 4 (FABP4)	Free fatty acids (FFAs) FOXO1 FATP1	Cell proliferation Invasion Metastasis Lipid storage Lipid metabolism
Matrix metalloproteinase (MMP)	Adhesion molecules	Extracellular matrix remodelling Invasion Metastasis
Interleukine-6 (IL-6)	JAK/STAT3	Invasion Local inflammation Immune cells activation
Extracellular vesicles (EVs)	Bioactive cargo	Cell proliferation Resist cell death Reprogramme stromal cells

Table 1.

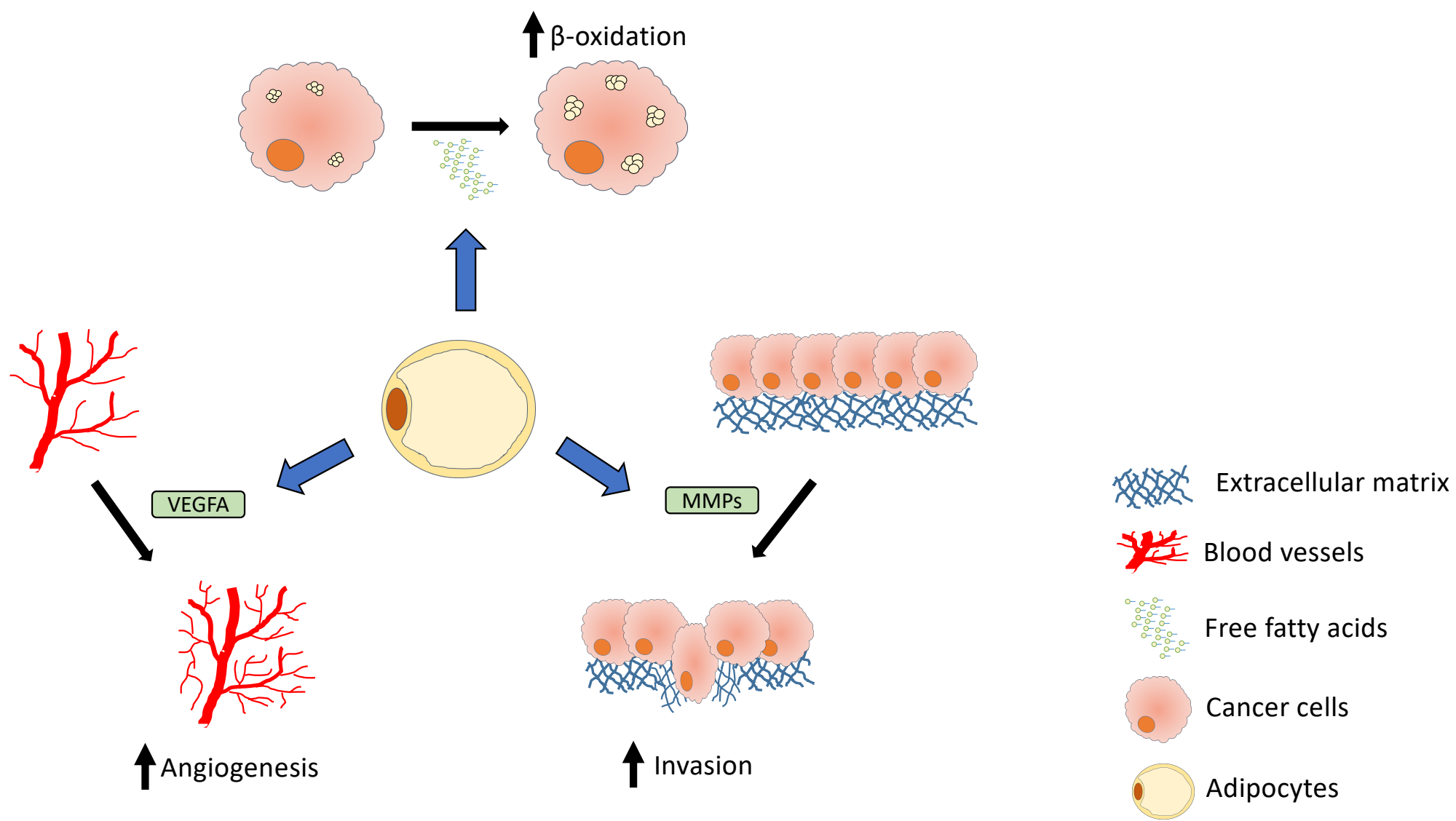


Figure 2.