J BONE ONCOL 46 (2024) 100609

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research Paper

Adipocytes and metabolism: Contributions to multiple myeloma

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HIGHLIGHTS

- How can bone marrow adipocytes be modulated to affect cancer cell growth or drug resistance?
- What roles do adipocyte-derived fatty acids play in cancer within the bone marrow?
- Will targeting cell-intrinsic or microenvironment-derived fatty acid binding proteins (FABPs), ACSLs (acyl-CoA synthetase long chain family members), lactate metabolism, or other metabolic pathways lead to novel cancer therapies?
- Can we target tumor cell metabolism specifically, while sparing healthy cells?

ARTICLE INFO

Keywords:
Multiple myeloma
Adipocytes
Metabolism
Drug resistance
Fatty acids

ABSTRACT

Obesity contributes to many cancers, including breast cancer and multiple myeloma, two cancers that often colonize the bone marrow (BM). Obesity often causes metabolic disease, but at the cellular level, there is uncertainty regarding how these shifts affect cellular phenotypes. Evidence is building that different types of fuel affect tumor cell metabolism, mitochondrial function, and signaling pathways differently, but tumor cells are also flexible and adapt to less-than ideal metabolic conditions, suggesting that single-pronged attacks on tumor metabolism may not be efficacious enough to be effective clinically. In this review, we describe the newest research at the pre-clinical level on how tumor metabolic pathways and energy sources affect cancer cells, with a special focus on multiple myeloma (MM). We also describe the known forward-feedback loops between bone marrow adipocytes (BMAds) and local tumor cells that support tumor growth. We describe how metabolic targets and transcription factors related to fatty acid (FA) oxidation, FA biosynthesis, glycolysis, oxidative phosphorylation (OXPHOS), and other pathways hold great promise as new vulnerabilities in myeloma cells. Specifically, we describe the importance of the acetyl-CoA synthetase (ACSS) and the acyl-CoA synthetase long chain (ACSL) families, which are both involved in FA metabolism. We also describe new data on the importance of lactate metabolism and lactate transporters in supporting the growth of tumor cells in a hypoxic BM microenvironment. We highlight new data showing the dependency of myeloma cells on the mitochondrial pyruvate carrier (MPC), which transports pyruvate to the mitochondria to fuel the tricarboxylic acid (TCA) cycle and electron transport chain (ETC), boosting OXPHOS. Inhibiting the MPC affects myeloma cell mitochondrial metabolism and growth, and synergizes with proteosome inhibitors in killing myeloma cells. We also describe how metabolic signaling pathways intersect established survival and proliferation pathways; for example, the fatty acid binding proteins (FABPs) affect MYC signaling and support growth, survival, and metabolism of myeloma cells. Our goal is to review the current the field so that novel, metabolic-focused therapeutic interventions and treatments can be imagined, developed and tested to decrease the burden of MM and related cancers.

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https://doi.org/10.1016/j.jbo.2024.100609
Received 21 January 2024; Received in revised form 3 May 2024; Accepted 15 May 2024
Available online 22 May 2024

1. Introduction

The emergence and maintenance of cancer within the bone marrow (BM) is now well known to be governed by the tumor niche [1]. The BM niche contains an assortment of cell types that are involved in the health and maintenance of bone cells, red blood cells, and white blood cells. When cancer cells invade the BM, they hijack the BM cells to promote their survival and recalcitrance to therapeutics [2]. One hallmark of cancers harbored by the BM is a skewing of the bone remodeling process: the coupling of bone-building activity through osteoblasts with bone-resorptive activity via osteoclasts is uncoupled to support cancer growth [2]. Osteolytic cancers destroy bone through the inhibition of osteoblast function and stimulation of osteoclasts, which releases bone-embedded growth factors, collagens, and other signals that can promote tumor growth, which in turn drives additional bone loss in a process known as the vicious cycle [2]. Conversely, osteoblastic cancers are characterized by excess bone matrix production, but this bone is irregular, weak, and often protruding. In all malignancies within the bone, the BM provides a fertile ground (soil) for the growth of metastatic cells (the seed) [2].

Multiple myeloma (MM) is an osteolytic plasma cell neoplasm that thrives primarily in the BM, where malignant cells interact with a plethora of non-cancerous cell types, growth factors, and fuel sources. Myeloma cell plasticity allows the cells to adapt to the hypoxic niche of the BM by initiating hypoxia-inducible factor (HIF) signaling mechanisms, as well as normoxic environments, by upregulating IRF4 and MYC signaling pathways [3]. Oxygen tension, soluble factors, and BM cells, such as endothelial cells, fibroblasts and immune cells, all modulate the responses of tumor cells to therapeutics [4]. For example, tumor-associated macrophages and bone marrow adipocytes (BMAds) have been shown to secrete many tumor-supportive molecules including lipids, cytokines, adipokines, and exosomes [5–7]. How bone marrow adipose tissue (BMAT) fuels tumor cells, and more broadly, how a myeloma cell's metabolism affects its proliferation, interactions with the microenvironment, or response to therapeutics is an active area of inquiry [7–9].

2. Obesity and multiple myeloma

The association between obesity and cancer has become of great interest due to the rapid increase in obesity and overweight rates globally, and obesity is now established as a risk factor for developing MM [10,11] and monoclonal gammopathy of undefined significance (MGUS) [5,12]. Nightly fasting is currently being investigated to target obesity and improve metabolism with the goal of preventing MM development in people at high risk for MM who are overweight or obese [13]; results from this work are forthcoming. Encouraging data from a recent *meta*-analysis found significantly reduced risk of MM in patients with obesity undergoing bariatric surgery compared to the control (non-surgical) group [14]. Similarly, the diabetic drug metformin has been investigated in combination with other myeloma therapies as a treatment option, but it has not been found to affect overall response rate yet in MM [15]. Metformin is also under investigation to prevent the transition from MGUS to MM [16]. *In vitro* and *in vivo* results vary and suggest that metformin may be effective on its own, or may need to be combined with other agents for therapeutic effects [17]. Obesity can also alter the immune system, and diet-induced obesity has been shown to contribute to MM progression in part through reducing the relative number of T and B cells in the mouse BM [18]. Thus, more research into the roles of obesity in cancer etiology and progression, and the potential for weight-loss therapies for cancer prevention or treatment would be greatly beneficial both at the preclinical and clinical levels.

3. Adipocyte-Myeloma crosstalk

Interestingly, two of the main risk factors for developing MM (aging and obesity), and common MM treatments (chemotherapy and irradiation) cause an increase in BMAT [5,11,19,20]. Researchers have investigated connections between adipose (BMAT and white adipose tissue (WAT)) and MGUS/MM etiology and progression, and a multitude of mechanisms have been unveiled that suggest targeting adipocytes or adipocyte-derived factors may lead to novel treatments. In support of the adipocyte-myeloma link, a recent study from Denmark found that MGUS patients who developed MM had a BMAd size distribution shifted to the right (indicating more larger, and fewer smaller adipocytes) compared to non-progressing (stable) MGUS patients [21]. Furthermore, adipokines such as leptin, IL-6 and adiponectin are key players in MM progression. While adiponectin has myeloma suppressive activities, leptin and IL-6 accelerate MM by activating AKT and JAK/STAT3 pathways respectively. Both ultimately lead to an anti-apoptotic state with excessive and uncontrollable myeloma cell proliferation [5]. However, not all BMAT seems to be supportive of myeloma; anorexia nervosa (AN) causes increased BMAT, but these patients do not have an increased risk for developing MM [22]. This is perhaps due to differences in etiology and physiology of obesity-induced BMAT compared to AN-induced BMAT, or due to other differences, such as systemic factors that differ between obese and anorexic individuals. Development of BMAT in AN is thought to be a survival mechanism in response to starvation, wherein the body is unable to meet the energy-intensive needs of hematopoiesis, unlike the etiology of increased BMAT resulting from obesity [23]. Thus, differences in the type of BMAT and its physiological roles should be considered in BMAT's effects on cancer.

There are many ways tumor cells can exploit or manipulate local adipocytes. Exposure of BMAds to myeloma cells reduces their lipid droplet content, alters BMAd metabolic activity, and skews BMAd-derived adipokine concentrations (eg. by decreasing expression of the anti-myeloma protein adiponectin). This crosstalk is at least in part due to myeloma cell-derived tumor necrosis factor alpha (TNFα) [24–26], and results in the development of a more tumor-supportive milieu. For example, soluble factors from MM-associated BMAds provide dexamethasone resistance to MM cells *in vitro* and patients who showed a complete response to treatment with high dose melphalan and dexamethasone, followed by BM transplantation, had significantly lower BM adiposity than patients who exhibited only a partial/very good response [26]. Recent work by Panaroni et al. [7] found that MM-associated adipocytes are smaller than those cultured alone and suggests this is tied to MM-triggered lipolysis. Our lab has seen that both adipocyte size and adipose volume per marrow volume is smaller in newly-diagnosed MM patient BM biopsies compared to controls [26]. Liu et al also analyzed MM patient BM biopsies and found that newly-diagnosed MM patients had decreased adipocyte numbers compared to normal samples, which was normalized for MM patients in remission (interestingly, despite no recovery of bone volume or trabecular thickness) [24]. These data support the theory that BMAd lipolysis may contribute to MM by fueling tumor cells with fatty acids. In alignment with this theory, when cultured with BMAds, myeloma cells upregulated fatty acid transporters (FAT) 1 and 4, allowing them to increase their uptake of free fatty acids (FFA) [7]. Treatment with exogenous FFAs led to a dose-dependent increase in intracellular lipid content, survival, and proliferation in myeloma cells *in vitro,* although the exact pathways driving this were not investigated [7]. However, the highest levels of FFAs caused ferroptosis and lipid toxicity as a result of lipid peroxide accumulation resulting from decreased expression of enzyme glutathione peroxidase 4 (GPX4) in myeloma cells [7]. Overall, regulating BMAd lipolysis and FFA uptake in MM cells could be a promising new approach to stop MM progression.

Adipocyte-derived conditioned media has also been shown to support myeloma cells *in vitro*, in part through adipocyte-derived angiotensin II, which upregulates acetyl-CoA synthetase 2 (ACSS2) in myeloma cells and subsequent IRF4 signaling through activation of lysine acetylation in IRF4 [9]. ACSS2 is overexpressed in myeloma cells derived from obese patients, contributes to MM progression, and is one of the key enzymes in generating acetyl-CoA [9]. Acetyl-CoA is a central

metabolic intermediate for pyruvate to enter the tricarboxylic acid (TCA) cycle, a precursor for *de novo* fatty acid (FA) synthesis, and required for acetylation of lysine [9]. All of these roles could affect MM, but so far what has been shown is that ACSS2-mediated lysine acetylation of IRF4 results in stabilization of this oncoprotein in myeloma cells [9]. *In vivo*, co-injection of purified, mature human adipocytes with myeloma cells in NSG mice subcutaneously induced more tumor growth than when myeloma cells were injected alone [9]. Moreover, myeloma cells with ACSS2 knockdown grew slower alone or in co-culture with adipocytes, compared to myeloma cells treated with a control shRNA, in an *in vivo* study, highlighting ACSS2 as a new target in MM in lean or obese conditions [9]. The study also revealed an important link between epigenetics and metabolism in directing myeloma survival and proliferation.

Relatedly, the same group found myeloma cells enhance the activity of methyltransferase like 7A (METTL7A), a RNA methyltransferase, in adipocytes, and that this creates a forward-feedback loop that further supports MM progression [6]. First they found that bortezomib-sensitive MM cells became resistant when they were provided normal or myeloma-exposed BMAd-derived exosomes [6]. Through extensive experimentation, they found that myeloma-exposed BMAd-derived exosomes contain certain long non-coding RNAs (LncRNAs) that prevent therapy-induced apoptosis in MM cells [6]. Specifically, they identified two LncRNAs (*LOC606724* and *SNHG1)* to be enriched in MM-adipocyte exosomes, and found these were associated with poor MM patient outcomes [6]. Transfer of these LncRNAs to myeloma cells triggered pro-survival pathways, such as increased c-Myc protein at the post transcriptional level, and *METTL7A* expression was shown to be essential in MM-associated adipocytes for loading these LncRNAs into exosomes [6]. Although more research into LncRNAs and adipocyte-derived exosomes is warranted, this work provides important new insights into ways through which adipocytes support myeloma cells through bidirectional signaling.

Combined, the newest findings from the manuscripts reported here suggest that MM-associated adipocytes contribute to a myeloma-supportive microenvironment through numerous mechanisms threading through the fields of metabolism, epigenetics, exosomes, non-coding RNA, and oxidative stress. A better understanding of FA metabolism, and safe ways to modulate it in myeloma cells, will be needed to engineer effective therapeutic approaches for MM. These works adds to the established understanding of the supportive effects of growth factors from adipocytes and demonstrate the complexity and interplay between many different mechanisms of survival and adaptation used by myeloma cells.

4. Metabolic pathways important in MM

In the past 3 years, tumor metabolism has been revealed as a powerful force, able to create tumor cells recalcitrant to therapies and adaptable to different microenvironments throughout the body. MM metabolism has recently been aptly termed a “treasure trove of therapeutic targets” in a comprehensive review on this topic [27]. Our laboratory recently found that the Acyl-CoA Synthetase Long Chain (ACSL) family is a novel target in myeloma [28]. ACSLs are enzymes that activate long chain FAs through the addition of the coenzyme A (CoA), which is required for FAs to be used in catabolic (energy production), anabolic (complex lipid synthesis), or other metabolic pathways. Myeloma cells treated with the ACSL inhibitor Triacsin C show decreased proliferation, mitochondrial dysfunction, and induction of apoptosis *in vitro* [28]. Other labs have similarly found that ACSL4 can have both myeloma-supportive (pro-proliferation) and anti-myeloma (pro-ferroptosis) effects [29]. Similarly, the Yang laboratory showed the importance of ACSS2 in MM in lean or obese conditions as described above, which is related, but distinct from, the ACSL family [9]. The group focused specifically on the downstream IRF4 pathway changes governed by ACSS2 and did not explore the specific metabolic changes that ACSS2 knockdown or inhibition induced. It seems likely that ACSS2’s pro-myeloma properties are also due to IRF-independent mechanisms, considering their data that increasing IRF4 protein expression in myeloma cell via lentivirus transfection to the control levels did not completely correct the myeloma cells’ growth capacity, colony forming ability, or *in vivo* expansion to control levels [9].

More recently, work from the Guikema lab in Amsterdam expanded on knowledge of the Warburg effect in MM [30]. The Warburg effect is the phenomenon where cancer cells predominantly rely on glycolysis to fulfill their energy demands, by shuttling pyruvate towards lactate rather than utilizing the more energy-efficient oxidative phosphorylation (OXPHOS)/TCA pathway for ATP generation [30]. This may be useful to cells because of the speed of this process, the ability to redirect TCA intermediates towards other anabolic processes required for rapid cell division, and a reduction in OXPHOS-generated reactive oxygen species (ROS) accumulation within the cell. This team showed that myeloma cell lines rely on glycolysis for survival and proliferation in an experiment where they blocked all glycolysis (using galactose rather than glucose-containing media) [30]. They also found that overall, myeloma cells can utilize both OXPHOS as well as glycolysis and explored how rewiring of metabolic pathways and flexibility in use of substrate type, often driven by genetic mutations, can induce evolution of therapy-recalcitrant tumors [30]. Their team specifically demonstrated a new role for AKT, a known MM oncogene that drives metabolism by phosphorylating metabolic genes. They showed, for the first time, that AKT also restrains the tumor-suppressive effects of forkhead box O (FOXO) transcription factors, which then leads to sustained glycolysis, OXPHOS, and tumor survival and proliferation [30]. This was supported clinically, as FOXO-dependent repression of metabolic genes predicted superior outcomes for MM patients (overall survival, OS) [30]. In general, metabolic targets and transcription factors related to FA oxidation, FA biosynthesis, glycolysis, OXPHOS, and other pathways hold great promise as new vulnerabilities in myeloma cells.

In further support of MM dependence on glycolysis, Dr. Fulciniti’s elegant work found that inhibition of cyclin-dependent kinase 7 (CDK7) impairs MYC-dependent glycolytic cascade proteins in myeloma cells, which is important as CDK7 inhibitors have proven effective preclinically, but their exact mechanisms of action had not been identified [31]. CDKs are a family of serine/threonine protein kinases that control key aspects of the cell cycle and transcription; they are frequently dysregulated (typically overexpressed) in cancers, including MM [31]. This group found that CDK7 inhibition downregulated the expression of key glycolytic genes and impaired aerobic glycolysis, highlighting a central role for CDK7 in MM metabolic reprogramming. Specifically, they showed that CDK7 inhibition decreased expression of hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA), along with many other components of the glycolytic cascade, and showed a role for these proteins in CDK7 support of MM cell metabolism and viability [31]. Since LDHA is required to elevate the rate of glycolysis, and ATP and lactate production in tumor cells during the Warburg effect, LDHA or lactate may also represent an important new target in MM or other cancers. MYC was found to bind to the DNA promotor region of both genes, suggesting that HK2 and LDHA are transcriptional targets of MYC in myeloma cells; this binding was diminished with treatment with the CDK7 inhibitor YKL-5-124, providing rationale for therapeutic targeting of CDK7 in MM as a novel way to interfere with glycolysis [31]. As an aside, since HIF1α could also regulate glycolytic phenotype in cancer, they also provided evidence that the actions of CDK7 were independent of HIF1α [31].

Recent studies further demonstrate the supportive role of lactate in MM and find lactate plays a central role in MM cell metabolism. Lactate is moved across the plasma membrane by the proton-linked monocarboxylate transporters (MCTs) such as MCT1 (bidirectional lactate transporter, mainly an importer) and MCT4 (mainly lactate exporter) [32]. In 2015, blocking lactate import (via MCAT1) was shown to induce myeloma cell apoptosis [33]. Recently, lactate has been found to be

elevated in MGUS, smoldering MM (SMM), and overt MM patient serum versus healthy serum [32]. Lactate also protected MM cell lines from proteasome inhibitor (PI)-induced apoptosis *in vitro*, and, PI-driven apoptosis was increased when the lactate importer (MCT1) was blocked [32]. Acute high concentrations of lactate increased OXPHOS, and expression of glycolytic- and OXPHOS-related genes, and helped protect MM cell mitochondria, which allowed MM cells to use OXPHOS more easily [32]. However, chronic lactate exposure decreased MM cell metabolism and growth, demonstrating that too much lactate can be detrimental for myeloma cells [32]. Primary peripheral blood mononuclear cells (PBMCs) were found to respond to lactate treatment, or co-culture with MM cells, by increasing subpopulations of immunosuppressive cells (T-regulatory cells and myeloid-derives suppressor cells, MDSCs). Inhibition of MCT1 in these cells, with the compound AZD3965, reversed this effect, suggesting the potential for targeting lactate uptake or metabolism both in MM cells and in the surrounding BM milieu as a novel therapeutic avenue [32].

Building on this work, a recent study explored myeloma cell responses to syrosingopine, a dual inhibitor of MCT1 and MCT4, in combination with metformin, an inhibitor of oxidative phosphorylation (OXPHOS) with a multitude of other effects [17,34]. The group found syrosingopine treatment resulted in increased intracellular lactate, reduced cell viability, reduced proliferation, and even cell death at very high doses, suggesting that the ability to export lactate is also required for myeloma cell survival, and again that too much lactate can be toxic for myeloma cells [17]. In concordance with this, they found that high expression of MCT1 and MCT4 both correlated with lower OS for MM patients, suggesting that the ability to regulate lactate is important in maintaining myeloma cell homeostasis [17]. As expected, lactate production as well as MCT1/MCT4 expression were significantly upregulated in hypoxia, confirming the Warburg effect in MM and demonstrating one mechanism by which myeloma cells adapt to hypoxia in the BM [17]. Metformin inhibits the generation of NAD + in cells by inhibiting complex I in the electron transport chain; MCT inhibitors also limit NAD + generation by decreasing conversion of pyruvate to lactate, a reaction that is coupled to NADH being oxidized to NAD + . Thus, this group hypothesized that metformin and syrosingopine could synergize to have negative effects on myeloma cells; this hypothesis was supported using myeloma cell lines *in vitro*, primary patient CD138 + cells, and in a myeloma mouse model. The combination of metformin and syrosingopine caused a metabolic blockage of both glycolysis and OXPHOS in myeloma cells (leading to decreased energy levels [17]), enhanced phosphorylation of the energy sensor AMPKα in some cell lines, and inhibition of the mTOR-pathway and a reduction in protein synthesis in all myeloma cell lines tested [17]. Overall, the dependency of myeloma cells on lactate, and on the ability to regulate lactate concentrations, may represent a new weakness that can be targeted in MM.

Exciting work from the Orthwein laboratory has found great potential for inhibiting the mitochondrial pyruvate carrier (MPC) in MM cells, and synergy of this approach with PIs [8]. The MPC transports pyruvate into the mitochondria, fueling the TCA and boosting OXPHOS, and was shown to be required for mitochondrial metabolism of MM cells [8]. When MPC was inhibited in MM cells, the cells became more sensitive to PIs and increased their use of glycolysis and glutaminolysis (the use of glutamine to feed the TCA) [8]. Altogether, the data suggested that glutamine anaplerosis, which they observed upon inhibition of the MPC complex in myeloma cells, may mimic glutamine starvation, thereby impairing proteasomal activity and potentiating PI-induced cell death [8]. The importance of pyruvate metabolism was further supported by their analysis of the MMRF CoMMpass database, which showed that their pyruvate metabolism gene signature correlated with poorer overall and progression-free survival [8].

Recently, our lab has also found that Fatty Acid Binding Proteins (FABPs) are a promising target in MM [35]. FABPs mediate FA transportation between organelles such as mitochondria, peroxisomes, endoplasmic reticula, and the nucleus, and play an important role in modulating FA metabolism in many other ways. We and another lab have reported that *FABP5* mRNA is highly expressed in myeloma cells, and that higher expression of this gene within myeloma cells is associated with worse clinical outcomes [35,36]. Moreover, our *in vitro* experiments demonstrated that treating myeloma cell lines with the chemical synthetic FABP inhibitors BMS309403 (which primarily inhibits FABP4, and also inhibits FABP3 and FABP5 at higher doses) or SBFI-26 (a FABP5 and FABP7 inhibitor) induced myeloma cell apoptosis, caused cell cycle arrest, and decreased proliferation in myeloma cells [35]. Genetic knockout (KO) of *FABP5* with CRISPR/Cas9 in MM.1R cells also induced a slight, but significant, decrease in myeloma cell number; the effects of this *FABP5*-KO could have been obfuscated by our use of a cell pool rather than cell line or the fact that *FABP6* was highly upregulated, likely as a compensatory mechanism, in the *FABP5*-KO cells [35]. Nonetheless, the data suggested that FABP5 inhibition leads to impaired mitochondrial respiration, decreased metabolic activity, and altered MYC and other metabolism-linked signaling cascades [35]. In myeloma mouse models, administration of these inhibitors showed no obvious toxicity and impeded myeloma growth in some, but not all, of the models, highlighting potential pharmacokinetic and pharmacodynamic challenges with these compounds and the need for further development [19].

5. Conclusion

Overall, there have been many recent advances in understanding the protective role of the BM niche and of tumor cell (and surrounding cell) metabolism in the survival and progression of myeloma. For a thorough summary on the BM microenvironment in MM and the challenges and mechanisms behind intrinsic and extrinsic drug resistance, please refer to Solimando et al. [37]. Here we discussed some of the recent advances in knowledge of the pro-cancer signaling pathways between adipocytes and tumor cells and the metabolic pathways relevant to myeloma cells that should be further investigated to develop new therapeutic treatments for MM patients.

Our review summarized important new insights into ways adipocytes support myeloma cells through bidirectional signaling including lipolysis and FFA uptake, signaling through the ACSS2-IRF4 axis, and transfer of exosomes. These signals support critical processes in myeloma cells such as proliferation and resistance to chemotherapies. Moreover, multiple studies have now shown that BMAds are modified by myeloma cells *in vitro* and *in vivo*, skewing adipokine production, altering lipid content, and stimulating the release of pro-myeloma cytokines. Inhibiting these mechanisms of cross-talk may provide unique opportunities for the development of future therapeutic targets to stop MM progression.

Moreover, we specifically highlight new and exciting findings in the field of myeloma metabolism- including a more thorough understanding of the Warburg effect in myeloma cells and the evolution of therapy-recalcitrant tumors. The novel studies summarized herein support the potential for developing new therapies (eg. novel FABP or ACSL inhibitors) or repurposing metabolically-targeted drugs that are already clinically available (eg. syrosingopine and metformin) to explore in combination with myeloma front-line therapies. Understanding how myeloma cell metabolic activity shifts in relation to its immediate microenvironment conditions or in response to the current standard-of-care therapies will be a critical next step in the exploitation of metabolic pathways in MM.

Author contributions

MRR, HF, AS, MK, YWQ wrote the paper. MRR and HF conceptualized and designed the manuscript. MRR compiled the final and revised versions. All authors approved submission.

CRediT authorship contribution statement

Heather Fairfield: Writing – review & editing, Writing – original draft, Conceptualization. **Michelle Karam:** Writing – original draft. **Allyson Schimelman:** Writing – original draft. **Ya-Wei Qiang:** Writing – review & editing. **Michaela R. Reagan:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Michaela Reagan reports financial support was provided by MaineHealth. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by the American Cancer Society (Research Grant RSG-19-037-01-LIB), the NIH (R50CA265331, R37CA245330, U54GM115516, P20GM121301), the Kane Foundation, and the Arthur Gary Family Fund.

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