## Obesity Comorbidity/Etiology and Pathophysiology

# Omentum and bone marrow: how adipocyte-rich organs create tumour microenvironments conducive for metastatic progression

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### Summary

A number of clinical studies have linked adiposity with increased cancer incidence, progression and metastasis, and adipose tissue is now being credited with both systemic and local effects on tumour development and survival. Adipocytes, a major component of benign adipose tissue, represent a significant source of lipids, cytokines and adipokines, and their presence in the tumour microenvironment substantially affects cellular trafficking, signalling and metabolism. Cancers that have a high predisposition to metastasize to the adipocyte-rich host organs are likely to be particularly affected by the presence of adipocytes. Although our understanding of how adipocytes influence tumour progression has grown significantly over the last several years, the mechanisms by which adipocytes regulate the metastatic niche are not well-understood. In this review, we focus on the omentum, a visceral white adipose tissue depot, and the bone, a depot for marrow adipose tissue, as two distinct adipocyte-rich organs that share common characteristic: they are both sites of significant metastatic growth. We highlight major differences in origin and function of each of these adipose depots and reveal potential common characteristics that make them environments that are attractive and conducive to secondary tumour growth. Special attention is given to how omental and marrow adipocytes modulate the tumour microenvironment by promoting angiogenesis, affecting immune cells and altering metabolism to support growth and survival of metastatic cancer cells.

Keywords: Adipose tissue, bone metastasis, MAT, omental metastasis, WAT.

With many epidemiological studies raising awareness and correlating Western diet and metabolic disturbances with cancer progression and metastatic development, it is imperative to understand the molecular basis for adiposity-driven tumorigenesis. Overeating and sedentary lifestyles are clearly predominant reasons for elevated fat depots, but other physiological factors and medical conditions such as age and hormonal status are associated with adipocyte hypertrophy, adipogenesis and increased body mass index (1,2). General involvement of adipocytes in lipid storage and secretion of endocrine factors underscores the importance of adipose tissue in metabolism and inflammation (3–8). Our current body of knowledge indicates that various adipose depots exhibit important differences in adipogenic progenitors, metabolism and effects they exert on system organs. Herein, we will review how omentum, an organ that is naturally rich in adipocytes, and bone marrow, which becomes fatty in response to physiological and pathological factors, contribute to creating a niche that attracts and supports secondary metastatic tumour growth.

## Metastatic microenvironment generated by white adipose tissue

According to National Cancer Institute, peritoneal metastases are the most common occurrences in the spread of ovarian, colorectal, gastric, pancreatic and uterine cancers (9), with the omentum often being the predominant metastatic site within the peritoneum (10,11). Direct intraperitoneal seeding is the most common route of dissemination of cancer cells to omentum because of the proximity of the primary abdominal tumours (10). Cancer cells that are shed from the primary tumour are initially spread via peritoneal fluid and eventually by the ascites accumulating in the abdominal cavity due to disruption of lymphatic system (12,13). Dissemination of ovarian tumours through the vasculature as a primary mode of metastasis is very rare, although pelvic and/or para-aortic lymph nodes can be involved in this process (13,14).

### Omentum as a visceral white adipose tissue depot

To better understand what lures cancer cells to the omentum, we shall first review its structure. The peritoneum is a continuous membrane sheet lining the peritoneal cavity (15). The omentum is a visceral fold of the peritoneum subdivided into greater and lesser components. The lesser omentum extends from the smaller curvature of the stomach to the liver. The greater omentum is a fatty pad that extends from the large curvature of the stomach and, like an 'apron', and covers the majority of the abdominal organs converging into parietal peritoneum. This organ is made of two types of tissues. First is a highly vascularized connective tissue rich in white adipocytes and covered by a mesothelial cell layer that rests on a basement membrane, except where structures known as milky spots are located (15). The other tissue type is a fenestrated, membranous and translucent layer composed of two mesothelial cell layers wrapping collagen fibres and fibroblast-like cells and not resting on basement membrane (15). The main functions of the omentum as an organ are to store lipids, pool immune cells, adhere to peritoneum to localize inflammation (16,17), regulate fluid exchange in the peritoneal cavity and supply angiogenic and neurogenic factors (18,19).

Omentum is one of the six visceral white adipose tissue (WAT) depots: omental, mesenteric, perirenal, gonadal, epicardial and retroperitoneal, whose developmental origin is a subject of an ongoing debate (20,21). Visceral WAT forms shortly after birth following prenatal development of subcutaneous WAT (22). All six visceral depots derive from progenitors positive for Wilms' tumour gene (Wt1) (20). Expression of Wt1 is specific for visceral WAT and does not trace to progenitors of subcutaneous WAT and brown adipose tissue (20). The Wt1-positive mesothelium,

a major source of visceral WAT, is the key characteristic differentiating visceral fat depots from subcutaneous fat (20,23–25). There is heterogeneity among the various visceral depots with respect to Wt1 expression, with most of the epidymal but only a portion of retroperitoneal WAT arising from Wt1-positive cells. This notion of heterogeneity is further supported by the fact that a significant portion of interscapular and retroperitoneal WAT but not epidymal fat arise from Myf5-positive precursors of brown adipose tissue (21).

### Omentum as a site of metastasis from ovarian cancer

With 80% of all serous ovarian carcinomas metastasizing to omentum, this organ appears to act as a very specific target for this type of tumour (11,26). Omentum is essentially a large fat pad and an endocrine tissue that can store lipids and serve as a potential source of energy for metastatic tumour cells (27). An experimental mouse model mimicking ovarian cancer metastasis by intraperitoneal injection of tumour cells revealed that ovarian cancer cells have high propensity to seed and proliferate in the omentum (11). High rate of homing towards the adipocytes in this model was attributed to a variety of factors, such as IL-8, IL-6, monocyte chemoattractant protein-1 and adiponectin, secreted by omental adipocytes. Omental fat cells were also shown to activate pro-survival pathways, p38 and stat3, in the ovarian cancer cells, indicating the potential importance of an adipocyte-rich environment for homing and growth of tumour cells in the omentum.

Apart from chemical signalling towards the tumour cells, fat cells are also known to affect cancer cell growth and behaviour through lipid-sharing. Specifically, *in vitro* co-culture of ovarian cancer cells with adipocytes was shown to result in transfer and accumulation of lipid droplets in the tumour cells (11). This observation was in line with the observed presence of lipid droplets in ovarian cancer cells bordering adipocytes in the human tissue. Importantly, this acquisition of adipocyte-supplied lipids appeared to be depot-specific with most accumulation occurring upon co-culture with omental and peritoneal adipocytes compared with co-culture with subcutaneous and bowel mesenteric adipocytes (11). The lipid transfer from adipocytes induced β-oxidation in tumour cells and enhanced their proliferation *in vitro* (11). Reciprocally, cancer cells affected metabolism in adipocytes by inducing hydrolysis of triglycerides stored in adipocyte lipid droplets into free fatty acids (FFA) and glycerol (11). Besides increased secretion of FFA and glycerol, activation of hormone-sensitive lipase (HSL), an enzyme central for lipolysis, and overexpression of perilipin A, a protein coating lipid droplets and activation of which is necessary for induced lipolysis (28), were detected (11). Essentially, it

appears that cancer cells forced adipocytes to 'give up' their lipids, which ultimately translated into increased tumour burden. This process would eventually lead to transformation of omentum from a fat pad into a solid tumour with few remaining adipocytes, a process often referred to as 'omental caking'. These observed molecular and histological changes upon adipocyte-tumour cell interactions cultivated the idea that cancer cells 'consume' the energy-rich lipids necessary for their survival and progression (29).

## Omental adipocytes and metabolic effects on tumour cells

It appears that through paracrine secretions and the abundance of readily transferable lipids, adipocytes create a microenvironment that alters tumour metabolism and supports more aggressive phenotypes. In the majority of cancers, the rapid mode of proliferation forces tumour cells to modify their energy metabolism (30), by increasing *de novo* lipogenesis (31,32). The newly synthesized fatty acids are used for storage, membrane composition and signalling, and are central for cancer thriving. In contrast, tumours such as ovarian cancers that grow in adipose-rich microenvironments have unconventional metabolism characterized by reduced lipogenesis and increased rates of β-oxidation (11). These observations are in line with other studies demonstrating that exogenous lipids sustain cancer cell survival when *de novo* lipogenesis is inhibited (33,34). It appears increasingly clear that instead of 'going through the trouble' of making their own fuel in order to proliferate, tumour cells growing in lipid-rich adipose environments take advantage of having these fuel molecules catered to them (27,35). Thus, a ready source of energy may be a key reason behind their aggressive phenotype. It is also noteworthy that although not directly demonstrated in a context of omental metastases lipids have been shown to enhance the Warburg Effect in tumour cells (32,36–39). Because omental adipocytes are capable of inducing lipolysis in tumour cells (11), this lipolysis-generated glycerol has a potential to feed into the glycolytic pathway (40–42). This could offer an additional mechanism for enhanced tumour growth and metabolic adaptation in the metastatic niche.

Supporting adipocyte involvement in modulating tumour metabolism and progression was a discovery of significant overexpression of fatty acid-binding protein 4 (FABP4) (or aP2 protein) in omental metastases from ovarian cancer, particularly at the tumour–adipocyte interface (11). This was the first demonstration that this lipid chaperone, originally discovered in adipocytes and whose expression increases in response to fatty acid uptake and lipolytic stimulation (43–45), gets upregulated in tumour cells exposed to adipocyte-derived lipids. Lipid exposure and cholesterol accumulation are known to induce FABP4 expression in other cell types, such as macrophages, where this chaperone contributes to foam cell

formation and atherosclerotic plaque instability (43,46,47). Interestingly, FABP4 is also present in endothelial cells, where it appears to regulate cell proliferation (48) and its high expression in endothelial glioblastoma cells has been linked to the robust angiogenesis associated with this disease (49). Endothelial expression of FABP4 in adipocyte-rich environments such as omentum could have a potential role in growth and progression of metastatic ovarian cancers. Indeed, reduced tumour burden and lower metastatic potential in FABP4-deficient mice was found to be associated with inhibitory effects on tumour vasculature (11). These findings stress the importance of the adipocyte-rich tumour microenvironment and both tumour-derived and host-derived FABP4 in metastatic development and progression and call for further investigations.

## Evidence of altered metabolic phenotype in clinical samples

To better appreciate the relevance of *in vitro* and *in vivo* animal studies, we performed Oncomine analyses and compared mRNA expression of genes linked to lipid metabolism in primary and metastatic ovarian cancers. A significant upregulation of genes encoding for FABP4 and CD36 (fatty acid translocase [FAT]), proteins involved in membrane transfer of fatty acids (43,50), was revealed in metastatic ovarian cancer when compared with primary tumours and confirmed in all four available datasets (Table 1). The changes in expression of specific isomers of fatty acid transport proteins (FATP1–6), which are known to regulate

**Table 1** Oncomine analysis of mRNA expression of genes involved in fatty acid binding, uptake, synthesis and metabolism in patients with ovarian cancer

| Gene | Ovarian cancer dataset | Fold change | *P* value | *n* |
|------|------------------------|-------------|-----------|-----|
| FABP4 | Bittner [158] | 5.78 | 4.76E-8 | P: 166; M: 75 |
| | Adib [159] | 37.42 | 0.004 | P: 6; M: 6 |
| | Anglesio [160] | 17.63 | 6.00E-5 | P: 74; M: 16 |
| | Tothill [161] | 10.51 | 3.91E-11 | P: 189; M: 54 |
| CD36 | Bittner [158] | 2.43 | 5.75E-8 | P: 166; M: 75 |
| | Adib [159] | 1.71 | 0.043 | P: 6; M: 6 |
| | Anglesio [160] | 5.02 | 9.31E-5 | P: 74; M: 16 |
| | Tothill [161] | 3.45 | 7.90E-10 | P: 189; M: 54 |
| FASN | Bittner [158] | 1.35 | 7.61E-4 | P: 166; M: 75 |
| HSL | Anglesio [160] | 1.21 | 0.009 | P: 74; M: 16 |
| | Tothill [161] | 1.15 | 3.93E-4 | P: 189; M: 54 |
| PLIN2 | Anglesio [160] | 2.18 | 0.004 | P: 74; M: 16 |
| | Tothill [161] | 1.46 | 0.001 | P: 189; M: 54 |

'The Oncomine database (Oncomine™ v4.5: 729 datasets, 91,866 samples) was used for the analysis of primary (P) vs. metastatic (M) tumors. Following genes were analyzed: Fatty acid binding protein 4 (FABP4), Cluster of differentiation (CD36; FAT), Fatty acid synthase (FASN), Hormone sensitive lipase (HSL), Perilipin2 (PLIN2); *n* = number of samples. Data were ordered by "overexpression" and the threshold was adjusted to P-value <1E⁻4; fold change, 2 and gene rank, top 10%. For each database, only genes that met the criteria for significance are reported'.

long-chain and very long-chain fatty acid uptake alongside CD36 (50,51), were not consistently significant across the analyzed datasets (data not shown). Both CD36 and FATP are known to be modulated by the microenvironment, particularly in obesity, and have been shown to synergistically enhance fatty acid uptake, although in some models CD36 was demonstrated to be far more effective than FATPs (50,52). The functional differences between CD36 and FATPs, especially in a context of tumour metabolism, are not known and need to be explored.

In addition to fatty acid transport genes, we also analyzed the expression data for genes involved in lipogenesis (i.e. fatty acid synthase, FASN) and lipolysis (i.e. HSL and *perilipin 2*). Only modest changes in FASN levels were detected (Table 1), likely because in adipocyte-rich microenvironments like omentum, tumour cells rely more on lipid uptake from adipocytes than their own lipogenesis. The changes in lipolysis genes were also moderate. It is reasonable to assume that expression of FABP4 and CD36, proteins facilitating transport of fatty acids, was increased in both cancer cells and adipocytes and thus easier to detect; whereas lipolysis occurred predominantly in adipocytes, and depending on the stage of the tumour, the observed changes in expression might have been too modest to detect. Expression of these genes was also likely affected by the tumour heterogeneity. One noteworthy caveat of the aforementioned analyses is that the available datasets do not distinguish omentum from other potential metastatic sites. However, the fact that the observed differences in expression between primary and metastatic sites were reproducible across several datasets speaks to potential involvement of lipid transport and metabolism in metastatic progression. Apparent differences in the lipidome between subcutaneous and omental fat depots as well as tumours in patients with malignant or benign ovarian or endometrial tumours have been previously shown in a small subset of Israeli patients (53). Significantly lower concentrations of linoleic acid (LA), a polyunsaturated fatty acid (PUFA) were shown in both fat depots in cancer patients as compared with healthy controls. Moreover, the malignant tumours appeared to have a significantly lower saturated-to-unsaturated fatty acid ratio compared with the benign tumours, suggesting that LA is mobilized from both WAT depots to be utilized by the tumours resulting in overall desaturation of the cancer. This potential link between fatty acid metabolism and ovarian cancer progression is an understudied concept that warrants further investigation.

## Immune microenvironment in adipocyte-driven omental metastasis

Closer histological investigation of the omental metastases led to the idea that adipocytes might not be the only incentive that attracts cancer cells to the omentum (29). The extensive vascular network of omentum converges in some areas into capillary beds comingled with aggregates of immune cells (macrophages, mast cells, B lymphocytes and T lymphocytes) and stromal cells forming 'milky spots' (54,55). Characteristically, milky spots are reminiscent of secondary lymphoid structures and are important representatives of the immune system in the peritoneal cavity (56,57). Initially viewed as defense structures against bacterial antigens (58–60), these highly vascularized areas have since been implicated as preferential sites for adhesion and proliferation of disseminated tumour cells of ovarian and colorectal origin (10,61–66). For tumours such as ovarian cancers, in which metastases occur primarily by direct seeding rather than through circulation, milky spots allow for rapid and selective attachment and provide an environment suitable for tumour growth and survival (10)

The initial tumour cell adhesion to the milky spots induces the influx of macrophages, which correlates with generation of new milky spots around tumour cell concentration (64,66). Studies utilizing a variety of immunodeficient strains of mice – Igh6, Nude, Rag1, and BN XID lacking functional B-cells, T-cells, T- and B-, or T-, B- and NK-cells respectively, but having intact macrophages – show that compromised B-, T- or NK-cell-mediated immunity does not affect abundance of milky spots or homing of tumour cells to these structures (29). The depletion of peritoneal macrophages, on the other hand, inhibits the metastatic potential of ovarian cancer potentially by affecting the expression of stromal vascular endothelial growth factor (VEGF) (67). Interestingly, among a variety of known peritoneal adipose depots that include omental, mesentery, uterine, gonadal and splenoportal – milky spots are only found in omental and splenoportal fat pads (29,68). In line with these findings, the i.p. injection of four different ovarian cancer cell lines into mice resulted in cancerous lesions forming predominantly in omental and splenoportal fat depots, as opposed to other depots, validating the importance of milky spots in tumour homing (29). This significantly increased migration of ovarian cells was attributed to factors secreted by omental and splenoportal fat depots (29). It appears that interaction of adipocytes with peritoneal macrophages might be important for the homing of the disseminating ovarian cancer cells and progression of metastasis. It has been demonstrated that adipocyte-supplied PUFAs serve as ligands for transcription factor peroxisome proliferator-activated receptor β/δ (PPARβ/δ) in macrophages, causing their polarization into tumour-associated phenotype (known as tumour-associated macrophage) (69). Accordingly, tumour-associated macrophages isolated from serous ascites of ovarian cancer patients contain lipid droplets with high composition of LA, and lower but high levels of AA and docasahexaenoic acid (DHA) PUFAs (69). This accumulation of fatty acids by macrophages leads to transcriptional deregulation and activation of pro-tumorigenic phenotype.

## Adipocyte-induced angiogenesis

Beside the aggregates of immune cells, milky spots are also characterized by microvascular beds and are areas of active angiogenesis (10,65), a known contributor to tumour progression (55,70). High levels of neovascularization in milky spots have been attributed to secretion of vascular endothelial growth factor A predominantly by mesothelial cells of the omentum and to a lesser degree by omental macrophages (10). Isolated and *in situ* omental adipocytes were shown to secrete VEGF (10,71) and express additional angiogenesis-associated factors and receptors, such as CD105 (10) and VEGFR3 (65). Notably, the expression of VEGF appears to be induced when omental adipocytes undergo hypoxia (71), which is in line with the evidence of clearly hypoxic phenotype in a portion of mesothelial cells and macrophages isolated from murine omentum (10). Both hypoxia and hypoxia-induced neovascularization have been linked to invasiveness, survival and chemoresistance of many cancers including ovarian tumours (72,73). A specific role for adipocytes and adipocyte-derived fatty acids in neovascularization is further suggested by the lower levels of angiogenesis associated with reduced tumour burden in mice deficient for FABP4 (11). These observations are underscored by our Oncomine analyses, which reveal that in addition to upregulation of genes encoding FABP4 and CD36, metastatic ovarian tumours, representing primarily omental metastases, exhibit significantly increased expression of angiogenic genes (VEGFR1, VEGFR2, CD31 and CD34) compared with primary tumours (Table 2). This implies that although extensive vasculature of the omentum is probably sufficient for the initial tumour colonization and survival, angiogenic factors released by the tumour as well as the microenvironment in response to tumour presence

further enhance neovascular growth to meet demands of increased tumour burden (65).

Taken together, it appears that upon dissemination, cancer cells are drawn to the milky spots, as sites of high neovascularization and immune cell presence conducive to initial tumour colonization and survival. Once adhered and viable, the abundance of energy from adipocytes allows for further tumour expansion. This 'parasitic' mode of survival of cancer cells reduces the number of adipocytes as tumour progresses (10,29) and naturally hypoxic omental cells drive the hypoxia-mediated angiogenesis (10). Hypoxia worsens as tumour burden increases, which further enhances angiogenesis and advances tumour progression even when fat depots are depleted.

## Metastatic microenvironment generated by bone marrow adipose tissue

National Cancer Institute lists bone as a main site of metastases from prostate, breast, lung, thyroid, melanoma, kidney, bladder and uterine cancers (9). Although bone contains few adipocytes at birth, the abundance of marrow fat cells increases dramatically as we age (22). Other factors, including metabolic imbalance associated with obesity, caloric restriction and anorexia nervosa, administration of select diabetes treatment drugs, such as members of thiazolidinedione class, as well as chemotherapy and radiotherapy represent additional contributors to increased bone marrow adiposity (22,74,75). This is of importance, as in parallel, the factors contributing to the development of MAT are also linked to the poor prognosis for tumours with high affinity for bone, such as prostate (76–78) and breast cancers (79).

### Defining marrow adipose tissue and its origin

In view of recent findings, the ontogeny of bone marrow adipocytes remains unclear. A recent study based on genome sequencing of subcutaneous WAT from patients who underwent allogenic transplantation with bone marrow or peripheral blood stem cells revealed evidence of donor genome in recipient WAT (80). This suggested the existence of mobile bone marrow-derived haematopoietic precursors of WAT, although whether the same precursors can give rise to MAT is not clear. Nevertheless, these findings put in question the previous notion of morphological structural differences in the origin of these two depots and introduced the idea that WAT and MAT might be deriving from the same progenitor populations (81). The additional evidence for common origin of MAT and WAT came from the observation that mesenchymal progenitors of bone marrow adipocytes and approximately half of MAT adipocytes can be traced by platelet-derived growth factor receptor-α, the same surface marker as progenitors of WAT (22). At the

**Table 2** Oncomine (Oncomine v4.5) analysis of mRNA expression of genes involved in fatty acid binding, uptake, synthesis and metabolism in patients with metastatic ovarian cancer sites (M) compared with primary sites (P)

| Gene | Ovarian cancer | Fold change | P value | n |
|---|---|---|---|---|
| VEGFR1 | Anglesio [160] | 1.07 | 0.032 | P: 74; M: 16 |
| | Tothill [161] | 1.16 | 0.031 | P: 189; M: 54 |
| VEGFR2 | Bittner [158] | 1.25 | 0.001 | P: 166; M: 75 |
| | Anglesio [160] | 1.36 | 0.006 | P: 74; M: 16 |
| | Tothill [161] | 1.26 | 2.87E-4 | P: 189; M: 54 |
| CD31 | Bittner [158] | 1.86 | 4.76E-4 | P: 166; M: 75 |
| | Tothill [161] | 1.46 | 0.026 | P: 189; M: 54 |
| CD34 | Bittner [158] | 1.13 | 0.044 | P: 166; M: 75 |
| | Tothill [161] | 1.08 | 0.040 | P: 189; M: 54 |

'Following genes were analyzed: Vascular endothelial growth factor receptor-1 (VEGFR1) and -2 (VEGFR2), Cluster of differentiation 31 (CD31), and cluster of differentiation 34 (CD34); n = number of samples. Data were ordered by "overexpression" and the threshold was adjusted to P-value <1E⁻4; fold change, 2 and gene rank, top 10%. For each database, only genes that met the criteria for significance are reported'.

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same time, these data also suggested that two distinct types of MAT precursors may exist, one common to MAT and WAT and one that is MAT-specific. Accordingly, only MAT and not WAT adipocytes express Osterix1 (22) a transcription factor involved in osteoblast differentiation (82,83). This not only speaks to the mesenchymal origin of at least a portion of marrow adipocytes but also indicates there are distinct differences between some populations of progenitors of MAT and WAT. As understanding of the origin of MAT is clearly an evolving field, the question of progenitors of different fat depots remains to be clarified.

Additional controversy related to origin of MAT comes from the fact that MAT adipocytes and osteoblasts were long thought to share the same mesenchymal stem cell precursor (84); however, newly emerging findings now show that bone marrow has two mesenchymal progenitor populations: one giving rise to osteoblasts, stromal cells and adipocyte lineages (22,85,86) and the other differentiating to all mesenchymal lineages but adipocytes (22,87). Numerous factors drive osteoblast differentiation: Runt-related transcription factor 2, Runt-related transcription factor 2 (Runx2), core binding factor β, core binding factor B (CbfB), Osx, activating transcription factor 4 (ATF4), and transcriptional co-activator with PDZ-binding motif (TAZ) (88). Osteoblasts are also sensitive to hormonal regulation, and because they express hormone receptors such as androgen receptors, oestrogen receptor-alpha and – beta (89), age-related hormonal decline (90) or androgen deprivation therapy (91) may contribute to bone loss by affecting osteoblast differentiation. There are also many transcription factors that can influence adipocyte differentiation, with peroxisome proliferatior-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein a (C/EBPa) considered the master regulators (88). Expectedly, exogenous agonists of PPARγ stimulate adipogenesis, with some, depending on the nature and affinity of the ligand, inhibiting bone formation by suppressing osteogenesis- driving transcription factors (92). One example is Rosiglitazone, a potent ligand of PPARγ, which promotes bone loss and development of marrow adipocytes (93–96). A significant plasticity between osteogenesis and adipogenesis pathways is thought to exist in adult bone allowing certain factors to shift the balance in either direction (88,97,98). Specifically, Wnt signalling was identified as a cue for stimulation of osteoblast differentiation at the expense of adipogenesis through inhibition of PPARγ and C/EBPα (99,100). Regulation of Wnt is thought to be one of the key contributors to the inverse relationship between fat and bone formation (99). However, the possibility that different postnatal lineages for adipocytes and osteoblasts exist may explain the lack of correlation between increased MAT and decreased bone density in various strains of mice (22,101) and in fatty bones induced by high-fat diet (102). Moreover, pharmacological inhibition of marrow adipogenesis with bisphenol-A-diglycidyl ether, or loss of

function mutations in kit receptor resulting in the absence of marrow adipose tissue in mice do not inhibit bone loss due to type 1 diabetes or ovariectomy, respectively, thus further challenging the existence of a causal link between augmented marrow adipocytes and osteopenia (103,104).

Although adipocytes are scarce in the bone microenvironment at birth, adipogenesis causes progressive replacement of the red marrow in the distal skeletal regions with adipocyte-rich yellow marrow (reviewed in (88). The red marrow, which remains centralized to the axial skeleton, continues to house the majority of the haematopoietic cells but can still retain a large proportion of adipocytes. The localization in the skeleton is what appears to be the determining factor in differential development and regulation of MAT (101). Specifically, MAT adipocytes that are interspersed with the red, haematopoietic marrow ('proximal' regulated MAT, rMAT) appear to be different from those that make up the adipocyte-rich, yellow marrow ('distal' constitutive MAT, cMAT). This is in line with early studies, which showed distinctly different lipid composition between adipocytes localized to red as opposed to yellow marrow (105). Although there is still a lot to be uncovered about specific characteristics of rMAT and cMAT, we know so far that the rMAT adipocytes preferentially develop within the red marrow throughout life and can be depleted with 21-day cold exposure (101). They are also smaller in size, contain more saturated lipids, express lower levels of *Cebpa* and *Cebpb* and are lost in a PTRF (Polymerase I and Transcript Release Factor) knockout mouse model of congenital generalized lipodystrophy (101). Conversely, cMAT adipocytes develop shortly after birth and do not respond to 21-day cold exposure. They are larger, contain more unsaturated lipids relative to total lipid content, have elevated *Cebpa* and *Cebpb*, and are preserved in the PTRF knockout mouse (101). Degree of lipid saturation and expression of adipocyte genes in rMAT are similar to WAT. Thus, cMAT has increased lipid unsaturation and elevated expression of these genes relative to both rMAT and WAT depots. The important question that warrants further investigation is how these differences in rMAT and cMAT affect attraction and progression of metastatic cells in bone.

## Role of pro-angiogenic factors in homing of cancer cells to the bone

Although many advances have been made in efforts to understand how the tumour microenvironment influences progression of skeletal metastases, deciphering what attracts circulating tumour cells to bone remains to be elucidated. Studies on bone colonization by the epithelial tumours, such as prostate and breast cancers, suggest that to initiate the metastatic cascade, primary tumour cells must undergo an epithelial-to-mesenchymal transformation (106). The mesenchymal phenotype includes invasive behaviour that

allows cells to penetrate the surrounding stroma of the primary site, enter circulation and thus reach the bone. According to Stephen Paget's 'seed and soil hypothesis', cancer cells preferentially metastasize to specific organs in a 'pre-determined' fashion (107). In line with this original hypothesis, primary tumour cells have been shown to be 'primed' for metastasis by haematopoietic progenitor cells (HPCs) expressing vascular endothelial growth factor receptor 1 (VEGFR1) (108). These HPCs reside within specified niches of the bone marrow and are recruited to the primary site to drive angiogenesis and tumour growth. Following interaction with primary tumour cells, the clusters of VEGFR1+ HPCs cells home to the metastatic site and generate a 'pre-metastatic niche' that attracts disseminated tumour cells (DTCs) (109).

Once in the bone, DTCs adhere to the endothelium of the sinusoidal blood vessels throughout bone marrow (106). In fact, initial micrometastatic formations in the bone marrow are observed at the perivascular areas of the sinusoidal vessels (110). Our own Oncomine analysis of mRNA levels of pro-angiogenic genes in patients with prostate cancer data revealed significant upregulation of Flt1 gene in metastatic compared with the primary prostate cancer in three out of 10 studies (Table 3). Other angiogenic genes induced in metastatic prostate cancer were CD31 (in 2/3 datasets), CD34 (in 2/11 datasets) and VEGFR3 (in 5/9 datasets) (Table 3). Additional evidence that marrow adipocytes contribute to the upregulation of angiogenesis-supporting factors comes from our own studies in metastatic prostate tumour cells *in vitro* and *in vivo* (111). Specifically, we have shown that exposure of prostate cancer cells to marrow adipocytes

induces expression of pro-angiogenic VEGF as well as genes coding for pro-inflammatory cytokines, CCL20, IL-1α and IL-1β (111). Our data also revealed an upregulation of hypoxia inducible factor-1α (111), a known regulator of angiogenesis, and a key driver of tumorigenesis (112). Collectively, neovascularization is an important factor in tumour colonization and growth in metastatic sites such as bone, and there is growing evidence that MAT via its effect on cancer cells might be promoting angiogenesis-mediated progression of skeletal metastases.

## Cytokine/chemokine signalling and inflammatory microenvironment in metastatic disease in bone

Cancer homing to the bone has been extensively linked to specific chemokine signalling pathways, particularly those driven by CXCL12/CXCR4 and CXCL16/CXCR6 chemokine/receptor axes (113–115). Tumour cells expressing CXCR4 receptor migrate towards endothelial cells and osteoblasts, which secrete its ligand, CXCL12. Interestingly, although not investigated in a context of MAT, CXCL12 has been shown to be secreted by WAT adipocytes and to be involved in the recruitment of macrophages (116). Upon arrival in bone, many DTCs, most of which have escaped chemotherapy, stay dormant (117,118). Factors such as bone remodelling (119), hypoxia (120) and cytokines like parathyroid hormone-related protein, endothelin, Transforming Growth Factor β, platelet-derived growth factor, insulin-like growth factor 1 are known to influence metastatic progression, potentially by allowing tumour cells to escape dormancy (121). One important factor credited with the ability to keep metastatic breast cancer cells in dormant state is thrombospondin-1 (TSP-1), an anti-angiogenic molecule expressed by endothelial cells of bone marrow microvasculature and shown to act as a tumour suppressor (122). The deposits of TSP-1 disappear around sprouting tips of microvascular endothelium, and this coincides with a high concentration of pro-tumorigenic factors, such as active TGF-β1 and periostin around neovascular tips (122). Therefore, it appears that established microvessels inhibit metastatic potential of DTCs, whereas, in contrast, the neovascular tips promote tumour cell growth (122). Surprisingly, bone marrow-derived CD11b+Gr1+ cells and subcutaneous and visceral adipocytes were shown to express anti-angiogenic TSP-1 and its overexpression positively correlated with obesity (123–125). To add to the confusion, the expression of TSP-1 by adipocytes was shown to be significantly reduced by pioglitazone, a PPARγ agonist with insulin sensitizing activities (123). On the other hand, there is also evidence to suggest that obesity-associated induced expression of TSP-1 may mediate recruitment of macrophages to adipose tissue and release of pro-inflammatory cytokines contributing to obesity-accompanied low-grade systemic inflammation (126). TSP-1 increases expression of its receptor

**Table 3** Oncomine (Oncomine v4.5) analysis of mRNA expression of genes involved in fatty acid binding, uptake, synthesis, and metabolism in patients with metastatic prostate cancer sites (M) compared with primary sites (P)

| Gene | Prostate cancer | Fold change | *P* value | *n* |
|------|-----------------|-------------|-----------|-----|
| VEGFR1 | Yu [162] | 1.20 | 7.87E-6 | P: 64; M: 24 |
| | Varambally [163] | 6.17 | 0.001 | P: 7; M: 6 |
| | Chandran [164] | 2.10 | 1.00E-7 | P: 10; M: 21 |
| VEGFR3 | Yu [162] | 1.26 | 6.49E-7 | P: 64; M: 24 |
| | Magee [165] | 1.76 | 0.004 | P: 8; M: 3 |
| | Varambally [163] | 2.25 | 0.002 | P: 7; M: 6 |
| | Chandran [164] | 2.57 | 1.77E-10 | P: 10; M: 21 |
| | Taylor 3 [166] | 1.09 | 0.030 | P: 131; M: 19 |
| CD31 | Taylor 3 [166] | 2.12 | 0.004 | P: 131; M: 19 |
| | Varambally [163] | 2.68 | 0.002 | P: 7; M: 6 |
| CD34 | Yu [162] | 1.10 | 5.74E-5 | P: 64; M: 24 |
| | Ramaswamy [167] | 2.13 | 0.033 | P: 10; M:4 |

'Following genes were analyzed: Vascular endothelial growth factor receptor-1 (VEGFR1) and -2 (VEGFR2), Cluster of differentiation 31 (CD31), and cluster of differentiation 34 (CD34); n = number of samples. Data were ordered by "overexpression" and the threshold was adjusted to P-value <1E⁻4; fold change, 2 and gene rank, top 10%. For each database, only genes that met the criteria for significance are reported'.

CD36 in bone marrow-derived macrophages (127) and activates macrophages via Toll-like receptor 4 (128). Therefore, aside from the earlier mentioned function in facilitating lipid transport, CD36 also appears to play a role in inflammation and angiogenesis (127). We have previously shown that culturing prostate cancer cells in bone marrow-derived adipocyte conditioned media results in mRNA overexpression of CD36 (111). Furthermore, our Oncomine analysis revealed significant overexpression of CD36 in metastatic prostate cancer when compared with primary tumour in four out of 10 available prostate cancer databases (Table 4). Although adipocytes clearly modulate tumour microenvironment to support aggressive phenotype of skeletal metastasis, the relationship between marrow adiposity and tumour cell escape from dormancy is not straightforward and remains to be further investigated.

## Role of adipogenesis in bone remodelling-mediated metastatic progression

It is becoming increasingly clear that the relationship between adipocytes and bone is complex, with some evidence of reciprocal association between increased adiposity and inhibition of osteoblast viability and function (129–132) and other studies revealing no apparent link between adipocyte numbers and bone density (103,104). It appears, however, that marrow adiposity may have definite promoting effects on tumour-driven osteolysis of the bone. Accelerated bone remodelling is one of the key factors associated with homing of tumour cells to the bone (133,134). Experimental treatment with calciotropic hormone (133) or oestrogen and androgen ablation (90) increases bone turnover, which in turn promotes tumour cell growth and occurrences of skeletal metastases (91,119). We have recently shown that bone marrow-derived adipocytes accelerate bone degradation by promoting osteoclastogenesis and augmenting osteoclast-specific expression of cathepsin K, MMP9 and calcineurin, proteins involved in bone remodelling (135). This process is at least partially mediated by adipocytic secretion of pro-inflammatory chemokines of CXC family, CXCL1 and CXCL2, whose levels are dramatically increased upon adipocyte interaction with prostate cancer cell line (PC3) and ARCAP(M) prostate carcinoma cells in bone. This is of importance in a context of metastatic tumour growth, as CXCL1 and CXCL2 are chemoattractants for macrophages, neutrophils and CD11b+Gr1+ cells (also known as myeloid-derived suppressor cells) (136,137). These immune cells express CXCR2 receptors and are capable of modulating tumour microenvironment and affecting progression by stimulating angiogenesis (138,139), suppressing anti-tumour immune responses (140) and promoting chemoresistance (137). This suggests the importance of bone marrow adiposity in bone remodelling associated with

**Table 4**  Oncomine (Oncomine v4.5) analysis of mRNA expression of genes involved in fatty acid binding, uptake, synthesis, and metabolism in patients with metastatic prostate cancer sites (M) compared with primary sites (P)

| Gene | Prostate cancer | Fold change | P value | n |
|---|---|---|---|---|
| FABP4 | Grasso [168] | 2.16 | 0.024 | P: 59; M: 35 |
| | Chandran [164] | 12.32 | 2.20E-6 | P: 10; M: 21 |
| | Yu [162] | 2.14 | 0.001 | P: 64; M: 24 |
| | Holzbeierlein [169] | 2.79 | 0.015 | P: 40; M: 9 |
| | Ramaswamy [167] | 6.37 | 0.013 | P: 10; M: 4 |
| | Ramaswamy 2 [170] | 5.86 | 0.018 | P: 10; M: 3 |
| | Tamura [171] | 2.23 | 0.005 | P: 25; M: 12 |
| | LaTulippe [172] | 6.87 | 0.003 | P: 23; M: 9 |
| CD36 | Grasso [168] | 2.73 | 0.024 | P: 59; M: 35 |
| | Varambally [163] | 2.95 | 5.34E-4 | P:7; M: 6 |
| | Chandran [164] | 2.98 | 0.001 | P: 10; M: 21 |
| | Yu [162] | 1.15 | 8.02E-6 | P: 64; M: 24 |
| FASN | Grasso [168] | 2.49 | 6.67E-5 | P: 59; M: 35 |
| | Chandran [164] | 1.66 | 0.041 | P: 10; M: 21 |
| | Yu [162] | 1.76 | 5.23E-4 | P: 64; M: 24 |
| | Holzbeierlein [169] | 1.67 | 0.029 | P: 40; M: 9 |
| | Ramaswamy [167] | 8.89 | 0.002 | P: 10; M: 4 |
| | Ramaswamy 2 [170] | 12.96 | 0.004 | P: 10; M: 3 |
| | Tamura [171] | 2.04 | 0.018 | P: 25; M: 12 |
| HSL | Chandran [164] | 1.62 | 1.23E-7 | P:10; M: 21 |
| | Lapointe [173] | 1.20 | 0.004 | P: 62; M: 9 |
| | LaTulippe [172] | 1.20 | 0.042 | P: 23; M: 9 |
| | Ramaswamy [167] | 5.96 | 0.027 | P: 10; M: 4 |
| | Grasso [168] | 1.80 | 2.93E-5 | P: 59; M: 35 |
| | Yu [162] | 1.10 | 7.50E-5 | P: 64; M: 24 |
| PLIN2 | Chandran [164] | 1.98 | 8.28E-4 | P: 10; M: 21 |
| | Vanaja [174] | 2.08 | 0.007 | P: 27; M: 5 |
| | Yu [162] | 1.77 | 9.59E-5 | P: 64; M: 24 |
| FATP1 | Grasso [168] | 2.04 | 2.33E-7 | P: 59; M: 35 |
| FATP2 | Varambally [163] | 1.46 | 0.012 | P:7; M: 6 |
| FATP3 | Lapointe [173] | 1.66 | 0.005 | P: 62; M: 9 |
| | Grasso [168] | 1.53 | 3.96E-5 | P: 59; M: 35 |
| | Varambally [163] | 2.11 | 0.014 | P:7; M: 6 |
| FATP4 | Grasso [168] | 1.20 | 0.037 | P: 59; M: 35 |
| | Varambally [163] | 1.58 | 0.002 | P:7; M: 6 |
| FATP5 | Chandran [164] | 2.20 | 2.12E-8 | P: 10; M: 21 |
| FATP6 | Chandran [164] | 1.40 | 0.029 | P: 10; M: 21 |

'Following genes were analyzed: Fatty acid binding protein 4 (FABP4), Cluster of differentiation (CD36; FAT), Fatty acid synthase (FASN), Hormone sensitive lipase (HSL), Perilipin2 (PLIN2); Fatty Acid Transporter Protein Family members (FATP 1-6); n = number of samples. Data were ordered by "overexpression" and the threshold was adjusted to P-value <1E⁻⁴; fold change, 2 and gene rank, top 10%. For each database, only genes that met the criteria for significance are reported'.

cancer-induced bone disease and opens avenues for further investigations.

Bisphosphonates are a class of drugs known primarily for their effects on osteoclast differentiation and survival (141) but are gaining recent attention with respect to their activity towards other cell types in bone (131,142–144). Of particular note is a recent study demonstrating that a single dose of bisphosphonate Zoledronic acid (ZOL) prevents ovariectomy-induced marrow adiposity in rats (131). This potential effect on adipocyte pool in bone could have clinical implications

as ZOL has been administered to patients with prostate (91,145) and breast cancer (119) for the treatment and prevention of skeletal-related events and showed some promise based on the randomized study in castrate resistant prostate patients with bone metastases (146). Unfortunately, a recent study revealed that administration of ZOL, within 6 months of androgen deprivation therapy to castration sensitive men with bone metastases does not reduce risks for skeletal-related events (147). More positive results came from preclinical studies in mice bearing androgen receptor negative (PC3) tumours, where ZOL administration at the time of castration was shown to inhibit castration-triggered metastatic growth (91). Analogous to castration in males, ovariectomy in female mice was shown to induce bone loss and increase growth of breast cancer cells in bone, processes, which were inhibited by ZOL treatment (91,119). These observations are in line with the results of recent epidemiological study showing that use of bisphosphonates can reduce the rate of skeletal-related events only in postmenopausal women (148), supporting the idea that bone remodelling and accumulation of MAT in response to hormonal deprivation may be playing an important role in activation of DTCs.

## Role of marrow adipose tissue in tumour metabolism

The important evidence that marrow adipocytes may have significant impact on progression of skeletal metastases came from our studies utilizing diet-induced marrow adiposity model (111). Intratibial injections of metastatic PC3 cells into high fat diet-induced fatty bones resulted in accelerated intraosseous tumour growth (111). Exposure of prostate cancer cells to marrow adipocytes *in vitro* led to a significant accumulation of lipid droplets in the tumour cells, a process that was accompanied by overexpression of three major regulators of lipid trafficking, FABP4, Perilipin 2 and CD36. In parallel, overexpression of FABP4 was also observed in the bone metastatic lesions as compared with benign and primary prostate cancer tissues (111). Co-culture of marrow adipocytes with prostate cancer cells turned out to be detrimental to adipocytes as observed by the loss of lipid droplets and cell shrinkage. We showed that adipocytes promote cancer cell proliferation and induce invasive behaviour in tumour cells, a process mediated, at least partially, by IL-1β- and FABP4-dependent mechanisms (111). These findings are in line with our Oncomine data, which show that metastatic prostate cancers exhibit highly increased expression of FABP4 (in eight out of 12 datasets) and CD36 (in 4/10 datasets) compared with primary tumours (Table 4). Although not consistently altered across all prostate cancer data sets, several of the *FATP* isomers are also significantly up-regulated in metastatic tissues. These data are in contrast to no observed significant changes in FATP transporters in omental metastases, which suggest there might be depot-specific differences in

fatty acid transport mechanisms between the two sites that differentially affect metastatic progression. Other noteworthy changes between primary and metastatic tumours include the increased levels of lipolysis-associated genes, *HSL* (in 2 out of 4 datasets) and *perilipin 2* (3/12 datasets), as well as lipogenesis-associated FASN (in 7/12 datasets) results further linking the presence of adipocytes in the microenvironment of cancer cells with altered metabolism.

## The role of fatty acyl lipidome

To better understand the role of MAT in tumorigenesis, it is important to evaluate its lipidome. Analysis of normal human bone marrow fatty acid composition showed a wide range of saturated and unsaturated fatty acids (149). Oleic, palmitic and omega-6 PUFA, LAs, are just a few examples of the most abundantly available fatty acids in the bone marrow (149). Arachidonic acid (AA) was found less abundant in bone marrow stroma cells, marrow plasma (150) and in bone marrow mononuclear cells (151) where it was shown to be incorporated into triglycerides and phospholipids. Availability of fatty acids in the tumour microenvironment has a potential to affect tumour cell behaviour and growth. Accordingly, *in vitro* studies have shown that PC3 prostate carcinoma cells migrate towards bone marrow stromal cells and bone marrow-derived adipocytes (152,153). The detailed translocation of lipids from human bone marrow-derived adipocytes to prostate cancer cells was further revealed by Fourier transform infrared microspectroscopy (154). LA and AA were shown to enhance proliferation and cellular invasion of prostate cancer cells, potentially as a result of lipid transfer (155). Direct treatment of PC3 cells with AA showed activation of phosphatidylinositol 3-kinase (PI3K)/AkT and NF-kB signalling pathways leading to rise in gene expression of cyclooxygenase-2 (COX-2), IL-8, IL-1β, IL-6, TNF-α, LTA, CXCL1, PPARγ, GM-CSF, NFkB2, IkBα and ICAM-1 (CD54) (156). The uptake of AA by PC3 cells was shown to induce proliferation (156) and promote invasion, a process inhibited by blocking synthesis of prostaglandin E2 (PGE$_2$) with omega-3 (ω-3/n-3) PUFAs (152). PGE$_2$ is a major COX-2 metabolite reported to induce cellular proliferation, increase expression of COX-2 and stimulate endogenous synthesis of PGE$_2$ (157). As an immunoregulator, PGE$_2$ was reported to play a role in cancer stem cell repopulation and chemoresistance, further implicating AA metabolism in prostate cancer progression (158). Notably, metabolic processing of AA by lipoxygenase is known to result in the production of pro-tumorigenic metabolites, and 5-LOX metabolites of n-6 PUFA, 5(S)-HETE and 5-oxoETE have been shown to inhibit apoptosis (159). Furthermore, overexpression of 12-LOX and the augmented levels of its metabolite 12(S)-HETE correlate with enhanced angiogenic potential and
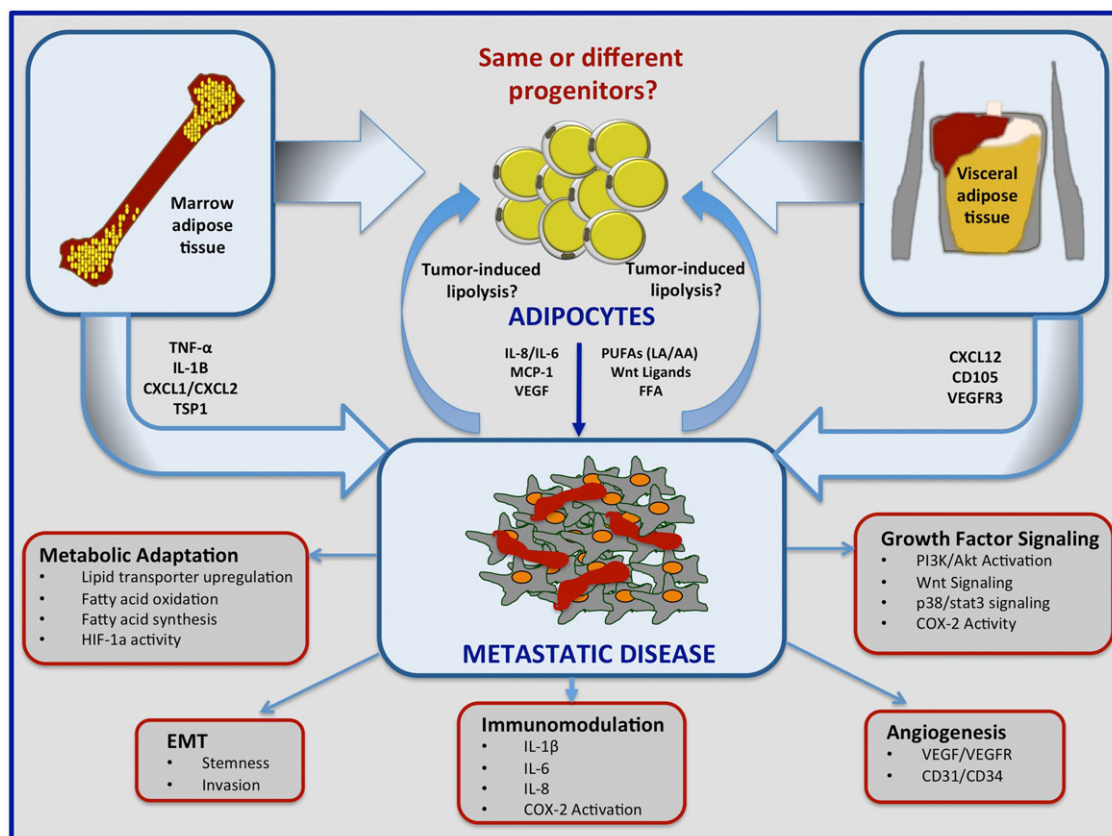
**Figure 1** A schematic of proposed mechanisms underlying involvement of white adipose tissue and marrow adipose tissue in metastatic colonization and progression in omentum and bone. Omentum and bone are adipocyte-rich organs. Adipocytes in either depot have the propensity to fuel tumour growth and survival within the metastatic niche. Both depots are major sources of polyunsaturated fatty acids, Wnt ligands, free fatty acids, cytokines IL-6 and IL-8, MCP-1, and vascular endothelial growth factor (VEGF), all of which are known contributors to tumorigenesis. The specific marrow adipose tissue-derived factors such as TNF-α, IL-β, CXCL1, and CXCL2 as well as white adipose tissue-derived CXCL12, CD105, and VEGFR3, have also all been linked to metastatic disease. Tumour cells within an adipocyte-rich microenvironment have the ability to modulate adipocyte function by stimulating lipolysis and affecting secretion of pro-tumorigenic, pro-angiogenic and immunomodulatory factors. The interaction between adipocytes and tumour cells within the metastatic niche promotes metastatic progression through metabolic reprogramming or adaptation, immunomodulation, angiogenesis, epithelial-to-mesenchymal transformation (EMT) and growth factor/survival pathway signalling.

increased tumour burden (160,161). Although little is known about specific involvement of LA and AA metabolites in tumour progression in bone, the aforementioned studies suggest that bone-marrow adipocyte-derived n-6 PUFAs in MAT may serve an important role in driving metastatic bone disease, which warrants further investigation.

It is important to note that despite its negative publicity, omega-6 fatty acids remain important lipid molecules and their role in cancer should be viewed in a ratio to ω-3. Omega-3 PUFAs are represented by α-linolenic acid (α-LNA, n-3) and its long-chain metabolites, eicosapentaenoic acid (n-3) and DHA, n-3, dietary consumption of which is demonstrated to decrease the risk of prostate cancer (162). It has been suggested that n-3 competes with n-6 for Δ4 and Δ6-desaturases (reviewed in (163)). With n-3 having a higher affinity for these enzymes, increased consumption of omega-3 PUFA results in decreased conversion of LA into AA and consequently its metabolites (163). As a result, the

cancer chemopreventive role of n-3 is usually described as its ratio to n-6 PUFAs (163). As expected, the level of $PGE_2$, a derivative of AA, in rat bone marrow was significantly increased in rats on high ratio of n-6/n-3 fatty acid diet (164). Furthermore, the analysis of fatty acids in prostatic tissues showed significantly higher n-6/n-3 (shown as lower n-3/n-6) ratio in cancer samples compared with benign hyperplasia (165). Based on these findings, it appears that effects of marrow adiposity on tumour cells might be dependent on the individual lipidome.

## Conclusions

A key characteristic of a metastatic tumour is its dependence on the environment that surrounds it. Colonization and growth at the secondary site are a complex process involving reciprocal interactions between the tumour cells and the host microenvironment. Visceral WAT and MAT

represent two distinct metastatic niches that have a common characteristic: they are adipocyte-rich depots that promote tumour progression by supplying lipids to disseminated cancer cells, stimulating growth factor signalling, modulating cancer cell metabolism and stemmness and priming the microenvironment for metastatic growth. Both WAT and MAT adipocytes evoke immunoregulatory effects on the environment by influencing the behaviour of immune cells and modulating the release of pro-inflammatory cytokines and lipid metabolites. They also appear to play a role in angiogenesis via direct release of pro-angiogenic factors or stimulation of their secretion by neighbouring cells, including the tumour cells. It is those effects on the host cells, in combination with direct impact on tumour cells via altered fatty acid metabolism, that provide an environment conducive to tumour adaptation and survival (Fig. 1). Little is known on whether heterogeneity of WAT and MAT has any effect on colonization and growth of tumour cells that homed to that site. There is evidence to suggest that more than one population of WAT and MAT adipocytes exist, some sharing common progenitors between the two fat depots and some of the origin that is distinct to a specific site. Time and additional research efforts will reveal whether the metabolic symbiosis between adipocytes and tumour cells at the metastatic site is driven by a specific population of adipocytes, and whether this opens avenues for therapeutic intervention.

## Conflict of interest statement

The authors disclose no potential conflicts of interest

## Acknowledgement

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