HubLE I MY MENTOR AND I **Perspective**

Multiple Myeloma and Fatty Acid Metabolism

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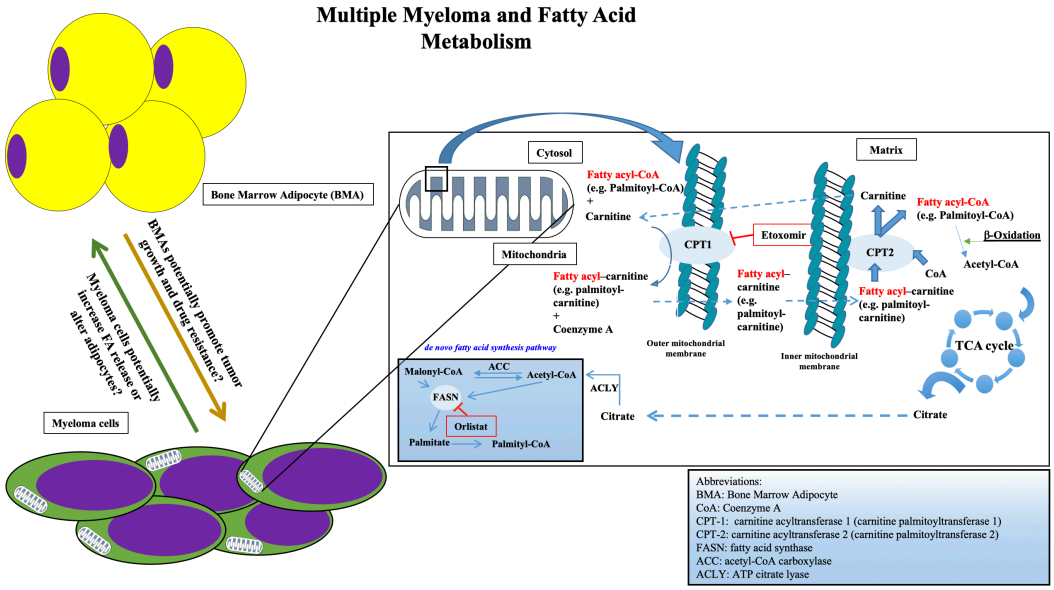
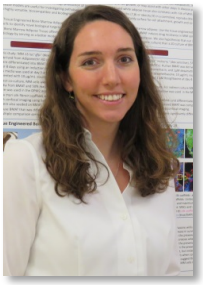
GRAPHICAL ABSTRACT





Assistant Professor Michaela Reagan, PhD, is head of the Maine Medical Center Research Institute (MMCRI) Reagan Laboratory, which focuses on myeloma and diseases of the bone and bone marrow. Her research examines how the bone marrow niche supports myeloma colonization, proliferation, and drug resistance. To do this, she has focused her research on the cells that make up the stroma of the bone marrow, such as the bone marrow adipocyte, which she has found play an important role in bidirectional signaling with myeloma cells. Her current research goal is to help the scientific community better understand the biology of the bone marrow adipocyte and its interactions with myeloma cells, with the overall aim of creating better therapies for myeloma patients and patients with other bone diseases.

Majdi Masarwi, PhD, is a post-doctoral fellow in the Reagan Laboratory at the MMCRI. His research project aims to understand the role of fatty acid and lipid metabolism in promoting multiple myeloma cell growth and how bone marrow adipocytes promote tumor progression and drug resistance.

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ABSTRACT

Multiple myeloma (MM) is a progressive and fatal cancer, characterized by clonal expansion of malignant monoclonal plasma cells within the bone marrow (BM)[1], resulting in BM infiltration and destructive bone lesions[2]. While MM is considered a rare disease, it is the second most prevalent hematological cancer, with almost 30,770 new cases (53% male) diagnosed and 12,770 deaths from myeloma estimated to occur in the United States in 2018 alone[3]. Despite therapeutic advancements in MM treatment, MM remains an incurable disease in a vast majority of cases. While patients respond very well to initial chemotherapeutic treatments, almost all patients relapse and develop a drug resistant disease, making any further treatment ineffective[4]. In this mini-review, we discuss what is known about myeloma growth in the bone marrow niche, and explore the theory that drug resistance may occur through changes in cell metabolism and interactions with neighboring bone marrow adipocytes (BMAs).

Introduction

The stages of multiple myeloma (MM) progress from a monoclonal gammopathy of undetermined significance (MGUS) to smoldering myeloma, to active MM disease, and finally to plasma cell leukemia (PCL), where myeloma cells no longer require the bone marrow niche for survival and proliferation. The biological transition between these stages consists of many oncogenic and epigenetic events, including the dysregulation of the cyclin D gene5 and activation of NF-κB pathways6. In addition to oncogenic, cell-intrinsic adaptations, myeloma cells also receive external signals, including important signals from the BM niche that accelerate the progression of the disease in many ways7,8. Myeloma cells are also very heterogeneous in their mutational make-up within and between patients, and throughout the course of therapy, and hence interact differently with different types of BM niche cells. The BM itself constitutes a unique, complex microenvironment; it is rich in immune cells, bone cells, mesenchymal stromal cells (MSCs), growth factors (IGF-I, VEGF) and cytokines (IL-6, TGFβ)9, that regulate myeloma cell differentiation, migration, proliferation, survival and drug resistance10–12.

Within the skeletal system, bone matrix is constantly being remodeled. Osteoblasts secrete osteoid and mineralize this matrix to make strong new bone, while osteoclasts reabsorb older bone matrix. Myeloma cells decrease osteoblast number and activity while increasing osteoclast number and activity, leading to increased bone resorption and release of stored factors that further accelerate tumor growth in a phenomenon termed the “vicious cycle”13. In this cycle, tumor cells release factors such as PTHrP, which directly interact with osteoblasts and osteoclasts and induce bone disease14. Therefore, targeting the BM microenvironment provides an antitumor strategy for impeding the “vicious cycle” of myeloma cells.

One of the major components of the BM niche is the bone marrow adipocyte (BMA), which comprises the main cellular compartment of bone marrow adipose tissue (BMAT). Over the last decade, BMAT has been shown to play an active

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role in bone metabolism and bone cancer metastasis15–17. In this review, we present an overview of BMAs and bone metastasis, with particular emphasis on lipid metabolism in myeloma cells.

Bone Marrow Adipose Tissue

The BM is a complex organ containing two types of stem cells: the hematopoietic stem cell (responsible for the production of blood cells) and the non-hematopoietic mesenchymal stem cells (MSCs). Bone marrow-derived MSCs (BM-MSCs) are multipotent cells that have the potential to differentiate into cells that comprise cartilage (chondrocytes), muscle (myocytes), bone (osteoblasts), and, importantly, adipose tissue (adipocytes), in response to appropriate factors. In recent years, greater interest in the adipose depot located within the BM has become an area of intense research interest due to a greater understanding of adipose biology in general, and improved imaging modalities to assess this depot in the bone. Adipose tissue is the primary energy depot in the human body. It has classically been categorized into three types: white adipose tissue (WAT), brown adipose tissue (BAT) and beige adipose tissue, depending on anatomical location and composition18. White adipose tissues store excess energy in the form of triglyceride droplets and release fatty acids in response to energy depletion. They also serve as an endocrine organ, capable of secreting several adipokines to regulate body metabolism and inflammation19. Brown adipocytes, on the other hand, are rich in mitochondria that contain the uncoupling protein-1 (UCP-1); UCP-1 functions to dissipate energy into heat20. Beige adipocytes are similar to brown adipocytes, but are found within WAT as a result of "beiging" of white adipocytes. Beige adipose tissue is rich in UCP-1 protein as well, and are activated in response to cold exposure or catecholamines21,22.

Fat accumulation within the BM is a normal process seen within bone maturation during puberty23 and during the process of aging. However, premature BM fat accumulation is also observed following diverse clinical conditions such as exposure to radiation, chemotherapy, and glucocorticoid treatment, or following starvation, as in patients with anorexia nervosa and significantly reduced caloric intake23–26. Furthermore, lifestyle influences (such as unloading of bones, seen in astronauts or during extensive bedrest) and obesity can also increase BMAT27, whereas exercise and mechanical stimulation can decrease BMAT. A high fat diet increased BMAT volume in C57BL/6 mice, whereas exercise reduced it and promoted bone formation27–29. Exercise may reduce BMAT by enhancing energy expenditure and fatty acid beta-oxidation27.

BMAT appears to share many properties of white and brown/beige adipose depots, but also functions as a distinct energy depot. For example, while WAT decreases during starvation, BMAT in fact increases and packs the BM, supporting its evolutionary function as the last energy depot during starvation and demonstrating a very different physiological response pattern from WAT30. BMAT is also the predominant tissue in the BM, where it constitutes 50-70% of BM volume, or even more than 70% in the elderly31. BMAT also accounts for 5-10% of the total fat mass in healthy

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adult humans30,32. BMAT has a gene expression that corresponds with WAT and BAT as well33. BMAT stores triglycerides and releases fatty acids (FAs) that can be subsequently used to generate adenosine triphosphate (ATP). BMAT has similar histological characteristics to WAT; BMAs store triglycerides as unilocular intracellular lipid droplets, but BAT expresses gene markers such as deiodinase 2 (Dio2), peroxisome proliferation activated receptor gamma coactivator 1-alpha (PGC-1□), Forkhead box protein C2 (FOXC2), and PR domain containing 16 (PRDM16)34. BMAT is also considered to be an endocrine organ, due to its capability to secrete several cytokines and adipokines, as well as hormones including leptin, which regulates energy intake, and adiponectin, which regulates glucose metabolism and insulin sensitivity30. BMAs also secrete cytokines such as IL-6, TNF□□ and others factors that enhance tumor growth, invasion and survival35,36.

The Supportive Effects of BMAT on Multiple Myeloma

The BM niche represents an attractive site for various types of cancer, including breast cancer, prostate cancer, and hematological malignancies such as MM. The BM microenvironment supports tumor growth, invasion, and survival through evasion of the immune system and induction of chemotherapy treatment resistance.

Recently, BMAT has been shown to support cancer bone metastasis and drug resistance17. Epidemiological studies have shown an association between BMAT and MM12,17,35–37. Since obesity and aging are both risk factors for MM and correlate with increased BMAT, BMAs may enhance MM engraftment and growth within the BM7,38. In vitro culture of BMAs isolated from MM patients has been shown to support myeloma growth and enhance chemoresistance by activating autophagy through leptin, leading to inhibition of caspase cleavage and apoptosis15. We have seen similar results in our lab39, and also observed that BMAs shrink when co-cultured with MM cells, perhaps indicating lipolysis or some other form of delipidation40. These studies suggest that BMAT might support myelomagenesis and enhance myeloma cell growth in patients.

A meta-analysis of prospective cohorts has shown an association between a high incidence of MM and being overweight, and obesity is a poor prognostic factor for myeloma disease. Obesity is also associated with increased BMAT, which may provide an optimal microenvironment of myeloma cells to grow and survive41,42. Adipocytes have been shown to support cancerous cell growth and survival by influencing cell mitochondrial activity and lipid metabolism43,44.

Multiple Myeloma and Metabolism

The interaction between myeloma cells and the BM microenvironment is well known to be essential for myeloma development and progression8. Alteration in cellular metabolism is one of the primary features in cancer, and interactions between MM cells and BM stromal cells might affect, and be affected by, metabolic changes in both myeloma and stromal cells. BMAs, which arise from BM mesenchymal stromal cells, provide a unique stromal cell type for myeloma cells

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to interact with. BMAs may produce FAs, released from their triglyceride stores that may feed neighboring myeloma or other tumor cells.

FAs are essential for the biosynthesis of membranes and signaling molecules, and as substrates for energy production. FA building blocks come either from exogenous sources or from de novo FA synthesis. FA synthesis is an anabolic process that relies on the tandem activation of the fatty acid biosynthetic enzymes adenosine triphosphate citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN). However, glycolytic and fatty acid synthesis pathways are known to be affected and deregulated by oncogenes and tumor suppressor genes45,46. Limited evidence suggests that cancer cells have altered expression or activity of the enzymes involved with fatty acid oxidation (FAO)47–49.

Recently, FAO has become an area of interest in cancer metabolism49. The process of FAO produces nicotinamide adenine dinucleotide (NADH), nicotinamide adenine dinucleotide phosphate (NADPH), flavin adenine dinucleotide (FADH2), and adenosine triphosphate (ATP). During FAO, FAs are converted into long-chain acyl-CoA by long-chain acyl-CoA synthetase (LACS). Once in the form of acyl-CoA, the FA enters the mitochondria via carnitine palmitoyltransferase 1 (CPT1), a mitochondrial enzyme expressed on its outer membrane (described more below). CPT1 is the rate-limiting step of FAO, transporting acyl-CoA and carnitine across the outer mitochondrial membrane49,50. Once inside the mitochondrial matrix, the acyl-CoA undergoes a series of reactions, each releasing NADH, and FADH2. This process produces a great deal of energy for the cell, and in fact, one gram of FA (e.g., Palmitic acid) can produce twice as much ATP as the metabolism of one gram of glucose (6 carbons) carbohydrates when the palmitic acid is fully oxidized51,52.

Long chain FAs (LCFA) range from 12 to 18 carbons long and are an important source of energy for most cells, exclusive of brain cells. As LCFAs cannot pass through the mitochondrial inner membrane by mere diffusion, these FAs have to be actively transported by a specialized system called the carnitine system/shuttle (CS)53. The CS consists of four enzymes the carnitine palmitoyltransferase I (CPT1), the carnitine palmitoyltransferase II (CPT2), carnitine-acylcarnitine translocase (CACT), and the carnitine acetyltransferase (CRAT).

CPT1 is the first component and the rate-limiting enzyme of the CS, catalyzing the transfer of the acyl group from CoA to carnitine to form palmitoylcarnitine. A translocase then shuttles the acylcarnitine across the inner mitochondrial membrane where it is converted back into palmitoyl-CoA. Over-expression of CPT1 has been shown to be associated with tumor progression in several cancer types such as breast cancer54, and prostate cancer55, as well as lymphoma and leukemia56. Similarly, others have shown that inhibition of this enzyme increased apoptosis and suppression of cancer cell proliferation, neovascularization and chemoresistance57–59. Furthermore, CPT1 is hypothesized to be involved in cell survival by stimulating histone acetylase activity60, protecting cells from apoptosis

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by removing long chain fatty acyl-CoA (e.g. palmitoyl-CoA) from the cytoplasm, and preventing the production of "palmitate/palmitoyl-CoA/ceramide" complex involved in apoptosis activation61.

Etomoxir (2[6(4-chlorophenoxy) hexyl] oxirane-2-carboxylate), is a safe irreversible inhibitor of CPT1 enzyme, commonly used to inhibit CPT1 in heart failure patients62. Etomoxir blocks the transfer of long chain fatty acids (LCFAs) into the mitochondria for beta-oxidation. Recently, researchers have found that pharmacological inhibition of CPT1 by etomoxir altered cancer cell proliferation in acute myeloid leukemia (AML) and Burkitt's lymphoma56,63. In the lymphoma study, inhibition of FAO reduced c-myc mediated lymphomagenesis, suggesting a potential role of CPT1 in the pathogenesis of c-myc-associated cancers63. In addition, Shao et al. showed inhibition of CPT1 reduced cellular ATP levels and induced cell cycle arrest at G0/G1 in ovarian cancer cells in vitro64. Concomitant pharmacologically inhibiting CPT1 and FASN enzyme with orlistat decreased cell viability in prostate cancer in in-vitro studies. Decreasing FAO and FA synthesis decreased mTOR and AKT signaling and increased caspase-3 activity65,66. Moreover, inhibiting FAO proved to be a successful strategy to increase leukemia cell sensitivity and provided a substantial therapeutic benefit in a leukemic mouse model67,68.

Another common metabolic pathway is that of glutaminolysis, the process by which glutamine is converted into glutamate in the cytosol, and then is broken down into α-ketoglutarate to enter the mitochondria. There, α-ketoglutarate can enter the Kreb's cycle to undergo oxidative phosphorylation to produce ATP43,69. Another common metabolic pathway for cancer cells is the use of glucose to produce ATP via glycolysis. Glucose is transported across the cell membrane by several transport channels (GLUT 1-4) and then is processed in the cytosol before entering the mitochondrial matrix in the form of pyruvate. As this is an oxygen-independent pathway, glycolysis is a well-investigated metabolic pathway for cancer cells that often survive in hypoxic environments. The pyruvate is then oxidized to form Acetyl-CoA as it enters the Krebs cycle (also known as the tricarboxylic acid cycle or citric acid cycle)69. A well-known metabolic alteration to this process in cancer cells is the Warburg effect43. During this process, pyruvate is converted into lactate even in the presence of oxygen (aerobic glycolysis), instead of entering into the mitochondria and completing oxidative phosphorylation43,69. This is seen with an overall increase in glucose uptake. Malignant cells utilize glucose through aerobic glycolysis in a higher rate than normal cells. The production of lactate from glucose is faster 10 to 100 times than the mitochondrial glucose oxidation, producing comparable amount of ATP70. Furthermore, cancer cells utilize more glucose to support their biosynthetic needs, such as uncontrolled proliferation. Consumed glucose is used as a source of carbon to synthesize NADPH as well as ribose phosphate required for nucleotides synthesis through the pentose phosphate pathway (PPP)71.

Conclusion

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Although not fully understood, FAO may play an essential role in MM metabolism. Beta-oxidation and aerobic glycolysis are compatible forms of metabolism. They can occur concurrently, and cross-signaling between beta-oxidation and glycolysis has been shown to promote the Warburg effect50. Although multiple myeloma cells have been shown to have abnormally high glucose intake, these cells are often found in an environment with relatively high adiposity, which perhaps provides long chain fatty acids that are metabolized anaerobically in the hypoxic environment of the BM72. Targeting enzymes, such as CPT1, involved in metabolism could be a promising treatment for MM and this has already been proven effective in leukemia67,68,73.

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