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1 **The role of bone-marrow adipocytes in cancer progression: the impact of** 2 **obesity**

3
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5 # Equal contribution

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15 16 **Statements and Declarations**

17 The authors declare no competing interests.

18 19 **Abstract**

20 Bone marrow adipose tissues (BMATs) and their main cellular component, bone marrow adipocytes (BMAds),
21 are found within the bone marrow (BM), which is a niche for the development of hematological malignancies as
22 well as bone metastasis from solid tumors such as breast and prostate cancers. In humans, BMAds are present
23 within the hematopoietic or “red” BMAT and in the “yellow” BMAT where they are more densely packed. BMAds
24 are emerging as new actors in tumor progression, however there are many outstanding questions regarding their
25 precise role. In this review, we summarized our current knowledge regarding the development, distribution, and
26 regulation by external stimuli of the BMATs in mice and humans and addressed how obesity could affect these
27 traits. We then discussed the specific metabolic phenotype of BMAds that appear to be different from “classical”
28 white adipocytes, since they are devoid of lipolytic function. According to this characterization, we presented how
29 tumor cells affect the *in vitro* and *in vivo* phenotype of BMAds and the signals emanating from BMAds that are
30 susceptible to modulate tumor behavior with a specific emphasis on their metabolic crosstalk with cancer cells.
31 Finally, we discussed how obesity could affect this crosstalk. Deciphering the role of BMAds in tumor progression
32 would certainly lead to the identification of new targets in oncology in the near future.

1 **Introduction**

2 In mammals, white adipose tissue (WAT) accumulates at various sites throughout the body [1]. WATs are often
3 found in close proximity to tumors in the breast, prostate and colon cancers in addition to melanoma (occurring in
4 mammary, periprostatic, visceral, and sub-cutaneous adipose tissues, respectively) [2–4]. Invasive cancer cells can
5 reach adipose tissue (AT) and interact with several cellular components of this tissue, including mature adipocytes
6 - the predominant component of AT [2–4]. White adipocytes are active metabolic cells, storing fatty acids (FA) as
7 triglycerides (TG) and mobilizing these lipids to fuel organs in energy-demanding conditions, through a process
8 called lipolysis [1, 5]. In addition to this metabolic function, adipocytes are important endocrine cells, releasing
9 more than 400 soluble factors (also known as adipokines), including hormones, chemokines, cytokines, and growth
10 factors [6, 7]. Due to their endocrine and metabolic functions, white adipocytes are now well-recognized for their
11 role in cancer progression [2, 3]. This relationship is of major clinical interest because of the established link
12 between obesity and cancer. In fact, since the seminal study conducted by Calle *et al* in 2003 [8], it has been
13 recognized that excess body weight increases cancer occurrence and worsens prognosis, however this depends on
14 cancer type [9]. Obesity is characterized by an increase in WAT size, whereby greater lipid accumulation in
15 adipocytes is associated with metabolic and secretory dysfunctions [10]. The precise mechanisms underlying the
16 obesity–cancer link are not yet well understood. However, it is tempting to speculate that, within the context of
17 obesity, proximal adipocytes create a favorable environment for the progression of tumors due to their
18 dysfunctional state.

19 The interaction between tumor cells and adipocytes also occurs at metastatic sites. For example, intra-abdominal
20 tumors such as ovarian, gastric, and pancreatic tumors metastasize to the omentum, a large fat pad present within
21 the peritoneum, where they interact with adipocytes [11, 12]. In mice, a subset of leukemic stem cells migrates to
22 visceral AT and changes its characteristics to obtain metabolic benefits [13]. Bones are also common metastatic
23 sites for prostate, breast, lung, melanoma, and kidney cancers [14]. Bones are also an adipocyte-rich environment
24 containing AT called bone marrow adipose tissue (BMAT), which is present within the bone marrow (BM) [15].
25 In addition to the homing and outgrowth of solid cancer cells, BM is a niche for the development of hematological
26 malignancies, such as acute myeloid leukemia (AML) and multiple myeloma (MM). Over the last few years,
27 accumulating evidence shows that BM adipocytes (BMAds), present in BMAT, have unique metabolic features
28 that distinguish them from “classical” white adipocytes, suggesting that their metabolic crosstalk with cancer cells
29 might be of a different nature.

30 In this review, we will summarize current knowledge on the specific phenotype of BMAds, address their
31 modifications with obesity, and discuss how these adipocytes may play a role in cancer progression.

32

33 **BMAds are unique adipocytes**

34 While known for more than a century, BMAds have long been portrayed as space fillers with no ascribed or
35 specific biological function. Over the last decade, the interest in BMAT has increased and several studies have
36 highlighted their role in hematopoiesis and bone homeostasis (for reviews see [16, 17]). However, compared to
37 other “classical” white adipocytes, their characterization remains incomplete, particularly in humans. This section
38 of our review will summarize our current knowledge on the phenotype of BMAds and distinguish their metabolic
39 specificities in comparison to white adipocytes.

1 *Not one, but two types of BMAds*

2 While Neumann observed red and yellow regions in the BM in the 19th century [18], Tavassoli was the first to
3 show the presence of two types of BMAds in rabbits by studying their response to phenylhydrazine-induced
4 hemolysis, in 1976 [19]. He observed a resorption of fat cells present in red BM, whereas those present in yellow
5 BM remained stable [19]. Forty years later, Ormond McDonald's group described these two types of BMAT more
6 precisely, identifying constitutive BMAT (cBMAT) and regulatory BMAT (rBMAT) [20]. These two types of
7 BMAT differ in their response to external stimuli, location, development, and proximity to hematopoietic cells, as
8 summarized in **Figure 1**. As for external stimuli, the volume of BMAT and the size of adipocytes were examined
9 after a 21-day cold exposure followed by osmium tetroxide staining in the tibia (proximal and distal) and in the
10 tail vertebrae of mice [20]. Although cold exposure decreased the volume of BMAT in addition to the size and
11 number of BMAds in the proximal tibia (corresponding to red marrow or rBMAT), the BMAT in the distal tibia
12 and tail vertebrae (mainly composed of yellow marrow or cBMAT) were unaffected [20]. Later studies also
13 reported a decrease in the size and number of adipocytes in rBMAT following other external stimulation, such as
14 exercise [21] or fasting [22], whereas cBMAT was unaffected. In rodents, cBMAT is present in the tail vertebrae
15 and in the distal tibia, whereas rBMAT is found in the lumbar/thoracic vertebrae as well as in the femur and the
16 proximal tibia (proximal epiphysis and growth plate to tibia/fibula junction) (**Figure 1**). cBMAT develops soon
17 after birth and remains constant throughout life, and rBMAT appears later in the tibia diaphysis at four-weeks of
18 age until total invasion of the whole tibia in 56-week-old C3H/HeJ mice [20]. Histologically, hematoxylin and
19 eosin (HE) staining shows that cBMAT contain adipocytes (called cBMAds) that are densely packed and resemble
20 white adipocytes, while rBMAds, being smaller than cBMAds, are scattered across hematopoietic tissue [15, 20].
21 3D electron microscopy of rBMAT shows that rBMAds are surrounded with osteoblasts, endothelial, and
22 hematopoietic cells, and the authors estimate that one rBMAd can interact with over 100 hematopoietic cells [23].
23 Additional characterization of these two types of BMAds also reveals that cBMAds contain more unsaturated
24 lipids compared to rBMAds, consistent with increased expression of several desaturases (enzyme introducing
25 double bonds in FA) in cBMAds [20]. Notably, a greater expression of adipogenic transcription factors C/EBP
26 (CCAAT-enhancer-binding proteins) α and β were also found in cBMAds, whereas PPAR γ (Peroxisome
27 proliferator-activated receptor gamma) was similar in both cBMAds and rBMAds, suggesting that the
28 transcriptional regulation of adipogenesis might be different between these two types of adipocytes [20].

29
30 In humans, BMAT is assessed using imaging techniques, such as magnetic resonance imaging (MRI), that quantify
31 the BM fat fraction (BMFF). More recently, the development of the single-voxel proton spectroscopy (1H-MRS)
32 allows quantification of BMAT in a standardized manner with high reproducibility, and is also capable of assessing
33 lipid saturation levels (for a review, see [24]). Using 1H-MRS, it is estimated that BMAT comprises more than
34 10% of the total fat mass [25] and can represent 70% of the BM volume in the iliac crest in adults [26]. Of note,
35 the total volume of BMAT is higher in human than in rodents [15].

36 As observed in rodents, BMAT volume also increases with age in humans, a process also known as “red to yellow
37 conversion” [17, 26, 27]. At birth, BM is primarily composed of hematopoietic cells, then red to yellow conversion
38 slowly occurs in the distal appendicular skeleton (legs and arms) [28] and continues throughout life in the red BM
39 of axial skeleton (sternum, ribs, pelvis, and vertebral bones) [27]. Higher amounts of BMAT are present in males
40 compared to female in the vertebrae, sacrum, and hips [29, 30] but following menopause, BMAT volume is higher

1 in the vertebrae of women [31]. Moreover, the presence of BMAT differs between the BM regions in adults.
2 Recently, the Cawthorn's lab used a PET/CT (Positron emission tomography/computed tomography) scan to
3 define a cartography of BMAT-rich or BMAT-deficient regions [32]. A high proportion of BMAT was found in
4 the sternum, arms, and legs (considered "yellow" BM), whereas the vertebrae and the ribs contain lower amounts
5 of BMAT (considered "red" BM) (**Figure 1**). They also observed an increase in BMAT volume with age (beyond
6 60-years of age) in the axial skeleton but not in long bones [32].
7 Despite these important studies showing differences in BMAT repartition in humans, none of these imaging
8 techniques can identify whether the two types of adipocytes described in rodents exist in humans. This information
9 can be obtained from BM biopsies for diagnostic purposes, including BM aspirates obtained during orthopedic
10 surgeries such as hip or knee replacements, or during post-mortem autopsies [33]. Using these various techniques,
11 BMAdS are observed to be more scattered in the femoral head and iliac crest and more densely packed within
12 femoral diaphysis [33]. These results could suggest that "red" and "yellow" BMATs are present in separate areas
13 within the bones. However, we recently reported that BM aspirates from femoral diaphysis contain interlaced
14 red/yellow BMAT [34]. It is unknown whether these two areas of BMAT, as defined by their macroscopic features
15 (red/yellow), also indicate functional differences for the adipocytes that they contain, as described in rodents for
16 cBMAT and rBMAT [15]. We recently demonstrated that human yellow BMAT contains BMAdS that closely
17 resemble classic white adipocytes on a morphological level, but are devoid of lipolytic activity, one of the main
18 metabolic functions of white adipocytes [35]. Similar morphological and functional characteristics are found in
19 cBMAdS in rodents [22], which strongly suggests that yellow BMAT in humans corresponds to cBMAT. The
20 nature of red BMAT and the adipocytes that are present within this tissue need to be characterized in humans.

21 22 ***Metabolic specificities of BMAdS***

23 As mentioned above, BMAd metabolic and endocrine functions have been characterized, and similarities and
24 differences with white adipocytes were found. *In vivo* arguments raised the notion that BMAdS might be deficient
25 in lipolysis, one of the main metabolic functions of white adipocytes. In fact, the primary role of white adipocytes
26 is to store FA as TG during energy intake, and release FA when energy is required (to provide energy for
27 demanding tissues). This is carried out through a process called lipolysis, leading to a decrease in WAT size [36].
28 Lipolysis is stimulated by catecholamines through adrenergic receptors allowing successive activation of three
29 lipases leading to the release of FA and glycerol [36]. In stark contrast to WAT, BMAT volume increases in mice
30 [25, 37] and rabbits [38, 39] upon caloric restriction, and in human patients suffering from anorexia nervosa [40,
31 41]. A decrease in BMAT only occurs during severe nutrient deprivation in rabbits [42] and at late stages of
32 anorexia nervosa in humans, associated with gelatinous transformation of the BM [40] (for a review see [43]). We
33 recently validated this hypothesis by demonstrating that human BMAdS isolated from yellow BM are devoid of
34 lipolytic activity due to a profound downregulation of monoacylglycerol lipase (*MGLL*) expression (the last lipase
35 involved in the lipolytic process) while the adrenergic signaling pathway remained functional [35]. However, it is
36 still unknown whether human BMAdS isolated from red BM display the same lipolytic defect. In rodents, the
37 Scheller's lab found that cBMAdS resist lipolysis after stimulation with beta 3 adrenergic agonist while a very low
38 lipolytic response was found in rBMAdS compared to subcutaneous adipocytes (SCAdS) [22]. Although adrenergic
39 receptors are expressed in BMAdS in rodents, they fail to activate (as shown by its phosphorylation) the hormone
40 sensitive lipase (HSL), the second lipase involved in lipolysis [22]. Nonetheless, the expression of *MGLL* has not

1 been investigated in these cells. Moreover, even if the lipolytic activity measured *ex vivo* in rBMAds is very low,
2 rBMAds decrease in size upon adrenergic stimulation [15, 20] suggesting that another mechanism might be
3 involved and explain their reduced size following stimulation. Interestingly, adrenergic stimulation induces an
4 increased number of small lipid droplets (LD) in the cytoplasm surrounding the unilocular LD in rBMAds [22], a
5 process that could contribute to the decreased size observed in rBMAds.

6 In addition to defective lipolysis, other features of lipid metabolism are differentially regulated in BMAds
7 compared to white adipocytes. BMAds display high uptake of polyunsaturated FA compared to saturated FA in
8 mice [44] and recent PET/CT studies in fasted volunteers showed a greater uptake of FA in BMAT than in WAT
9 [45]. Finally, during starvation, lipogenesis is decreased in WAT but maintained in rabbits [38] and mice [46].
10 Moreover, two recent studies showed an increased basal glucose uptake (measured by PET/CT with ¹⁸F-
11 fluorodeoxyglucose) in BMAT (in vertebrae but not in the femur) compared to WAT in humans [32, 47]. More
12 precisely, transcriptomic analysis performed on both rodent and human BMAT and BMAds (from proximal
13 femoral diaphysis) showed modifications of genes related to glucose uptake and insulin responsiveness (i.e.
14 decreased expression of insulin receptor, IRS1 (Insulin receptor substrate 1) and GLUT4 (Glucose transporter
15 type 4) and increased expression of GLUT1 and GLUT3 in BMAds compared to SCAd). Moreover, in rodent,
16 cBMAT resist insulin-stimulated Akt phosphorylation which is consistent with the higher basal glucose uptake
17 measured *in vivo* [32]. Thus, intracellular glucose (following conversion to glycerol 3-phosphate) and intracellular
18 FA could be used for lipogenesis to produce TG. As summarized in **Figure 2**, these various metabolic features
19 converge to maintain BMAT during caloric restriction. The preserved fat storage in BMAT under energy-
20 demanding conditions at the body level could suggest that this tissue supports critical local functions that need to
21 be preserved.

22 These results, however, do not signify that BMAds are inert cells unable to deliver lipids in response to appropriate
23 local signals. Using proteomic analysis, we recently demonstrated that BMAds from yellow BM expressed high
24 levels of lysosomal acid lipase (LIPA) compared to SCAd [35]. LIPA is involved in lipophagy, a metabolic
25 pathway that degrades LD into the lysosome and releases cholesterol and FA in the extra-cellular medium [48].
26 Our study further demonstrated that BMAds exhibit a cholesterol-orientated metabolism. BMAds express high
27 protein levels involved in cholesterol transport (apolipoproteins A2 and C1-C3) and in cholesterol cytoplasmic
28 hydrolysis (Neutral Cholesterol Ester Hydrolysis, NCEH1) that are associated with an increase in free cholesterol
29 content compared to white adipocytes [35]. Future research should investigate whether these two pathways
30 (lipophagy and cytoplasmic cholesterol hydrolysis) are activated by BMAd-surrounding cells, including cancer
31 cells to favor liberation of lipid metabolites (**Figure 2**).

32 Overall, these studies highlight that BMAds are a distinct subtype of adipocytes in term of metabolism, different
33 from classic adipocytes. However, new studies are clearly needed to better characterize metabolic differences
34 between rBMAds and cBMAds in rodents and humans.

36 ***Endocrine function of BMAds***

37 As mentioned in the introduction, besides their metabolic function, adipocytes secrete adipokines including
38 hormones (adiponectin and leptin), chemokines, cytokines, and growth factors [6, 7]. The endocrine function of
39 BMAds has been investigated over several studies using BM mesenchymal stem cells (BM-MSCs) differentiated
40 *in vitro* in adipocytes. These studies show that BM-MSC-derived adipocytes can secrete several adipokines such

1 as adiponectin, leptin, RANKL (receptor activator of nuclear factor- κ B ligand), stem cell factor, pro-inflammatory
2 cytokines (Interleukin (IL-6), tumor necrosis factor α (TNF α)), and chemokines (Chemokine (C-X-C Motif)
3 Ligand 1, 2, and 12 (CXCL1), (CXCL2), (CXCL12)) (for a review, see [49]). A handful of studies have reported
4 the secretory profile of BMAT or isolated BMAdS compared to classical adipose depots. Compared to WAT,
5 adiponectin expression and secretion were higher in cBMAT in rodents and in human tibia BMAT [25]. In contrast,
6 rBMAT or femoral BMAT in humans express and release the same amount of adiponectin relative to WAT [35,
7 50–52]. Femoral BMAdS also express [35] and secrete [52] similar levels of leptin compared to paired human
8 SCAdS. High expression of proinflammatory cytokines such as TNF α , IL-6, and IL-1 β was found in rBMAdS in
9 mice [53] and femoral BMAdS in humans compared to paired SCAdS [52, 54].

10 Although the use of *in vitro* models of BMAdS could be of interest, studies performed with BMAT and isolated
11 BMAdS highlighted that heterogeneity exists within different areas and types of BMAT that may be
12 underestimated in these *in vitro* models as discussed in a recent review [49]. We also found that BM-*MSC*-derived
13 adipocytes do not recapitulate the defect in lipolysis activity observed in human BMAdS isolated from yellow
14 marrow [35]. Taken together, these results suggest that any findings associated with these *in vitro* models should
15 be interpreted with caution, as we will discuss further below.

16 **Changes in BMAT and BMAdS during obesity**

18 During obesity, white adipocytes undergo hyperplasia (an increase in cell number) and hypertrophy (an increase
19 in adipocyte size) resulting in an important expansion of WAT to increase energy storage. Hyperplasia corresponds
20 to the recruitment and differentiation of adipose precursor cells, and hypertrophy occurs due to increased lipid
21 storage in adipocytes leading to hypoxia and mechanical stress that contribute to adipocyte dysfunction and death
22 [55]. Larger adipocytes display changes in their lipid composition [56, 57], increase in basal lipolysis [58], and
23 modifications in adipokine secretion with an increase in proinflammatory cytokine release [59]. Moreover,
24 immune cells are recruited in response to adipocyte death contributing to obesity-induced inflammation in WAT
25 [60]. Therefore, obesity leads to both changes in the white adipocyte phenotype, and in the cellular composition
26 of WAT. Whether these changes also take place in the BMAT is still an open question. The following section will
27 describe global changes of BMAT volume *in vivo* in obese mice and humans, and will summarize our current
28 understanding around the BMAd phenotype in the context of obesity.

29 ***Does BMAT volume increase with obesity?***

31 Several studies have measured BMAT volume by osmium staining and micro-CT (μ CT) in mice fed with a high
32 fat diet (HFD) to induce obesity. This work showed increased rBMAT in the femur and proximal tibia compared
33 to normal diet (ND)-fed mice [21, 61–64]. To our knowledge, no studies have assessed the cBMAT volume in
34 HFD-fed mice. As BMAT increases with age in rodents [20, 24], the response of BMAT to HFD-induced obesity
35 differs between young and older mice [61]. While HFD significantly increases the volume of rBMAT in young
36 mice (3-months old), only a slight increase is observed in older mice (11-months old). A transcriptomic analysis
37 of BMAdS (from both the femur and tibia) showed that the changes in gene expression observed under HFD is
38 quantitatively different in young versus older HFD-fed mice and mostly affect genes involved in adipogenesis,
39 inflammation, and mitochondrial dysfunction [61]. The low impact of HFD on older mice could be explained by
40 the fact that the gene changes induced by HFD are very similar to age-related gene changes [61].

1 In humans, few clinical reports studied changes of BMAT in obese compared to normal-weight subjects. These
2 studies measured the BMFF by 1H-MRS or MRI and showed that changes in BMFF in obesity vary depending on
3 the location of BMAT and age (summarized in **Table 1**). The most important variations of BMFF have been
4 reported when comparing axial and appendicular BMAT in adults. Indeed, Bredella *et al* showed an increased
5 BMFF in the L4 lumbar spine [41, 65] in obese compared to normal-weight patients, whereas an inverse correlation
6 between femoral metaphysis/diaphysis BMFF and abdominal SAT was reported in obese patients [66].
7 Interestingly, similar location-specific changes (the increase of BMFF in the L4 lumbar spine and decrease in
8 femoral metaphysis) have been reported in normal-weight patients on a HFD [67]. Differences in BMFF
9 composition have been also observed with an increased lipid saturation index in the lumbar spine BMAT, however
10 no changes were found in femur BMAT [68]. Regarding the age-dependent response, a significant decrease of
11 BMFF of lumbar spine was reported in young obese patients compared to their age-matched normal-weight
12 subjects [69, 70] in contrast to results obtained in older subjects [41, 65]. This decrease in adiposity in red marrow-
13 rich regions contradicts results obtained in mice, where the increase in rBMAT volume is higher in young
14 compared to older mice [61].
15 Overall, these results suggest that during obesity, BMAT increased in the axial skeleton (in regions rich in “red
16 marrow”), whereas a decrease is observed in “yellow marrow”-rich areas contained in the diaphysis/metaphysis
17 of long bones such as the femur. Nevertheless, the impact of obesity is less pronounced compared to other WAT
18 [41, 67]. It is important to mention that, despite the high reproducibility of 1H-MRS used in the reported studies,
19 this technique can have limited accuracy and precision in areas of low-fat content such as axial BMAT [24].
20 Overall, these studies remain fragmentary and studies including large numbers of patients with simultaneous
21 analysis of the different BMAT-containing regions are required to confirm these findings. Furthermore, any gender
22 differences should also be considered.

23 ***Modifications of BMAds with obesity***

24 The notion that obesity-related increases of BMAT are due to hyperplasia or hypertrophy of BMAds has only been
25 addressed in a limited number of studies. The presence of hyperplasia in cases of obesity is supported by several
26 studies. An enhanced expression of adipogenic genes (i.e., *PPARG2*, *LEP*, and *ADIPOQ*) associated with a
27 decreased expression of pro-inflammatory genes (*TNF α* , *IL-1 β*) has been reported in BM-MSCs from HFD
28 compared to ND-fed mice [64, 71]. These BM progenitor cells from HFD-fed mice display an increased adipogenic
29 differentiation capacity and remain insulin-sensitive with obesity [64]. In humans, obese BM-MSCs also exhibit
30 a shift in molecular phenotype toward committed adipocytic progenitors and display increased insulin signaling
31 compared to BM-MSCs obtained from lean subjects [72]. Although these studies suggest that BMAT increases in
32 obesity through hyperplasia, they are insufficient to conclude whether adipocyte hypertrophy is absent in this
33 process.

34 Very few studies have reported changes in BMAT and BMAds secretory and metabolic functions in case of
35 obesity. At the tissue level, obesity has not been associated with the occurrence of an increased inflammatory state
36 in mouse BMAT, in contrast to WAT [64]. Interestingly, a higher expression of *TNF α* and *IL-6* in BMAT
37 compared to WAT is observed in the ND condition [64] and similar results have been found in human BMAds
38 *versus* white adipocytes in normal-weight patients [52, 54]. This basal inflammatory phenotype might explain the

1 absence of further regulation in obesity. To our knowledge, the metabolic function of BMAds in obesity has not
2 been addressed to date.

3 **What is the role of BMAds in cancer progression?**

4 As mentioned in our introduction, the role of white adipocytes in cancer progression is now widely acknowledged
5 [2–4]. Adipocytes promote cancer cell proliferation/survival, migration/invasion, and resistance to chemotherapy
6 through their ability to secrete soluble factors, extra-cellular matrix (ECM) proteins as well as ECM remodeling
7 proteins and lipid release [2–4]. In the tumor microenvironment, mature adipocytes are a tremendous reservoir of
8 lipids and their ability to release these lipids to fuel cancer cells is considered as one of their most specific and
9 potent role in tumor progression [2–4]. Initially described in breast cancer [73], delipidation of adipocytes (marked
10 by major decreases in size and lipid content) is found at the invasive fronts of solid tumors, and these modified
11 adipocytes are called Cancer-Associated Adipocytes [3, 4, 74]. This delipidation is due to the activation of lipolysis
12 in adipocytes leading to the release of FA [11, 75]. These FA are taken up by cancer cells and trigger a complex
13 metabolic remodeling that improve their survival, invasive, and metastatic abilities as well as resistance to
14 treatment (for a review see [3, 4]). This metabolic symbiosis between adipocytes and cancer cells is demonstrated
15 in a wide range of models such as breast, ovarian, and prostate cancers in addition to melanoma [11, 75–77], but
16 differences in the nature of this metabolic crosstalk is observed between the various types of cancer as we recently
17 reviewed [4].

18 Although the role of white adipocytes in cancer progression is now well-established, the impact of BMAds on the
19 aggressiveness of both bone metastasis of solid tumors and hematological malignancies has not been thoroughly
20 studied. Considering that BMAds display specific metabolic features and that the metabolic symbiosis is at the
21 forefront of adipocyte's effect on cancer cells, we will focus on this aspect of the crosstalk. Since an alteration in
22 lipolytic activity in BMAds was reported in humans and rodents [22, 35], we will first focus on the presence or
23 absence of modifications to BMAds (e.g., number and size) in the vicinity of tumor cells *in vivo*. We will then
24 discuss how BMAds affect cancer cells' behavior and how obesity impacts this interaction.

25 ***Do cancer cells induce modifications of BMAds in vivo?***

26 To study the impact of cancer cells on BMAds, most studies have evaluated the number and size of human BMAds
27 in trephine biopsies of the posterior iliac crest from patients with hematological cancer. To our knowledge, this
28 type of study has not been conducted in bone metastasis of solid cancers. The number of adipocytes depends on
29 the balance between adipogenesis (formation of new adipocytes) and cell death, whereas adipocyte size reflects
30 the relative rate of lipid storage and mobilization. Thus, the comparison of these parameters between patients and
31 healthy donors could enhance our understanding of cancer cell impact on BMAds. Contrary to primary solid tumor
32 sites, the phenotype of BMAds in close proximity to cancer cells is less clear and appears to be highly dependent
33 on the disease of concern (**Figure 3**).

34

35 **In multiple myeloma**

36 First, reports on the number and size of BMAds in patients with MM were contradictory. Indeed, Liu *et al* showed
37 a decreased number of BMAds in patients with MM [78]. However, two other studies found same number of
38 BMAd in MM patients compared to healthy donors [79, 80]. Moreover, although an increase in BMAd size was

1 first reported [79], recent studies found no size changes [78] or even a decrease of the mean size (with an increase
2 in small adipocytes and a decrease larger adipocytes) [80]. Interestingly, the reduced size of BMAd in MM
3 samples is independent of the tumor load in the BM suggesting the presence of an active process [80]. Although
4 delipidation of larger adipocytes under MM cell secretion may be considered, these studies also raise the possibility
5 of a deregulated adipogenesis process. In fact, a significantly greater number of early precursors (preadipocyte
6 factor 1 positive cells) is observed in the BM of patients with MM compared to healthy donors [79], however the
7 expression of PPAR γ , a key regulator induced later during the adipogenesis process [81], is reduced in BMAd
8 from MM patients [78]. Moreover, the adipogenic capacity of BM-MSCs from MM is reduced compared to BM-
9 MSCs from healthy patients [82]. Taken together, these results suggest that MM inhibits the first stages of
10 adipogenesis leading to the accumulation of early adipocyte precursors.

11 Although the mechanisms that contribute to changes in BMAd size and number in MM remain to be determined,
12 the plasticity of BMAd during the evolution of disease suggests that they actively contribute to its development.
13 At possible precursor states of MM, such as monoclonal gammopathy of undetermined significance (MGUS), no
14 changes in BMAd number and size are observed [80]. However, the number and the size of BMAd are restored
15 in treated patients in remission (where most of MM-associated abnormalities are normalized except the osteolytic
16 lesions) [78, 80] and they are found close to resorbed bone areas, suggesting the role of BMAd in bone resorption
17 [78]. Moreover, patients with lower BMAd before treatment show complete remission, suggesting that BMAd
18 protect MM cells against chemotherapy and participate in residual disease, as discussed below [80].

19

20 **In leukemia**

21 Unlike MM, Boyd et *al* reported a substantial decrease in the number of BMAd and a slight decrease in their size
22 in patients with AML [83]. These effects are recapitulated in AML-engrafted mice in the active hematopoietic
23 region (red marrow), which contains rBMAT [83, 84], a region with a constant accumulation of newly formed
24 adipocytes [20]. In contrast, the size and number of BMAd present in yellow marrow (cBMAT) are unaffected
25 [83]. It is important to remember that in rodents, BMAd from both areas have an altered lipolytic activity [22].
26 However, in “classical” adipose depots, a dramatic decrease in adipocyte size was observed in VAT [13] or SAT
27 [83] colonized by AML cells *in vivo*, which demonstrates that leukemic cells are able to induce lipolysis *in vivo*
28 (**Figure 3**). Although the mechanism involved in the decreased size of rBMAd in AML has not been identified
29 yet, several hypotheses can be proposed such as a partial restoration of lipolysis, a release of small lipid droplets
30 [22] or other mechanisms of delipidation (still unknown). Additionally, the reduced number of BMAd suggests a
31 decrease in adipogenesis induced by leukemic cells. First, it is electively observed in rBMAT in mice, a region
32 where there is continual accumulation of newly formed adipocytes [20]. A reduced adipogenic differentiation
33 capacity of BM-MSCs from AML patients has also been described *in vitro* [83]. However, the induction of
34 adipocyte death and its capacity to account for its substantial effect on BMAd number warrant further investigation.
35 These *in vivo* studies highlight the considerable impact of AML cells on BMAd and appear to involve complex
36 mechanisms, including delipidation, inhibition of adipogenesis, and induction of cell death.

37 BMAd also evolve during AML pathogenesis and therapy, and the plasticity of BMAd offers indirect indications
38 regarding potential underlying mechanisms. BMAd numbers progressively decline with disease severity starting
39 with the occurrence of myelodysplastic syndrome that drastically decrease at AML diagnosis [83]. Boyd et *al* also
40 found that PPAR γ agonist administration reverses AML-induced suppression of BMAd number and partially

1 restores the defect in myelo-erythroid hematopoiesis observed in AML while repressing leukemic growth [83].
2 These results suggest that BMAds possess a positive effect on normal hematopoiesis while inhibiting leukemic
3 growth [83]. Conversely, Jun Shi's group reported an increased number of small adipocytes in refractory subjects
4 following chemotherapy compared to patients in remission [85]. Moreover, patients with high amounts of small
5 adipocytes [85] or increased BMAd volume [86] exhibit shorter relapse-free survival, suggesting a positive effect
6 of BMAds on leukemic growth.

7 Dynamic remodeling of BMAds was also shown during ALL (acute lymphoblastic leukemia) pathogenesis with a
8 profound loss of BMAd number at diagnosis and a notable decrease in their size [87]. A decrease in BM-MSC
9 progenitors due to defective regenerative growth was observed in the ALL-BM, which is associated with the
10 presence of progenitors blocked within the differentiation process [87]. Although these results suggest an effect
11 on adipogenesis, additional mechanisms explaining the major reduction in pre-existing large adipocytes require
12 further investigation. Interestingly, the authors of this study showed a decrease in ALL engraftments in adipocyte-
13 rich tissue (tail and gonadal AT) compared to femoral engraftment in mice. This is due to increased quiescence of
14 ALL cells in adipocyte-rich tissue, suggesting that BMAds may limit the expansion of ALL in BM [87]. Following
15 chemotherapy, an apparent reconstitution of BMAds is observed, however these BMAds do not reach normal
16 levels compared to healthy donors [87]. Critically, the restoration of the adipocytic niche increases ALL cell
17 quiescence and multistress resistance, which could contribute to leukemia re-evolution following remission [87].
18

19 Overall, these *in vivo* studies and the analysis of BM biopsies reveal that the BMAd niche is dynamic and plastic
20 during hematological malignancies, however these effects differ depending on cancer type (**Figure 3**). While
21 present in both MM and leukemia, adipogenesis seems to be affected and partially explain the decreased number
22 of adipocytes, other mechanisms are responsible for the disappearance of existing BMAds (mainly observed in
23 leukemia). Even if these mechanisms remain unknown, adipocyte death is conceivable. While the decrease in size
24 of existing mature adipocytes observed in AML and in ALL could be due to a restoration of lipolytic activity,
25 additional mechanisms (i.e., an alternate pathway of delipidation) are likely involved but remain to be identified.
26 We will discuss in the next chapter how *in vitro* studies could provide compelling clues. Additionally, these studies
27 highlight the fact that BMAds are vital actors in the progression of these diseases and the mechanisms involved in
28 this process will be discussed in the next chapter.

29 ***Is there metabolic crosstalk between cancer cells and BMAds in vitro?***

30 Several *in vitro* studies have been performed using cell lines derived from hematological malignancies as well as
31 solid tumors (mainly prostate or breast cancer) to study the metabolic symbiosis with BMAds. These studies are
32 conducted using *in vitro* differentiated BM-MSCs. Using BM-MSC-derived adipocytes loaded with isotopically
33 labeled palmitate, a direct transfer of lipids from BMAds to prostate cancer cells was demonstrated in 2007 [88].
34 Similar results were obtained in AML [89] and in MM [90] using primary BM-MSCs or the murine BM-MSC
35 OP9 cell line, grown under adipogenic conditions and loaded with fluorescent FA. As identified with white
36 adipocytes (for a review see [4]), FA are released by BMAds due to lipolysis activation [84, 89–92]. In BMAds,
37 the activation of lipolysis is attributed to acute activation of HSL (by phosphorylation) in AML [89] or upregulation
38 of the expression of *ATGL* and *HSL* in AML and prostate cancer cells [91–93]. The lipolytic signals may differ
39 depending on the tumor considered. Although IL-1 β is implicated in lipolysis induced by prostate cancer cells

1 [93], GDF15 (Growth/differentiation factor 15) has been reportedly involved for AML cells [84]. FA released by
2 BMAd are taken up by cancer cells through different transporters such as the fatty acid binding protein 4 (FABP4)
3 [89, 94, 95] or FATPs (Fatty Acid Transport Protein) [90] and are then stored [92] and/or oxidized in the
4 mitochondria [95]. Herroon also found that COX2 (cyclooxygenase-2) expression is increased in BMAd co-
5 cultivated with prostate cancer cells leading to PGE2 (Prostaglandin E2) release [93]. BMAd can also release
6 glutamine showing that in addition to lipids, other metabolites could be released by BMAd [96]. This metabolic
7 symbiosis between BMAd and cancer cells leads to increased cancer cell proliferation [89–91], migration and
8 invasive capacities [94], protection against apoptosis [89, 95], and resistance to treatment [93, 96]. Altogether,
9 these results illustrate a metabolic crosstalk between BMAd and cancer cells, supporting tumor progression by
10 affecting various processes (**Table 2**) as previously described with white adipocytes (for a review see [4]).

11 As previously stated, all of these studies were performed using *in vitro*-differentiated human or mouse BM-MSCs,
12 or using the OP9 cell line. These models do not recapitulate the alteration in lipolysis observed in primary BMAd
13 suggesting that experiments performed with these cells should be interpreted with caution [22, 35]. Co-culture
14 experiments of cancer cells with primary BMAd should be preferred to assess the relevance of this metabolic
15 crosstalk and the implicated metabolic pathways. Importantly, the lipolytic activity in BMAd in presence of
16 cancer cells has never been investigated but a restoration of the lipolytic activity in BMAd by cancer cells can be
17 considered.

18 We described earlier the apparent decrease in the number and/or size of BMAd observed in BM of hematological
19 malignancies. Therefore, mechanism(s) allowing the release of lipids by BMAd certainly exist. Like SCAd,
20 BMAd contain more than 90% of TG [35] suggesting that other pathways allowing TG hydrolysis are likely
21 involved. Interestingly, Scheller's group found that even if rBMAd do not release FA in the medium upon
22 lipolysis stimulation, this stimulation induces a remodeling of LD that includes an increase in the number of small
23 LD in the cytoplasm surrounding the unilocular LD [22]. Whether these small LDs could be released in the
24 extracellular medium and transferred to cancer cells remains to be investigated. Another interesting hypothesis is
25 the implication of lipophagy. We have recently demonstrated that human BMAd from yellow BM express high
26 levels of LIPA in comparison to paired SCAd, and this enzyme allows the liberation of FA and cholesterol through
27 lipophagy [35]. Whether LIPA is also activated by cancer cells in human and murine BMAd from hematopoietic
28 rich areas, and whether this activation leads to FA and cholesterol transfer needs to be examined.

29

30 ***How do BMAd affect cancer cells through the release of adipokines?***

31 Two recent studies highlight the importance of lipid-independent mechanisms in the impact of BMAd on cancer
32 cells [87, 97]. While lipids from BMAd are taken up by MM cells, these BMAd-derived lipids do not promote
33 cancer cell proliferation unlike the BMAd-conditioned medium that contains soluble factors [97]. In ALL, Heydt
34 *et al* found that even if co-culture with 3T3-L1 adipocytes leads to the lipid transfer to cancer cells, adding FA
35 transporter- or FA oxidation- inhibitors to the co-culture does not reverse the effect of adipocytes on proliferation
36 [87]. Therefore, the soluble factors (still unidentified) are likely to be involved in the effect of BMAd on the
37 quiescence and chemoresistance in this ALL [87].

38 Several adipokines are involved in this crosstalk *in vitro*. Leptin stimulates the proliferation and migration of MM
39 cells and protects them against chemotherapy-induced cell death [98–100] and similar results were documented in
40 breast cancer [101]. Adiponectin, another major adipokine known to have anti-tumor effects [74], is decreased in

1 BMAds co-cultivated with MM cells [78, 97], which could contribute to increased proliferation and migration
2 induced by BMAds [97]. Proinflammatory cytokines such as IL-6, TNF α , and IL-1 β are also released by BMAds
3 [78, 80, 101, 102] and are involved in the effect of BMAds on proliferation [101], migration [78, 80, 101], and
4 resistance to treatment [80]. Several studies implicate chemokines in this crosstalk, including MCP-1 (monocyte
5 chemoattractant protein 1; also known as chemokine ligand 2 (CCL2)) and SDF-1 (stromal cell-derived factor 1;
6 also known as CXCL12)), which are released by BMAds and have been involved in enhanced proliferation and
7 migration induced by BMAds in MM cells [79]. We recently reported that the chemokine CCL7 (C-C Motif
8 Chemokine Ligand 7) is secreted by human primary BMAds and promotes directed-migration of prostate cancer
9 cells [103]. Notably, the secretion of CXCL1 and CXCL2 by BMAds is increase in prostate cancer [104] and MM
10 [80], however their impact on cancer cells was not evaluated in these studies.

11 Altogether, these studies show that several adipokines are involved in proliferation, migration, and resistance to
12 treatment in several cancers (summarized in **Table 3**). Very few studies use primary BMAds due to the difficulty
13 in obtaining BM, isolating them in sufficient quantity, and maintaining the viability and functionality of these
14 adipocytes *in vitro*. To our knowledge, only one study performed co-culture experiments between cancer cells and
15 primary human BMAds [78]. In this study the authors showed that MM cells reprogram BMAds, which in turn
16 produced bone resorption soluble factors involved in the lytic lesions observed in MM [78]. This induction of
17 osteoclastogenesis [78] may be due to the release of CXCL1 and CXCL2 by co-cultivating BMAds as observed
18 in prostate cancer [104]. RNAseq analysis of BMAds isolated from MM patients in remission (but with remaining
19 bone lytic lesions) compared to healthy donors demonstrated persistent phenotypical changes in MM patients
20 marked by a decrease in adiponectin and visfatin with increased TNF α expression [78]. Michaela Reagan's group
21 reanalyzed these microarray data and found an increased expression of SASP (senescence-associated secretory
22 phenotype) genes [80]. This senescent phenotype was reproduced in BM-MSD-derived adipocytes and co-
23 cultivated with MM cells *in vitro* [80]. These data indicate that although differentiated BM-MSCs might not be an
24 appropriate model for the study of metabolic symbiosis, it could be a fitting alternative to study other actor(s)
25 involved in the crosstalk with cancer cells, such as adipokines. Finally, as we mentioned above the secretory profile
26 of rBMAds and cBMAds can be different but cannot be assessed using BM-MSD-derived adipocytes (using the
27 current protocol of adipogenic differentiation). It would be important to address this question using primary
28 rBMAds or cBMAds to better understand whether these subtypes of adipocytes release different amount of
29 adipokines that could differentially affect cancer progression.

30

31 ***Impact of obesity on the crosstalk between BMAds and cancer cells***

32 As mentioned in the introduction, obesity worsens the prognosis of several cancers [9]. Several meta-analyses
33 reveal a positive correlation between body mass index and the incidence of several hematological cancers such as
34 MM and leukemia [105, 106], in addition to an increased risk of mortality in obese patients with MM [8] or
35 leukemia [107–109]. Moreover, obesity is linked to cancer death by promoting bone metastasis in prostate cancer
36 [110] and is associated with shorter overall survival in metastatic (primarily visceral and bone) breast cancer [111].
37 As such, obesity has a clear detrimental effect on several cancers localized in BM suggesting that obese BMAds
38 may play a significant role in this relationship. Importantly, we have previously shown that the metabolic
39 symbiosis with white adipocytes is increased in cases of obesity with melanoma [112, 113] or prostate cancer [76].

1 Few studies have assessed the impact of BMAds on cancer progression in obesity. In HFD-fed mice (who display
2 increased adiposity in BM), increased tumor size was identified after intratibial injection of prostate cancer cells
3 [94, 104], favoring the occurrence of osteolytic lesions [104]. Based on a similar experimental procedure, increase
4 of melanoma cell growth were observed through osteopontin and IL-6 [102], as well as an accelerated tumor
5 progression and metastasis after injection of breast cancer cells [114]. Moreover, HFD-fed mice developed
6 leukemia earlier than ND-fed mice and demonstrated a decrease in survival rate that was correlated with increased
7 plasma IL-6 and leptin rates [115].

8 These experiments performed in mice clearly indicate that obesity increases bone tumor growth in several cancer
9 types, however *in vitro* experiments are also necessary to confirm that BMAds are directly involved in this effect
10 and to characterize the mechanisms that are amplified by obesity. To achieve this, primary adipocytes isolated
11 from obese subjects are mandatory since the hallmark signs of obesity are not reproduced by *in vitro* differentiated
12 BM-MSCs isolated from obese subjects. Using conditioned media of BMAds from obese compared to lean
13 subjects, we have demonstrated that CCL7-dependent directed migration is amplified in obesity, as well as aging
14 [103]. To our knowledge, the metabolic crosstalk between cancer cells and BMAds from obese patients has never
15 been studied directly.

16
17 Overall, these data highlight that BMAds are not passive bystander cells, but are instead real actors on cancer cells,
18 contributing to cancer progression. More studies are required to identify the mechanisms involved in metabolic
19 symbiosis and its regulation by obesity using primary BMAds. Moreover, while BMAds can act on other cells
20 which are present in the tumor microenvironment, such as hematopoietic cells [83] and bone cells [78], their impact
21 on immune cells remain to be studied.

22 23 **Conclusion**

24 BMAds have recently emerged as key players in cancer progression. Currently, most of the evidence describing
25 their implication has been obtained in hematological malignancies. Additional studies, particularly *in vivo* studies,
26 are necessary to decipher their role in the progression of bone metastasis from solid tumors. In addition to the
27 secretion of soluble factors, data collected to date suggest that their role may depend on lipid mediators.
28 Undoubtedly, a decrease in the number and size of BMAds is observed *in vivo* in hematological malignancies,
29 suggesting the release of lipids into the tumor microenvironment. Modeling the metabolic crosstalk between
30 BMAds and cancer cells *in vitro* is hampered by the fact that most of the models applied, specifically those issued
31 from *in vitro* differentiation of BM-MSCs, do not recapitulate the metabolic specificity of BMAds. Studies using
32 primary isolated murine or human adipocytes co-cultivated with tumor cells are needed to explore the metabolic
33 crosstalk that could involve lipids (e.g., FA, cholesterol) in addition to other metabolites. Although obesity affects
34 the occurrence and prognosis of hematological malignancies, the impact of BMAd accumulation and phenotype
35 remains poorly understood. This characterization is a mandatory first step in better understanding how obesity
36 could affect BMAds and cancer cell crosstalk. With additional research and progress in our understanding of this
37 relationship, the crosstalk between cancer cells and BMAds will undoubtedly lead to new therapeutic strategies in
38 the treatment of hematological malignancies and bone metastases.

1 **Tables**

2

3 **Table 1. Modifications of BMAT with obesity**

4 ♀: Female; ♂: Male; ^{Ado.} Adolescent/young; N: Normal-weight; OB: Obese

5

BMAT location	Imaging method	Subject	Change with Obesity	Reference
Lumbar spine	1H-MRS (Lipid/water %)	♀ (N + OB)	↗	[41]
	1H-MRS (Lipid/water %)	♂ + ♀ (N vs OB)	↗	[65]
	1H-MRS (Lipid/water %)	♀ ^{Ado.} (N vs OB)	↘↘	[69]
	1H-MRS (Lipid/water %)	♀ ^{Ado.} (N vs OB)	↘↘	[70]
	MRI scan	♂ ^{Ado.} + ♀ ^{Ado.} (OB)	=	[116]
Femoral metaphysis/ diaphysis	1H-MRS (Lipid/water %)	♂ + ♀ (OB)	↘	[66]
	1H-MRS (Lipid/water %)	♀ ^{Ado.} (N vs OB)	↘↘	[70]

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1 **Table 2: Metabolic crosstalk between cancer cells and BMAd**

2 AMoL (acute monocytic leukemia)

3 FAO (fatty acid oxidation)

Cancer	BMAd model	Effect on BMAd	Effect on cancer cells	Reference
Prostate	BM-MSC-derived adipocytes	<i>Not studied</i>	FA transfer	[88]
Prostate	BM-MSC-derived adipocytes	Delipidation	Increase lipid storage Increase FABP4 Increase migration /invasion	[94]
Prostate	BM-MSC-derived adipocytes	Increase lipolysis (increase ATGL expression)	Metabolic reprogramming: lipid accumulation and Warburg phenotype	[92]
Prostate	BM-MSC-derived adipocytes	Lipolysis activation by IL-1 β released by cancer cells Increase COX2 expression and release of PGE2	Protect against chemotherapy	[93]
AML	BM-MSC-derived adipocytes	Increase lipolysis (P-HSL)	Lipid transfer through FABP4 Increase proliferation and survival	[89]
AML	BM-MSC-derived adipocytes	Increased ATGL and HSL expression Lipolysis activation by GDF15 released by AML cells	Increase proliferation	[91]
AML	BM-MSC-derived adipocytes	TRPV4 mediate GDF15-induced lipolysis	<i>Not studied</i>	[84]
ALL	3T3-L1 and OP9 cell lines	Release of glutamine	Protect against chemotherapy	[96]
AMoL	BM-MSC-derived adipocytes	<i>Not studied</i>	Increase FABP4 and CD36 expression Increase FAO Prevent apoptosis	[95]
MM	OP9 and BM-MSC-derived adipocytes	Increased lipolysis	Lipid transfer through FATPs Increased proliferation	[90]

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1 **Table 3: Crosstalk between BMAds and cancer cells involving adipokines**

Cancer	BMAd model	Effect on BMAds	Effect on cancer cells/other cells	Reference
MM	BM-MSC-derived adipocytes 3T3-L1	Induction of SASP Increased IL-6 CXCL1 and CXCL2	Protect against chemotherapy	[80]
MM	3T3-L1	Release of MCP1 and SDF1	Increase proliferation Increased migration	[79]
MM	14F1-1 Human BMAds	Release of leptin	Increase proliferation Increase migration	[98]
MM	Human BMAds	MM cells modify BMAd endocrine function: decreased expression of adiponectin, adipon and visfatin Increased TNF α expression	Increase osteoclastogenesis Decrease osteoblastogenesis	[78]
MM	BM-MSC-derived adipocytes	Increase leptin and adiponin	Protect against chemotherapy Autophagy activation	[99]
MM	3T3L1	Release of leptin	Increase proliferation Protect against chemotherapy	[100]
MM	BM-MSC-derived adipocytes ST2 cell line	Decreased adiponectin	Increase proliferation Increase migration	[97]
ALL	BM-MSC-derived adipocytes	<i>Not studied</i>	Decrease proliferation (induce quiescence) Protect against chemotherapy	[87]
Prostate	BM-MSC-derived adipocytes	Released of CXCL1 and CXCL2 induced by cancer cells	Increase osteoclastogenesis	[104]
Prostate	Human BMAds	Release of CCL7	Increase migration	[103]
Breast	Fragments of human bone tissue containing BMAds	Release of leptin and IL-1 β	Increase migration	[101]
Melanoma	BM-MSC-derived adipocytes	Release of IL-6	Increase proliferation	[102]

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1 **Figure legend**

2 **Figure 1: Location of the two types of bone marrow adipose tissue (BMAT) in rodents and humans.**

3 (A) Regulated BMAT (rBMAT) and constitutive BMAT (cBMAT) are found in rodents and differ in terms of
4 development and localization as well as in the phenotype of adipocytes (BMAds) they contain. (B) Location of
5 red Bone Marrow (red BM) and yellow Bone marrow (yellow BM) in humans.

7 **Figure 2: Specific metabolic function of bone marrow adipocytes (BMAds).**

8 BMAds are devoid of lipolytic activity, the principal function of « classical » adipocytes but they have a
9 cholesterol-oriented metabolism. High expression of Lysosomal Acid Lipase (LIPA) involved in lipophagy
10 pathway could be involved in the hydrolysis of cholesterol ester (CE) but also triglycerides (TG) to release free
11 cholesterol (FC), fatty acid (FA) and glycerol. High expression of Neutral Cholesterol Ester Hydrolysis 1 (NCEH1)
12 could also participate to CE hydrolysis in FC. Another specificity of BMAds is the important uptake of FA and
13 glucose that may favor TG storage through lipogenesis.

15 **Figure 3: Modification of the number and size of bone marrow adipocytes (BMAds) in hematological 16 malignancies compared to white adipocytes.**

17 (A) Colonization of white adipose tissue (WAT) by acute myeloid leukemia (AML) cells stimulate lipolysis in
18 adipocytes leading to decreased size of adipocytes. (B) The phenotype of BMAds is different in patients with
19 AML, acute lymphoblastic leukemia (ALL) and multiple myeloma (MM). In both MM and leukemia, a defect in
20 adipogenesis contribute to the decreased in BMAd number while other mechanisms such as BMAd death are likely
21 involved. In MM, the impact on BMAd size is controversial. In leukemia, the decrease size of BMAds is not likely
22 due to lipolysis activation (as found in white adipocytes) and mechanisms involved in delipidation remain to be
23 defined.

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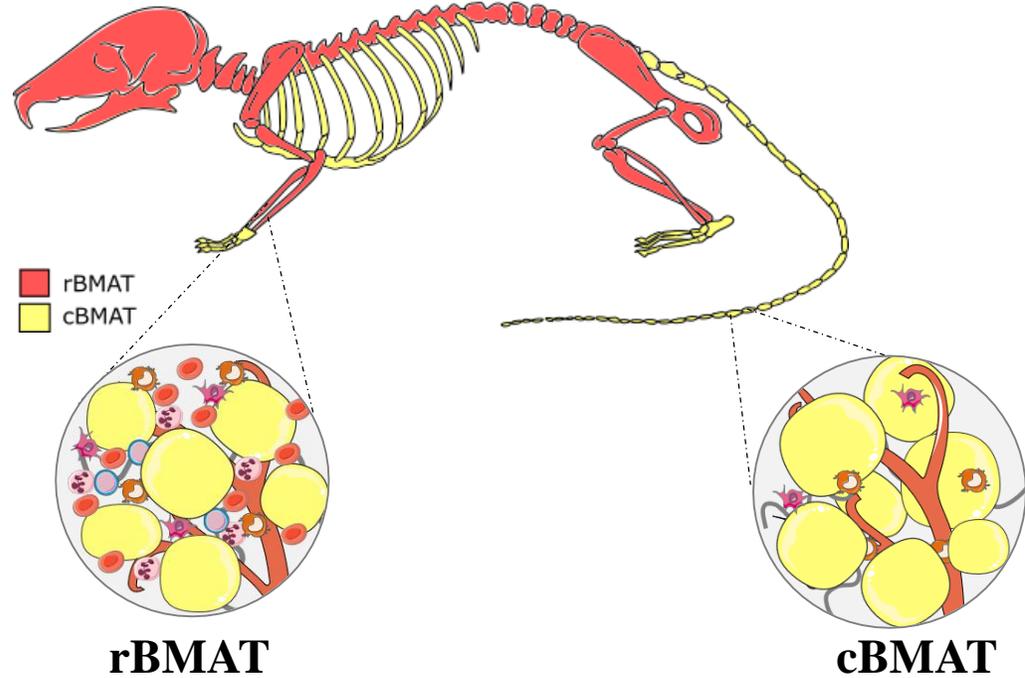
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55

Figure 1

A



- In red BM, in femur and tibia
- Develop later
- Contain more saturated lipids
- Smaller BMAds
- BMAds surrounded by hematopoietic cells
- Decreased size of BMAds with fasting, exercise and cold exposure

- In yellow BM, in tail vertebrae
- Develop first
- Contain more unsaturated lipids
- Larger BMAds
- Cohesive BMAds
- No effect of fasting, exercise and cold exposure on BMAd size

B

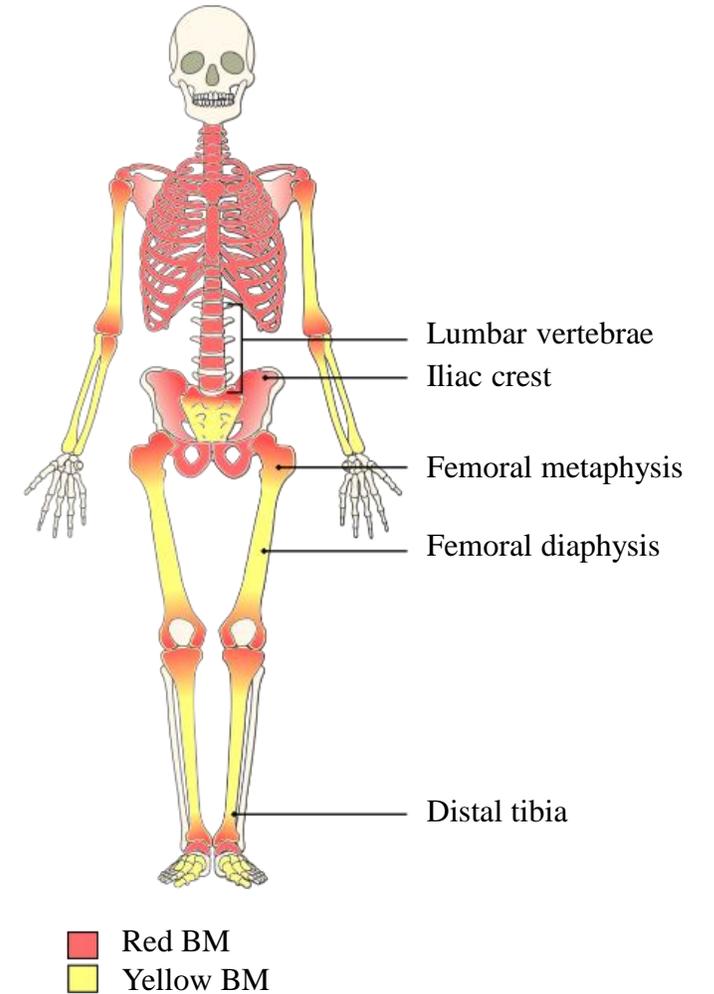


Figure 2

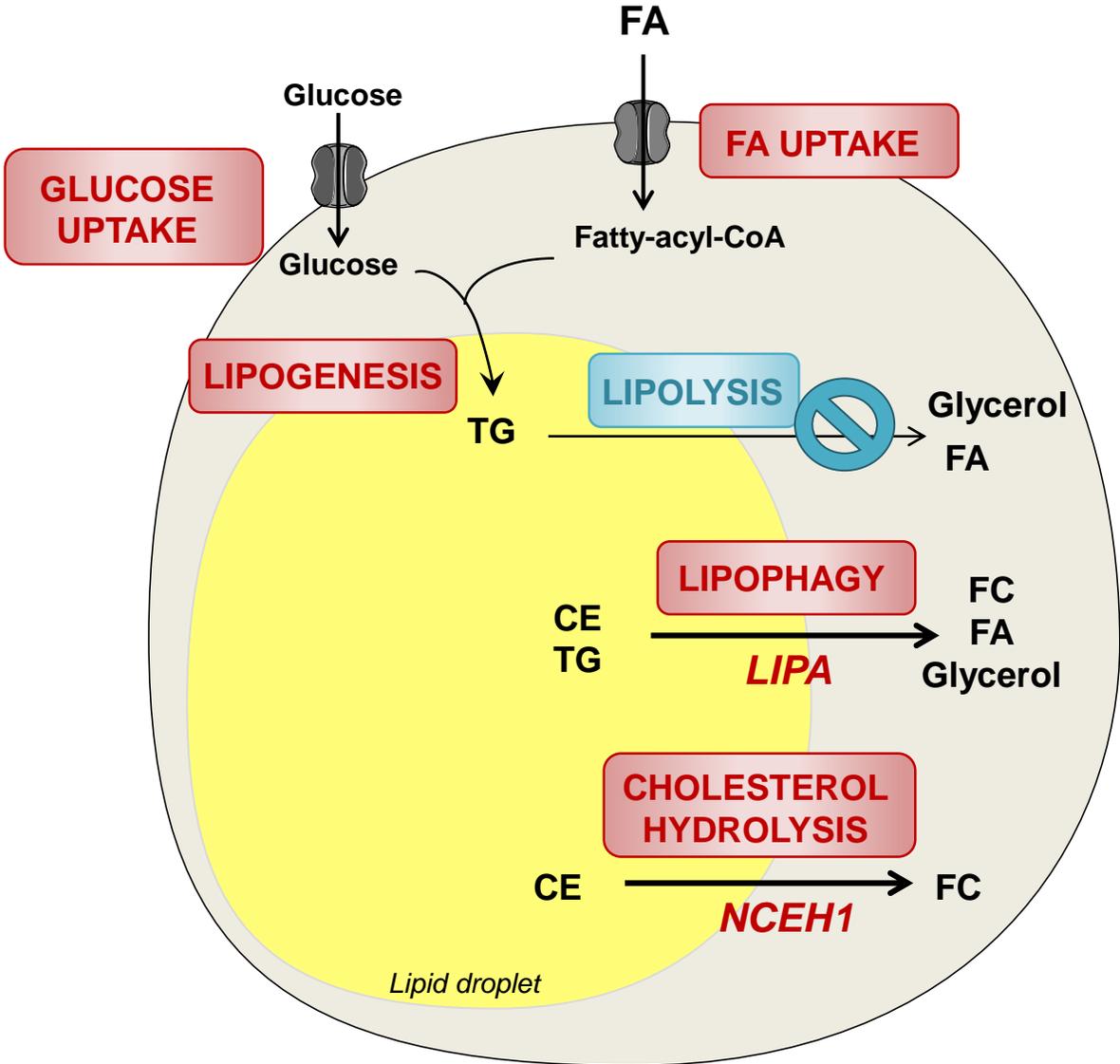
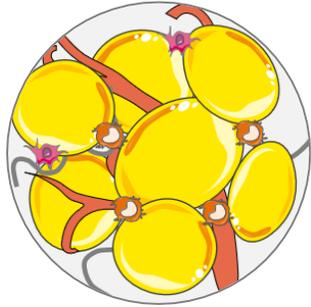


Figure 3

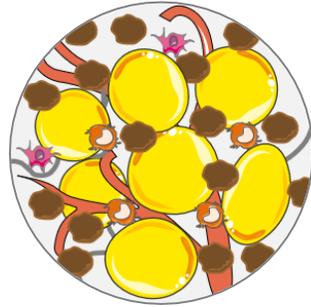
A

**Healthy
WAT**



Lipolysis ↑

**WAT colonized
by cancer cells**

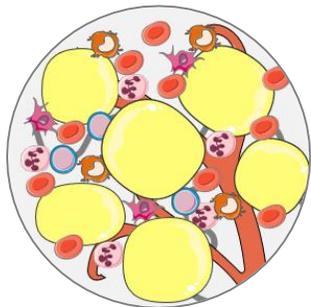


Size ↓

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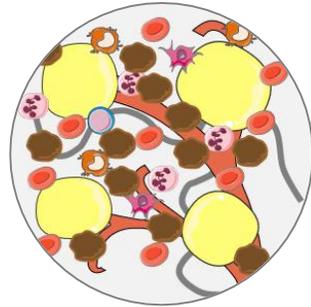
B

Healthy BM



Adipogenesis ↓

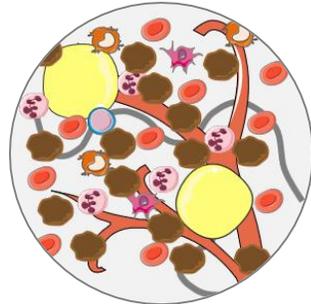
MM



Size ↑↓ ↔

Number ↓ ↔

AML/ALL



Size ↓

Number ↓

