

REVIEW

Adipokines, adiposity and bone marrow adipocytes; dangerous accomplices in multiple myeloma

Emma V. Morris¹ and Claire M. Edwards^{1,2}

¹Nuffield Dept. of Surgical Sciences, University of Oxford, Oxford, UK. ²Nuffield Dept. of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

Corresponding author: Emma Morris,
Botnar Research Centre, University of Oxford
Old Road
Oxford OX3 7LD
Email: emma.morris@nds.ox.ac.uk

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Abstract

Obesity has become a global epidemic influencing the establishment and progression of a wide range of diseases such as diabetes, cardiovascular disease and cancer. In 2016, IARC reported that obesity is now associated with 13 different cancers, one of which is multiple myeloma (MM) a destructive cancer of plasma cells which predominantly reside in the bone marrow. Obesity is the accumulation of excess body fat, which causes metabolic, endocrine, immunologic, and inflammatory-like changes. Obesity is usually associated with an increase in visceral and/or subcutaneous fat, however, an additional fat depot that also responds to diet-induced changes is bone marrow adipose tissue (BMAT). There have been several studies over the past few decades that have identified BMAT as a key driver in MM progression. Adipocytes secrete numerous adipokines such as leptin, adiponectin, resistin, adipsin and visfatin which when secreted at normal controlled levels have protective properties. However, in obesity these levels of secretion change, coupled with an increase in adipocyte number and size causing a profound and lasting effect on the bone microenvironment, contributing to MM cell growth, survival and migration as well as potentially fuelling bone destruction. Obesity is a modifiable risk factor making it an attractive option for targeted therapy. This review discusses the link between obesity, MGUS (a benign condition that precedes MM) and myeloma, and the contribution of key adipokines to disease establishment and progression.

Introduction

Obesity is now being described as a global epidemic. In 2014, it was estimated that 640 million adults were suffering from obesity worldwide (a 6-fold increase since 1975). Obesity increases the risk of many serious diseases and health conditions such as type 2 diabetes, heart disease, stroke and cancer. Lifestyle and environmental factors, rather than inherited genetic defects are now thought to regulate the development of 90–95% of all cancers [1] and around 20% of these have been attributed to obesity [2]. Over a decade ago, the International Agency for Research on Cancer (IARC) confirmed the association of excess body fatness with the risk of cancers of the colon and rectum, oesophagus, kidney, breast and endometrium [3]. However, in a report published in August 2016 this list was reviewed and a further 8 cancer types were added, to include cancers of the gastric cardia, liver, gallbladder, pancreas, ovary, and thyroid, and meningioma, and multiple myeloma [4].

Obesity

Body-mass index (BMI) is widely used as a measurement of adiposity. By definition, people with a BMI between 25 and 29.9 kg/m² are considered overweight, while a BMI of 30 kg/m² and above is considered obese [5]. Obesity is due to an imbalance between energy intake (diet) and expenditure (physical activity). When energy intake exceeds energy expenditure in a chronic manner, obesity ultimately occurs. According to estimates from Public Health England, two thirds of adults and a quarter of children between two and 10 years old are overweight or obese, and obese children are more likely to become overweight adults. These statistics highlight the growing problem and the need for prevention strategies. Obesity is still very much on the rise as food becomes more available and the average level of physical activity decreases [6]. Even though obesity is now well recognized as a disease in its own right, it is often not thought of as a stand-alone condition, as excess body fat not only causes direct effects on the body, but it is also known to be a key driver of many other severe health issues. Obesity causes metabolic, endocrine, immunologic, and inflammatory-like changes that may amplify cell mutation rate, dysregulate gene function, disrupt DNA repair, and/or induce epigenetic modifications. In turn, these changes may create a favourable environment for abnormal neoplastic transformation (inductive), or a permissive environment in which pre-existing clones that are dormant are permitted to emerge (selective) [7]. It is unclear whether obesity creates an inductive or selective environment, or as is most likely, a combination of both. Nonetheless, the end result is that people who suffer from the condition have a higher risk of developing a number of different malignancies, one of which is multiple myeloma.

Multiple myeloma

Multiple myeloma (MM) is a condition caused by the clonal proliferation of abnormal plasma cells in the bone marrow. MM represents around 10% of all haematological malignancies and despite a vast improvement in treatment strategies over the last few decades; it remains an incurable disease. Patients often suffer with bone pain, pathologic fractures, weakness, anaemia, infection (often pneumococcal), hypercalcemia, spinal cord compression, and renal failure. There are a number of risk factors associated with the disease such as age, race, gender, family history and more recently, obesity [8]. The association between obesity and MM began to emerge in the 90's as large cohort studies became a popular way in which to study disease correlations [9]. Since then these initial findings have been validated using larger more in-depth studies [10, 11], and over the years as more data has been collected a dose-response effect has been reported suggesting that as BMI increases from normal to overweight to obese, there is an increase in the associated risk [10].

MM is consistently preceded by a premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS). Patients suffering from MGUS have abnormal immunoglobulin protein in the blood or urine without myeloma related-organ damage or bone disease; these patients are asymptomatic and so are usually diagnosed as a result of routine blood screening for an unrelated health issue. There is no treatment for MGUS only monitoring. The prevalence of this condition is around 3.2% of adults over 50 years of age, and it is estimated that around 1% of these patients will progress to MM each year [12]. Obesity has also been correlated as a risk factor for progression with obese patients being 20% more likely to progress from MGUS to MM than patients of normal weight [4, 13]. This is an important finding as it provides evidence of a potentially modifiable risk factor associated with progression. One question that remains unanswered is whether obesity is correlated with MGUS incidence. The link between MGUS and obesity and MM progression is a powerful one as this allows intervention on diagnosis. However, if future studies reveal a link between obesity and MGUS development, this would need a population wide intervention that would be unrealistic. Unfortunately though, evidence suggests that obesity in early adulthood could be significantly associated with MM [10, 14] and may even have an influence in childhood [15]. However, the highest risk of MM mortality appears to be among those that were heavier in both young adulthood and later adulthood [10]. Since MGUS develops before MM it could be postulated that the changes that occur during prolonged periods of obesity may promote the development of MGUS and ultimately MM in a subset of the population.

However, because MGUS is an asymptomatic condition it is difficult to accurately assess the influences that promote its development.

Adipose tissue

Adipose tissue is now recognized as the body's largest endocrine organ, capable of secreting over 50 different adipokines, cytokines, and chemokines [16]. Adipose tissue is often classified into two main subtypes; white adipose tissue (WAT) and brown adipose tissue. WAT is the most abundant and is found both subcutaneously and viscerally, its main function is to store energy in the form of lipids. Brown adipose tissue (BAT) is localised in more distinct sites and mediates adaptive thermogenesis through an abundance of uncoupled mitochondria [17]. In addition to these two well studied tissue types there is a third type of adipose tissue; bone marrow adipose tissue (BMAT). This is the least studied fat depot, although in recent years that has started to change as evidence has begun to emerge that suggests BMAT may have an important contribution to cancer progression, particularly in cancers that metastasise to the bone such as breast and prostate, as well as cancers that arise in the bone, such as myeloma.

Bone marrow adiposity

Adipocytes are a major component of human bone marrow (BM), comprising up to 70% of BM volume and accounting for over 10% of total adipose mass in a healthy lean adult [18]. BM adipocytes are smaller than their visceral counterparts; although their fatty acid uptake is similar due to enhanced triacylglycerol synthesis [19]. These cells were first thought of as inert space filling cells, however, over the years it has become clear that they are both an endocrine target and have endocrine-like functions: responding to growth hormones, insulin and thyroid hormone, as well as releasing cytokines such as IL-6, IL-1 β , and TNF- α [20]. BM adipocytes also secrete adipokines, such as leptin, and adiponectin, which regulate calorie uptake and insulin sensitivity, respectively. They are now considered an influential component of the bone microenvironment with the ability to influence neighbouring cells via autocrine, paracrine, and endocrine signalling [21]. BMAT is made up of two types of adipocytes: constitutive (cBMAT) and regulated (rBMAT) which reside in different locations in the bone. cBMAT is found in the distal areas of the bone and more closely resembles the densely packed arrangement of WAT. In contrast, rBMAT is found in the more metabolically active areas of the bone, these adipocytes are found scattered among neighbouring hematopoietic cells. The exact contribution to circulating and local levels of cytokines and adipokines from these two cell types is not clear. However, the lipid content is thought to differ with rBMAT preferentially storing saturated fats and cBMAT unsaturated fats [22], this could

suggest they have distinct functions which may influence the adipokines they secrete. The ratio of adipocytes to other cells in the marrow has become of great interest in the field, as more data is collected the importance of maintaining a healthy level of adiposity in the bone is becoming clearer. BM adipocytes support and regulate the hematopoietic cells they surround by preventing hematopoietic progenitor expansion while preserving the hematopoietic stem cell pool [23]. They originate from a common mesenchymal progenitor that has the potential to differentiate into an osteoblast or an adipocyte. In childhood, the differentiation decision favours osteoblastogenesis, however, as we age this preference changes in favour of adipogenesis. In old age the percentage of fatty marrow is much higher, and these changes alone may cause our ageing population to be more vulnerable to disease establishment [24]. Therefore, a change in adipocyte size and number in response to environmental cues such as diet, coupled with the effect of ageing could have a profound impact on the functionality of neighbouring cells. It is well established that obesity increases WAT cells in both number and size, overwhelming their storage capacity and causing a level of dysfunction [25]. Obesity is associated with low-grade and chronic levels of inflammation in WAT. As adipocytes increase in size, some become apoptotic which results in the infiltration of immune cells such as macrophages, mast cells and neutrophils [26]. Interactions between adipocytes and immune cells can enhance lipolysis and secretion of lipids, as well as the adipocyte and immune cell production of multiple pro-inflammatory factors. This in turn can have a negative effect on peripheral tissues inducing insulin resistance, hyperglycaemia and hyperlipidaemia which are associated with oxidative stress and cancer development and/or progression. These changes can cause sustained proliferative signalling and activation of migration and metastasis [27]. Although these are changes that have been studied in the context of WAT a similar response was observed in the BM of mice fed on a high fat diet (HFD) suggesting that obesity may have a detrimental effect on adipose tissue as a whole [28].

Bone marrow adiposity and MM

The relationship between obesity and BM adiposity is still unclear, although, there is mounting evidence to suggest that obesity is positively correlated with an increase in BMAT. Scheller and colleagues showed that mice fed on a HFD had a significant expansion of BMAT. Interestingly they also demonstrated that mice fed on a HFD that were subsequently fed a normal diet to mimic weight loss did not exhibit an expansion in BMAT, suggesting that BMAT volume was modifiable through changes in diet. However, using this model of diet-induced obesity and weight loss they measured changes in bone morphology and mechanical strength and concluded that HFD causes long-term, persistent changes in bone quality,

despite prevention of marrow adipose tissue accumulation [28]. The observation that the bone microenvironment is affected by diet is an interesting one. A study published in 2015 by Lwin et al. showed how a HFD could detrimentally modify the environment to promote myeloma. This study demonstrated that C57Bl6 mice fed on a HFD prior to inoculation with 5TGM1 MM cells developed a myeloma-like condition, when compared to control mice [29]. Moreover, Trotter and colleagues showed that MM cells could also influence cell lineage determination by causing osteoblast progenitors to shift towards adipogenesis. Patients suffering from MM were found to have a higher proportion of preadipocytes, coupled with significantly larger mature adipocytes [30]. These findings support the notion that an increase in adiposity is pro-tumorigenic, therefore, coupled with an increase in adiposity induced by diet, this would further exacerbate disease progression. BMAT acts as an energy supply to fuel bone physiological functions, including bone remodelling. Adipose-rich areas of the bone are found near the more metabolically active areas of the bone such as the growth plate and around the trabeculae, therefore an increase in BMAT may lead to elevated levels of bone resorption. These changes in bone turnover could be advantageous to tumour cell growth and survival. The way in which MM cells interact with, and utilise their environment is often described in the context of a vicious cycle. The MM cells release factors that activate osteoclasts to breakdown the bone matrix, releasing bone-derived growth factors, such as transforming growth factor- β and insulin-like growth factor 1, and raising extracellular calcium concentrations. The growth factors bind to receptors on the cell surface of the tumour cells and activate SMAD and MAPK signalling, extracellular calcium binds and activates calcium pumps leading to tumour cell proliferation. Therefore, this increase in BMAT could potentially fuel cancer progression by increasing osteoclast activity and thus bone resorption, leading to the development of associated bone disease. Future studies need to be carried out to address whether there is a correlation between the location of a patient's bone lesions and the level of adiposity in the surrounding area. It could be that the secretions from the neighbouring BM adipocytes are contributing to local bone disease, raising the question as to whether areas of high adiposity contain more and/or larger lesions. Adipocytes have also been implicated as drivers of chemoresistance, one proposed mechanism for this is that mature adipocytes activate autophagy and upregulate the expression of autophagic proteins resulting in the suppression of chemotherapy-induced caspase cleavage and apoptosis in myeloma cells [31]. There have been several studies demonstrating that adipocytes support MM cell growth and survival as well as promoting migration [20, 32]. These effects are mainly due to adipokine secretion levels. There is a fine balance in the levels of adipokines secreted by a healthy individual, promoting homeostasis and protecting against disease development. However, in the event

of increased adiposity, imbalance occurs which has an opposing effect; the protective function is lost, resulting in the promotion of disease establishment and progression.

Adipokines: good or bad?

Leptin

Leptin is a peptide hormone that acts centrally via the hypothalamus to regulate food intake and energy expenditure, and on peripheral organs. Its main function is to mediate satiety, stimulate lipolysis and suppress lipogenesis. The levels of serum leptin correlate with fat mass as leptin secretion increases in conjunction with adipocyte size. Leptin has been shown to induce pro-tumour effects in several cancers [33, 34] one of which being MM. A study carried out by Wen Yu and colleagues in 2016 demonstrated that the upregulation of leptin could stimulate proliferation of MM cells and reduce the anti-tumour effect of chemotherapy via activation of AKT and STAT3 pathways. Leptin was also shown to induce an upregulation of Bcl-2 expression and the inhibition of caspase-3 activation resulting in protection from chemotherapy-induced apoptosis. [35] Leptin was shown to upregulate autophagy, again leading to suppression of chemotherapy-induced apoptosis [31]. Interestingly several studies have found elevated leptin in patients suffering from MM [36, 37]. However, this elevated expression was not found to be correlated with risk [38, 39] suggesting that leptin levels are potentially associated with MM progression but not development.

Adiponectin

Adiponectin is the most abundant adipokine secreted by adipose tissue accounting for around 0.01% of total serum proteins. Different fat depots secrete varying concentrations with BMAT having the largest contribution [40]. It is often referred to as a 'good' adipokine as it has anti-inflammatory, anti-atherogenic and insulin sensitizing properties. Adiponectin acts centrally to enhance energy homeostasis by increasing energy expenditure via activating hypothalamic leptin and insulin signalling pathways. It also improves glucose homeostasis by attenuating insulin resistance. As well as acting centrally, adiponectin also has autocrine and paracrine effects, which influence adipose tissue functions, overexpression of the Adipoq gene increases fat tissue mass via an increase in number of adipocytes rather than size. This increase allows for an expansion of triglyceride storage capacity thereby avoiding the stress that lipid-gorged adipocytes sustain. Increased adiponectin levels also reduce the secretion of pro-inflammatory factors such as IL-6 and TNF- α which results in a reduction of macrophage infiltration [41]. Paradoxically adiponectin expression is decreased in obesity. Considering adipose tissue is the main source of adiponectin in the body it is counterintuitive that it should reduce as adiposity increases.

However, this is a good example of how adipokine secretion changes in response to diet. Low levels of adiponectin have been associated with several obesity-related complications such as metabolic syndrome and its related disorders: type 2 diabetes [42] and cardiovascular disease [43] as well as several types of cancer [44-47] including myeloma [38]. The mechanisms behind this down regulation are still unknown, whether the stress sustained by adipocytes due to the overload of lipid causes the cells to become dysfunctional is unclear. However, what is clear is that this alteration in adipokine secretion appears to cause a permissive environment for cancer establishment and progression. A number of studies have reported decreased adiponectin levels in the serum of both MGUS and myeloma patients [38, 48, 49]. As obesity also causes adiponectin down regulation this, could exacerbate and maybe even accelerate progression from MGUS to MM. *In vitro* studies demonstrated that adiponectin decreases cellular proliferation and increases apoptosis of myeloma cells via the activation of AMPK and MAPK [48]. Moreover, adiponectin can also activate cell cycle arrest and apoptosis through the activation of p21 and p53 [50]. Adiponectin has been the focus of much interest with a number of molecules being engineered to activate its signalling pathways in an attempt to rescue its protective properties; unfortunately, these drugs have had minimal success.

Resistin

Resistin was first identified as a protein abundantly secreted from the adipocytes of obese mice, providing a link between obesity and insulin resistance hence the name resistin (for “resistance to insulin”) [51]. Since its discovery in 2001, its physiological role has started to emerge as being more complex than originally supposed. Resistin has been shown to participate in inflammation, cancer development and metastasis [52, 53]. It is also expressed by osteoblasts and osteoclasts as well as bone marrow adipocytes suggesting that it may have a role in bone remodelling [54]. In the context of MM it has been reported to be both protective and damaging. Low resistin levels were found to be associated with increased risk [38] particularly in men [55]. However, Pang and colleagues demonstrated that resistin could play a role in drug resistance, abrogating chemotherapy-induced apoptosis in myeloma cells via the inhibition of chemotherapy-induced caspase cleavage [56]. Taken together these two studies suggest that resistin could be protective against early stages of disease development while detrimental in later stage. Future studies are needed to further elucidate the role of this adipokine, and to understand whether it could be a potential therapeutic target.

Adipsin

Another adipokine known to play a role in chemotherapy resistance is adipsin. Adipsin was first described in 1987 as a serine protease that was secreted into the bloodstream by adipocytes; due to its

abundance in the serum it was postulated that it could have systemic effects [57]. Since then it has been shown to be involved in the alternative complement pathway of the complement system, to be a requirement for proper insulin secretion by the pancreatic β cells, and to stimulate glucose transport for triglyceride accumulation in fat cells as well as inhibiting lipolysis [58]. However, the levels of adipsin in obesity are less clear, some studies have shown that low levels of adipsin are associated with obesity [59]. Whereas others have shown elevated levels which positively correlate with fat mass [60]. It maybe that the source of adipsin is important and that patients who suffer from abdominal obesity may have different levels of adipsin compared to those who present with visceral obesity. The levels secreted from the bone marrow remain unclear. The question as to the contribution of adipsin to cancer development and progression has not been extensively studied; one study showed that adipsin secreted by mature human adipocytes activates autophagy, thereby suppressing chemotherapy-induced apoptosis in myeloma cells [31]. It maybe that adipsin levels are variable under different conditions and its contribution to disease states is multifactorial, being influenced by the combination of other secreted factors as well as genetic and environmental ques.

Visfatin

Visceral fat-derived protein, visfatin also known as nicotinamide phosphoribosyltransferase (NAMPT) or pre-B cell colony-enhancing factor (PBEF) is encoded by the PBEF-1 gene and is found both intracellularly and extracellularly. The intracellular form is the rate-limiting enzyme that catalyses the first step in NAD biosynthesis; the extracellular form has a more cytokine-like activity [61]. Visfatin was originally thought to be produced mainly by adipose tissue (i.e. adipocytes and infiltrating macrophages) [62] however it has now been shown to be secreted by many more tissue types such as liver, skeletal muscle, bone marrow and brain. Its widespread secretion is mirrored by its potential involvement in a wide range of disorders such as inflammatory diseases, metabolic diseases and cancer [61]. Visfatin regulates growth, apoptosis and angiogenesis of mammalian cells and has been found to be upregulated in breast [63], colon [64] and prostate cancer [65]. Moreover, a number of studies have shown that visfatin promotes MM progression; myeloma cells treated with the PBEF1 inhibitor APO866 had a reduction in cellular proliferation coupled by an induction of apoptosis [66]. Visfatin inhibition also enhanced the apoptotic effect of Bortezomib [67]. Visfatin secretion appears to contribute to MM progression however, the source of visfatin is unclear, whether the bone marrow contributes significantly to circulating levels has yet to be established. The dual role of visfatin and its role as an adipokine remains to be fully elucidated, future studies will hopefully shed light on whether it has the potential as a therapeutic target.

Conclusion

Obesity is becoming one of the most challenging conditions worldwide with the number of people suffering with the condition rising annually. The growing body of evidence implicating adiposity as a key driver of tumourigenesis is overwhelming. The systemic changes that occur as a result of this condition appear to have profound and lasting effects. MM is a malignancy associated with increased risk due to excess body fatness. MM is known to develop from the precursor condition MGUS. It is important to identify factors that increase the risk of progression, thus by modifying patient behaviour on diagnosis could decrease their risk of progression. An increase in adiposity causes inflammation and the accumulation of free fatty acids as well as a dysregulation of adipokine secretion. Obesity promotes the increased secretion of adipokines known to play a role in cancer development and progression, along with the reduction of adiponectin, an adipokine with protective properties. These changes promote a more permissive environment where myeloma cells are able to thrive (Figure 1). Obesity is one of the few modifiable risk factors, which could have great therapeutic potential. The adipokine secretion profile from each of the different fat depots is beginning to shed light on how adiposity is promoting cancer. Different types of obesity such as abdominal versus visceral express different levels of adipokines, which could have a profound effect on the type of cancers that develop. The bone marrow adiposity field is increasing rapidly as it becomes clearer that these adipocytes are contributing significantly to circulating levels of adipokines. Bone marrow adipocytes are often overlooked in the study of obesity. However, studies have now shown that even though the bone does not have the potential to increase its marrow space, the marrow itself has the potential to be modified in response to dietary demands. Many studies have already demonstrated that an increase in marrow adiposity can fuel tumour development and metastasis. Future studies are needed to not only develop educational strategies to help patients decrease their risk, but also to develop targeting strategies to manipulate adipokine secretion without compromising adipocyte function.

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References

1. Anand, P., et al., *Cancer is a Preventable Disease that Requires Major Lifestyle Changes*. Pharmaceutical Research, 2008. **25**(9): p. 2097-2116.
2. Calle, E.E., et al., *Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults*. (1533-4406 (Electronic)).
3. Vainio, H., R. Kaaks, and F. Bianchini, *Weight control and physical activity in cancer prevention: international evaluation of the evidence*. Eur J Cancer Prev, 2002. **11 Suppl 2**: p. S94-100.
4. Lauby-Secretan, B., et al., *Body Fatness and Cancer — Viewpoint of the IARC Working Group*. New England Journal of Medicine, 2016. **375**(8): p. 794-798.
5. Health, N.I.o., *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report*. National Institutes of Health. Obesity, 1998(1071-7323 (Print)).
6. Hill, J.O., H.R. Wyatt, and J.C. Peters, *Energy Balance and Obesity*. Circulation, 2012. **126**(1): p. 126-132.
7. Lichtman, M.A., *Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma*. (1549-490X (Electronic)).
8. Beason, T. and G. Colditz, *Obesity and Multiple Myeloma*, in *Energy Balance and Hematologic Malignancies*, S.D. Mittelman and N.A. Berger, Editors. 2012, Springer US: Boston, MA. p. 71-95.
9. Friedman, G.D. and L.J. Herrinton, *Obesity and multiple myeloma*. (0957-5243 (Print)).
10. Teras, L.R., et al., *Body size and multiple myeloma mortality: a pooled analysis of 20 prospective studies*. Br J Haematol, 2014. **166**(5): p. 667-76.
11. Birmann, B.M., et al., *Young Adult and Usual Adult Body Mass Index and Multiple Myeloma Risk: A Pooled Analysis in the International Multiple Myeloma Consortium (IMMC)*. (1538-7755 (Electronic)).
12. Wadhera, R.K. and S.V. Rajkumar, *Prevalence of Monoclonal Gammopathy of Undetermined Significance: A Systematic Review*. Mayo Clinic Proceedings, 2010. **85**(10): p. 933-942.
13. Chang, S.H., et al., *Obesity and the Transformation of Monoclonal Gammopathy of Undetermined Significance to Multiple Myeloma: A Population-Based Cohort Study*. J Natl Cancer Inst, 2017. **109**(5).
14. Hofmann, J.N., et al., *Body mass index and physical activity at different ages and risk of multiple myeloma in the NIH-AARP diet and health study*. (1476-6256 (Electronic)).
15. Birmann, B.M., C.A. Suppan, and G.A. Colditz, *Abstract A79: Body shape throughout life, long-term weight cycling, and risk of multiple myeloma in the Nurses' Health Study*. Cancer Prevention Research, 2014. **4**(10 Supplement): p. A79.
16. Deng, T., et al., *Obesity, Inflammation, and Cancer*. (1553-4014 (Electronic)).
17. Sulston Rj Fau - Cawthorn, W.P. and W.P.A.-O.h.o.o. Cawthorn, *Bone marrow adipose tissue as an endocrine organ: close to the bone?* (1868-1891 (Electronic)).
18. Cawthorn, W.P., et al., *Expansion of Bone Marrow Adipose Tissue During Caloric Restriction Is Associated With Increased Circulating Glucocorticoids and Not With Hypoleptinemia*. Endocrinology, 2016. **157**(2): p. 508-521.
19. Trubowitz, S. and A. Bathija, *Cell size and plamitate-1-14c turnover of rabbit marrow fat*. Blood, 1977. **49**(4): p. 599-605.
20. Caers, J., et al., *Neighboring adipocytes participate in the bone marrow microenvironment of multiple myeloma cells*. Leukemia, 2007. **21**(7): p. 1580-4.
21. Rosen, C.J., et al., *Marrow Fat and the Bone Microenvironment: Developmental, Functional, and Pathological Implications*. Critical reviews in eukaryotic gene expression, 2009. **19**(2): p. 109-124.

22. Scheller, E.L., et al., *Region-specific variation in the properties of skeletal adipocytes reveals regulated and constitutive marrow adipose tissues*. (2041-1723 (Electronic)).
23. Naveiras, O., et al., *Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment*. *Nature*, 2009. **460**(7252): p. 259-63.
24. Takeshita, S., et al., *Age-related marrow adipogenesis is linked to increased expression of RANKL*. (1083-351X (Electronic)).
25. Skurk, T., et al., *Relationship between adipocyte size and adipokine expression and secretion*. (0021-972X (Print)).
26. Wang, X., W. Liu, and X.A.-O.h.o.o.X. Xie, *Energy imbalance and cancer: Cause or consequence? LID - 10.1002/iub.1674 [doi]*. (1521-6551 (Electronic)).
27. Hanahan, D. and L.M. Coussens, *Accessories to the crime: functions of cells recruited to the tumor microenvironment*. (1878-3686 (Electronic)).
28. Scheller, E.L., et al., *Changes in Skeletal Integrity and Marrow Adiposity during High-Fat Diet and after Weight Loss*. (1664-2392 (Print)).
29. Lwin, S.T., et al., *Diet-induced obesity promotes a myeloma-like condition in vivo*. *Leukemia*, 2015. **29**(2): p. 507-10.
30. Trotter, T.N., et al., *Adipocyte-Lineage Cells Support Growth and Dissemination of Multiple Myeloma in Bone*. (1525-2191 (Electronic)).
31. Liu, Z., et al., *Mature adipocytes in bone marrow protect myeloma cells against chemotherapy through autophagy activation*. (1949-2553 (Electronic)).
32. Bullwinkle, E.M., et al., *Adipocytes contribute to the growth and progression of multiple myeloma: Unraveling obesity related differences in adipocyte signaling*. *Cancer Lett*, 2016. **380**(1): p. 114-21.
33. Ando, S. and S. Catalano, *The multifactorial role of leptin in driving the breast cancer microenvironment*. (1759-5037 (Electronic)).
34. Alshaker, H., et al., *Leptin signalling, obesity and prostate cancer: molecular and clinical perspective on the old dilemma*. (1949-2553 (Electronic)).
35. Yu, W., et al., *Adipocytes secreted leptin is a pro-tumor factor for survival of multiple myeloma under chemotherapy*. (1949-2553 (Electronic)).
36. Pamuk, G.E., et al., *Leptin and resistin levels in serum of patients with hematologic malignancies: correlation with clinical characteristics*. (1812-9269 (Print)).
37. Reseland, J.E., et al., *Abnormal adipokine levels and leptin-induced changes in gene expression profiles in multiple myeloma*. (1600-0609 (Electronic)).
38. Dalamaga, M., et al., *Low circulating adiponectin and resistin, but not leptin, levels are associated with multiple myeloma risk: a case-control study*. (1573-7225 (Electronic)).
39. Hofmann, J.N., et al., *A prospective study of circulating adipokine levels and risk of multiple myeloma*. (1528-0020 (Electronic)).
40. Cawthorn, W.P., et al., *Bone marrow adipose tissue is an endocrine organ that contributes to increased circulating adiponectin during caloric restriction*. *Cell Metab*, 2014. **20**(2): p. 368-75.
41. Kim, J.Y., et al., *Obesity-associated improvements in metabolic profile through expansion of adipose tissue*. (0021-9738 (Print)).
42. Aleidi, S., et al., *Adiponectin serum levels correlate with insulin resistance in type 2 diabetic patients*. (1319-0164 (Print)).
43. Siasos, G., et al., *Adiponectin and cardiovascular disease: mechanisms and new therapeutic approaches*. (1875-533X (Electronic)).
44. Ishikawa, M., et al., *Plasma adiponectin and gastric cancer*. (1078-0432 (Print)).
45. Tworoger, S.S., et al., *Plasma adiponectin concentrations and risk of incident breast cancer*. (0021-972X (Print)).

46. Goktas, S., et al., *Prostate cancer and adiponectin*. (1527-9995 (Electronic)).
47. Cust, A.E., et al., *Plasma adiponectin levels and endometrial cancer risk in pre- and postmenopausal women*. (0021-972X (Print)).
48. Fowler, J.A., et al., *Host-derived adiponectin is tumor-suppressive and a novel therapeutic target for multiple myeloma and the associated bone disease*. *Blood*, 2011. **118**(22): p. 5872-82.
49. Hofmann, J.N., et al., *Low levels of circulating adiponectin are associated with multiple myeloma risk in overweight and obese individuals*. *Cancer Research*, 2016.
50. Nigro, E., et al., *New insight into adiponectin role in obesity and obesity-related diseases*. (2314-6141 (Electronic)).
51. Steppan, C.M., et al., *The hormone resistin links obesity to diabetes*. (0028-0836 (Print)).
52. Kim, H.J., et al., *Expression of resistin in the prostate and its stimulatory effect on prostate cancer cell proliferation*. (1464-410X (Electronic)).
53. Kuo, C.H., et al., *Lung tumor-associated dendritic cell-derived resistin promoted cancer progression by increasing Wolf-Hirschhorn syndrome candidate 1/Twist pathway*. (1460-2180 (Electronic)).
54. Thommesen, L., et al., *Expression and regulation of resistin in osteoblasts and osteoclasts indicate a role in bone metabolism*. (0730-2312 (Print)).
55. Santo, L., et al., *Circulating resistin levels and risk of multiple myeloma in three prospective cohorts*. *LID - 10.1038/bjc.2017.282 [doi]*. (1532-1827 (Electronic)).
56. Pang, J., et al., *Resistin induces multidrug resistance in myeloma by inhibiting cell death and upregulating ABC transporter expression*. (1592-8721 (Electronic)).
57. Cook, K.S., et al., *Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve*. *Science*, 1987. **237**(4813): p. 402.
58. Lo, J.C., et al., *Adipsin is an Adipokine that Improves β Cell Function in Diabetes*. *Cell*, 2014. **158**(1): p. 41-53.
59. Rosen, B.S., et al., *Adipsin and complement factor D activity: an immune-related defect in obesity*. (0036-8075 (Print)).
60. Vasilenko, M.A., et al., *The role of production of adipsin and leptin in the development of insulin resistance in patients with abdominal obesity*. (1608-3091 (Electronic)).
61. Dahl, T.B., et al., *Visfatin/NAMPT: A Multifaceted Molecule with Diverse Roles in Physiology and Pathophysiology*. *Annual Review of Nutrition*, 2012. **32**(1): p. 229-243.
62. Fukuhara, A., et al., *Visfatin: a protein secreted by visceral fat that mimics the effects of insulin*. (1095-9203 (Electronic)).
63. Hung, A.C., et al., *Extracellular Visfatin-Promoted Malignant Behavior in Breast Cancer Is Mediated Through c-Abl and STAT3 Activation*. (1078-0432 (Print)).
64. Yang, J., et al., *Visfatin is involved in promotion of colorectal carcinoma malignancy through an inducing EMT mechanism*. *Oncotarget*, 2016. **7**(22): p. 32306-32317.
65. Patel, S.T., et al., *A novel role for the adipokine visfatin/pre-B cell colony-enhancing factor 1 in prostate carcinogenesis*. (1873-5169 (Electronic)).
66. Venkateshaiah, S.U., et al., *NAMPT/PBEF1 enzymatic activity is indispensable for myeloma cell growth and osteoclast activity*. *Experimental hematology*, 2013. **41**(6): p. 547-557.e2.
67. Cagnetta, A., et al., *Intracellular NAD(+) depletion enhances bortezomib-induced anti-myeloma activity*. *Blood*, 2013. **122**(7): p. 1243-1255.