



Lipid Metabolism in Tumor-Associated Myeloid-Derived Suppressor Cells

Wei Liu, Hua Song, Xiaojing Li, Deshan Ren, Shuai Ding, and Yan Li

Abstract

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of myeloid cells with immature phenotypes and immunosuppressive functions. This population of cells has been extensively studied over the past decade owing to an increasing recognition of their pivotal role in pathological conditions including cancers, infectious diseases, sepsis, and autoimmune diseases. Various treatments targeting MDSCs are currently under development or in clinical trials with the aim to restore functional immunity against tumors or pathogens. Recent advances in immune metabolism demonstrate the role of metabolic pathways, especially lipid metabolism, in the differentiation and function of MDSCs in tumor environments. Therefore, a comprehensive understanding of lipid metabolism in MDSCs would facilitate the development of

novel therapies against tumors through metabolic reprogramming of MDSCs.

Keywords

Lipid metabolism · MDSC · Fatty acid
Tumor microenvironment · Immune
metabolism · Humanized mice

7.1 Lipid Metabolism and the Origin of MDSCs

Lipid metabolism involves lipid catabolism and anabolism, providing energy and substrate to sustain cellular activities. Lipid metabolism begins with food digestion to breakdown triglycerides into fatty acids, glycerol, and cholesterol by lipases. Small intestinal epithelial cells absorb fatty acids and monoglycerides to reassemble into triglycerides. Subsequently, triglyceride and cholesterol are packed with lipoproteins to form lipid transport complexes like chylomicrons, which travel into the blood circulation [1]. When lipid transport complexes move across tissues, capillary endothelial cells release and breakdown triglycerides into fatty acids and glycerol for consumption in metabolizing cells [2]. Glycerol participates in glycolysis or gluconeogenesis mostly in the cytosol of liver cells whereas fatty acids are stored mainly in the form of triglycerides or used through fatty acid beta-oxida-

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tion (FAO) for energy [3]. Long-chain fatty acids are transported via carnitine palmitoyltransferase system from cytosol to mitochondrial where the FAO takes place. The sequential removal of two carbon units from a beta position of fatty acyl-CoA molecules produces acetyl-CoA, a key intermediate for carbohydrate, protein, and lipid metabolism. Acetyl-CoA sustains tricarboxylic acid cycle (TCA) and oxidative phosphorylation (OXPHOS) [4]. If fatty acids are completely oxidized to CO₂ and water, they yield the highest ATP on an energy per gram basis compared to carbohydrates and proteins. On the contrary to FAO, fatty acid synthesis commences with carboxylation of acetyl-CoA derived from citrate in cytosol into malonyl CoA by acetyl CoA carboxylase 1 (ACC-1). Malonyl CoA in turn potently inhibits the carnitine palmitoyltransferase 1 (CPT-1) activity, the rate-limiting enzyme in FAO. Condensation of malonyl CoA to acetyl CoA and another seven cycles of reaction to produce a saturated long-chain fatty acid palmitate by fatty acid synthase. De novo synthesized fatty acids and intermediates of other metabolic pathways participate in the generation of other lipids or incorporated into triglycerides for lipid droplet formation.

Tissue-specific metabolic environment has a great influence on the hematopoiesis and peripheral immune homeostasis. Take bone marrow (BM) as an example (Fig. 7.1), adipocytes occupy up to 70% of adult BM cavity and thus make BM the third largest fat depot in the body behind subcutaneous and visceral fat [5]. These cells are not just “space fillers” [6], but rather metabolically active and release fatty acids from triacylglycerol droplet into hematopoietic milieu, therefore creating a lipid rich microenvironment for hematopoietic cells [7]. While long-term hematopoietic stem cell (LT-HSC) relies on anaerobic glycolysis for energy [8], short-term HSC (ST-HSC) and committed progenitors live on FAO for self-renew and differentiation [9]. When LT-HSCs differentiate, the expression of genes related to lipid metabolism became increasingly vigorous. HSC numbers in BM of mice and human increase with age, partially due to loss of quiescence for LT-HSCs and enhanced proliferation of ST-HSCs [10, 11]. A similar observation was reported in diet-induced obesity mice [12]. Moreover, aged

and obese mice manifest biased hematopoiesis toward myeloid lineages and reduced lymphoid progenitors [13, 14]. Excessive accumulation of fat content in the marrow with aging and obesity is thought to contribute to this altered hematopoiesis through lipolysis of triglycerides in adipocytes. Indeed, fatty acids released from BM adipocytes are utilized by leukemic blasts via fatty acid-binding protein (FABP)-4, supporting the survival and proliferation of acute myeloid leukemia blast cells [15]. As such, lipid-rich BM microenvironment may favor the hematopoiesis toward myelopoiesis through metabolic reprogramming of HSC for FAO.

Myeloid-derived suppressor cells (MDSCs) (mouse: CD11b⁺ Gr1⁺; human: CD11b⁺ CD33⁺ HLA-DR^{-/lo}) are immunosuppressive myeloid cell populations first described in tumors, subsequently identified in chronic inflammation, and recently in neonates [16–19]. Inhibition of MDSC mediated suppression of innate and adaptive immunity is crucial for effective immunotherapy against tumor and pathogens. Based on surface markers, MDSCs resemble neutrophils and monocytes with immature phenotypes, thus can be further divided into PMN-MDSCs (mouse: Ly6G⁺Ly6C^{-/lo}; human: CD15⁺CD14⁻) and M-MDSCs (mouse: Ly6C^{+/hi}Ly6G⁻; human: CD14⁺CD15⁻) subpopulations, respectively [20]. The origin of MDSCs is still under debate. Initially, MDSCs are proposed as myeloid precursors blocked from differentiation in BM and recruited by chemokines secreted from tumor cells. This hypothesis is supported by in vivo experiments that all-trans retinoic acid and vitamin D3 drive the immature myeloid cells in tumors into functional macrophages, granulocytes, and DCs [21, 22]. However, recent studies challenge this theory by demonstrating that monocytes and neutrophils are plastic and acquire immunosuppressive function within tumor microenvironment (TME) [23]. In any case, both hypotheses acknowledge the role of TME in the development of MDSCs. Although cytokines secreted by tumor cells have been indicated in the manipulation of myelopoiesis in BM or TME [24, 25], accumulating evidence points that metabolic reprogramming of MDSCs from

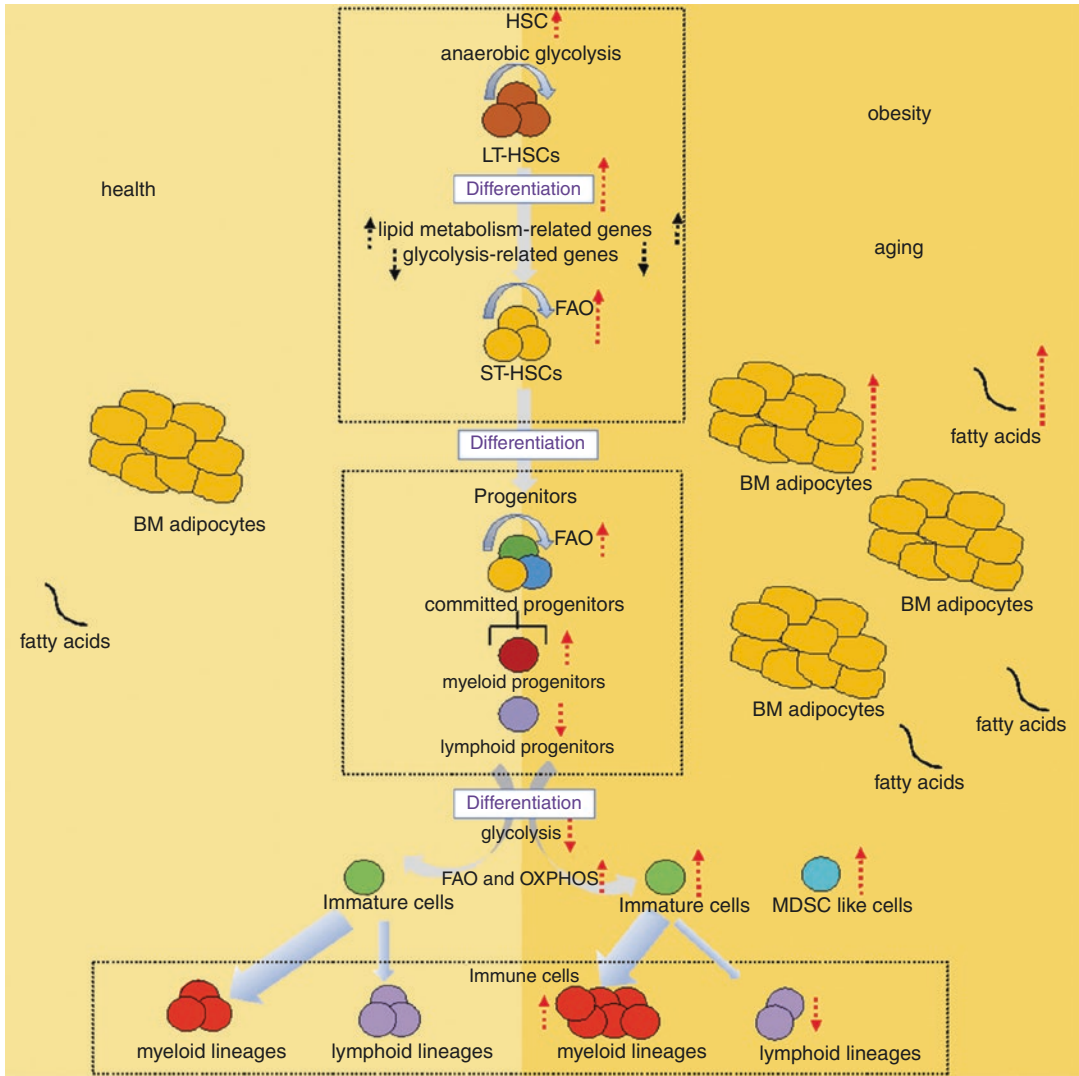


Fig. 7.1 Lipid metabolism and the origin of MDSCs. (i) LT-HSC relies on anaerobic glycolysis for energy, while ST-HSC and committed progenitors live on FAO for energy. (ii) During LT-HSC differentiation, the expression of lipid metabolism-related genes increases, accompanied by a decrease in the expression of glycolysis-related genes. (iii) Aging or obesity would lead to an increase in adipocytes and fatty acids in BM, forming a lipid-rich microenvironment. In the BM of aged and obese human or mice: (iv) the quiescence of LT-HSC is disrupted and

ST-HSCs prefer to differentiate into myeloid progenitors, accompanied by a metabolic switch from glycolysis to FAO and OXPHOS for energy supply. (v) Immature myeloid cells accumulate and generate immunosuppressive MDSCs. *MDSC* Myeloid-derived suppressor cells, *LT-HSCs* Long-term hematopoietic stem cells, *ST-HSCs* Short-term hematopoietic stem cells, *FAO* Fatty acid beta oxidation, *BM* Bone marrow, *OXPHOS* Oxidative phosphorylation

glycolysis to FAO and OXPHOS by tumor cells play a pivotal role in the generation and function of MDSCs. Besides tumor tissues, MDSCs also accumulate in adipose tissue and bone marrow, two other lipid-rich environments. It has been reported that MDSCs are elevated in obese indi-

viduals, as well as in spleen and adipose tissue in obese mice. The level of MDSCs in adipose tissue of mice on a high-fat diet is 1.5–3 times higher than their lean counterparts [26]. As discussed above, bone marrow of obese and aged individuals also harbors a large reservoir of

immature myeloid cells. These evidence together suggest that tissue-specific lipid microenvironment greatly impacts MDSC generation.

7.2 Influence of TME on MDSC Energy Metabolism

Four distinct mechanisms are employed by MDSCs in TME to promote tumor growth and metastases: (a) suppression of tumor-specific immunity, (b) establishing a TME to benefit tumor growth, (c) facilitating tumor metastasis,

(d) induction of tumor stem cell and promotion of epithelial-to-mesenchymal transition [27]. In TME, factors determining MDSC expansion, differentiation, migration, and immunosuppression, include cytokines and growth hormones (e.g., PGE2, TGF- β , GM-CSF, IL-6, and IFN- γ), low PH, hypoxia, and nutrient availability [28]. These triggers participate in shaping MDSC functions by exploiting their plasticity and reprogramming their metabolic fate [29]. Below, we discuss the key metabolic features in TME and its influence on the MDSC energy metabolism (Fig. 7.2).

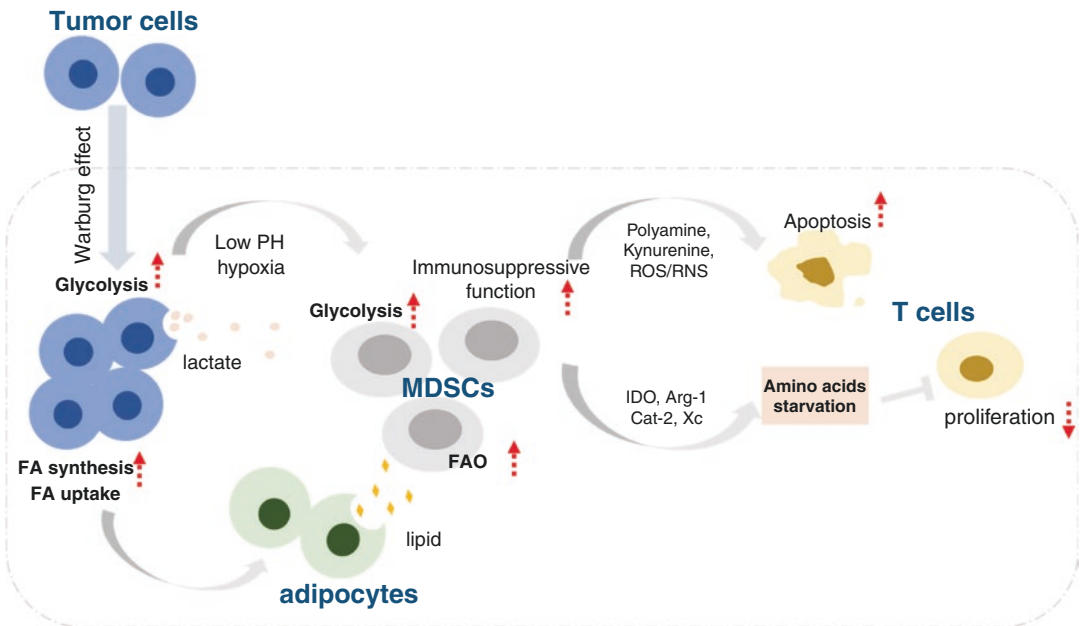


Fig. 7.2 TME shapes the energy metabolism of MDSCs. (i) To meet the demand for rapid proliferation, tumor cells initiate a metabolic shift toward glycolysis, which is known as Warburg Effect. The high glycolytic rate in tumor cells results in massive lactate release, forming an acidulated microenvironment. Besides, uncontrolled proliferation of tumor cells and abnormal blood vessel formation cause hypoxia in TME. (ii) MDSCs reprogram their metabolic pathways toward glycolysis to compete with tumor cells for limited oxygen and glucose. (iii) Tumor cells enhance fatty acid uptake and synthesis and recruit adipocytes in TME to produce excessive exogenous fatty acids, which makes a lipid-rich environment for infiltrating MDSCs. MDSCs are then driven to adopt FAO as their primary energy source. (iv) The acidic and lipid-rich TME promotes the develop-

ment of MDSCs and enhances their immunosuppressive function. MDSCs consume amino acids in the TME through enzymes (Arg-1, IDO, iNOS, etc.) and transporters like Cat-2 and Xc, contributing to amino acid starvation in the TME, which in turn leads to inhibition of tumor antigen-specific proliferation of T cells. (v) Toxic ROS/RNS and amino acid metabolites (polyamine and kynurenine) released by MDSCs induce apoptosis of T cells and promote the generation of Treg from naïve CD4 T cells. *TME* Tumor microenvironment, *MDSC* Myeloid-derived suppressor cells, *FAO* Fatty acid beta oxidation, *Arg-1* arginase-1, *iNOS* induced nitric oxide synthase, *IDO* indoleamine 2,3 dioxygenase, *Cat-2* amino acid transporter 2B, *Xc* cysteine-glutamine antiporter, *ROS* reactive oxygen species, *RNS* reactive nitrogen species

Rapid proliferation of tumor cells requires large amounts of ATPs and substrates to fulfill energetic and biosynthetic demands. As such, tumor cells rewire their metabolic pathway toward glycolysis even under aerobic condition, also known as Warburg Effect [30]. Although aerobic glycolysis is insufficient to generate ATP per unit of glucose compared to mitochondrial respiration, it generates a comparable amount of ATP within a given period of time [31]. Massive lactate secretion from tumor glycolysis acidifies TME and altered the myelopoiesis to promote the generation of MDSCs [32]. Uncontrolled proliferation of tumor cells and abnormal blood vessel formation cause hypoxia in TME. Hypoxia stimulates the expression of HIF-1 α in tumor-infiltrating immune cells, which is the downstream of PI3K-AKT-mTOR pathway [33]. Activation of HIF-1 α favors the glycolysis over OXPHOS by upregulation of glucose and lactate transporters, along with glycolytic enzymes [34, 35]. This results in dampened lymphocyte activation and blocked maturation of myeloid subsets, which requires sufficient glucose for effector functions. Dynamic metabolic flux analysis (dMFA) study shows that MDSC maturation in TME correlates with a high glycolytic flux contributing to up to 95% of the global ATP turnover rate, demonstrating that developing MDSCs obtain energy primarily through glycolysis [36]. In addition, glycolysis activation by metformin or providing lactate promotes the proliferation of MDSCs in TME [37]. Hence, MDSCs would compete with tumor cells for limited glucose and oxygen, but eventually acclimate its metabolic pathway to the available nutrients and hypoxia in TME.

Nitrogen metabolism of MDSCs has been extensively studied in the context of immunosuppression of T cell function in TME. Amino acids such as L-arginine, tryptophan, and cysteine are either depleted from TME by MDSCs expressed enzymes like Arginase-1 (Arg-1), iNOS, and indoleamine 2,3 dioxygenase (IDO), or sequestered by transporters like cationic amino acid transporter 2B (Cat-2) or cysteine-glutamine antiporter (Xc) in MDSCs [38–40]. Amino acid starvation leads to inhibition of tumor antigen-

specific proliferation of T cells through downregulation of CD3 ζ and induction of cell cycle arrest at G0–G1 phase [41–43]. Moreover, products from amino acid metabolism such as polyamine, kynurenine, and toxic ROS/RNS (NO, O²⁻, H₂O₂, and PNT) can further induce apoptosis of cytotoxic CD8 T cells and promote conversion of naïve CD4 T cells into Tregs [43–46].

Aerobic glycolysis provides tumor cells with excessive carbon for de novo synthesis of nucleotides, lipids, and proteins to support their uncontrolled proliferation. Of note, enhanced uptake of glucose promotes synthesis of reducing agent NADPH from oxidative branch of pentose phosphate pathway to participate in lipid synthesis [47, 48]. As a result, reactivation of lipid biosynthesis and storage have been frequently reported in cancer tissues, especially when tumor cells outgrew tissue blood supply of nutrients and oxygen. Despite that tumor cells synthesize most fatty acids de novo [49], aggressive tumor cells often intermingle with adipocytes in TME to obtain exogenous fatty acids [50, 51]. Therefore, similar to BM and adipose tissue microenvironment, TME is also a lipid-rich environment for infiltrating immune cells. We will discuss further on how this lipid-rich TME influences immunosuppressive function of MDSCs.

7.3 Lipid Metabolism and Immunosuppressive Function of MDSC

Recent studies on mouse models conclude that tumor-associated MDSCs upregulate FAO as a primary energy source as opposed to glycolysis to exert immunosuppressive functions, in comparison to peripheral myeloid cells and spleen MDSCs. This conclusion is supported by increased mitochondrial mass, fatty acid uptake via CD36, expression of key enzymes in FAO (CPT-1, acyl-CoA dehydrogenase, 3-hydroxyacyl-CoA dehydrogenase), and oxygen consumption rate (OCR)/extracellular acidification rate (ECAR) ratio [52]. Of note, consistent with what has been observed in the mouse study, enhanced fatty acid uptake and increased level of FAO-related

enzymes in MDSCs were also detected in the blood and tumor from cancer patients. Along this line, lipid overload in MDSCs correlates with their suppressive function. Interestingly, most lipids in MDSCs are found to be oxidized via MPO and ROS, and the polyunsaturated fatty acids, which are more susceptible to oxidation, could promote the suppressive function of MDSCs [29]. Importantly, pharmacologic inhibition of FAO in mouse significantly alleviated tumor progression and improved antitumor outcome of adoptive T-cell therapy. Mechanically, this is because pharmacologic inhibition of FAO decreased the production of inhibitory cytokines and prevented the immune inhibitory capability of MDSCs. Moreover, combining chemotherapy and pharmacologic FAO inhibition eliminated the immunosuppressive effects of MDSCs and consequently enhanced the therapeutic outcome [52]. Lysosomal acid lipase (LAL) is required for hydrolysis of cholesteryl and triglycerides in lysosomes to generate fatty acid for FAO. MDSCs in LAL-deficient mice switched from FAO to glucose-dependent oxidative pathway, with enhanced proliferation but compromised immunosuppression [53]. Together, these results indicate that modulating FAO activity may provide an interesting option to inhibit the immunosuppressive function of MDSCs and improve the outcome of clinical therapy [54].

Besides FAO for ATP supply, fatty acid synthesis, lipogenesis, and lipid accumulation also link to suppressive function of MDSCs [55, 56]. Gabrilovich et al. demonstrated that targeting key enzymes of lipid synthesis ACC-1 with 5-tetradecyloxy-2 furoic acid (TOFA) to block fatty acid synthesis in MDSCs revert the suppression of T cell activation. Recently, Veglia, et al. identified MDSCs utilize fatty acid transport protein 2 (FATP-2) for transporting arachidonic acid and synthesizing prostaglandin E2 (PGE-2) to suppress T cell-mediated antitumor immunity. Selective inhibition of FATP2 abolished the suppressive activity of PMN-MDSCs and substantially delayed tumor progression in mice [57]. Interestingly, PGE2, a lipid mediator, generated by COX-2 from fatty acid arachidonic acid [58]

was proved to promote MDSC generation in tumor-bearing mice [59]. And further research indicated that inhibiting PEG2 or COX2 could decrease MDSC generation and delay tumor progression [59, 60]. Prevention of lipid droplet formation in MDSC like cell line MSC-2 by diacylglycerol acyltransferases impairs the immunosuppression [61]. Therefore, although fatty acid synthesis and oxidation cannot occur under classical view, it appears that MDSCs adapt to hypoxic and nutrient-deprived TME to activate both metabolic pathways simultaneously to exert its suppressive function (Fig. 7.3).

7.4 Genetic and Epigenetic Pathways Involved in Lipid Metabolisms of MDSC

Although how lipid metabolism in MDSCs influences their immunosuppressive function is not fully understood, several signaling pathways have been implicated to play a role in this process. For example, liver X receptors (LXR) are members of nuclear hormone receptor family that regulate lipid homeostasis. Their physiological activators are oxysterols and intermediates in the cholesterol biosynthetic pathway. Under the administration of LXR agonist, PMN-MDSCs and M-MDSCs were effectively decreased in mouse models and cancer patients [62]. In addition, the LXR target gene ApoE triggers activation of cytotoxic T cells to enhance antitumor immune defenses [62]. Another known “lipid sensing” receptor is peroxisome proliferator-activator receptors (PPARs), which are activated by free fatty acids, prostaglandins, and sterols. Several PPARs subtypes elicit the expression of FAO genes and coordinate cell fate and inflammation. Cardiolipin, the main phospholipid in the inner mitochondrial membrane, promotes IL-10 expression in MDSCs of tumor-bearing mice by activating PPAR γ [63, 64], and the effect can be reversed by PPAR γ inhibitor [65]. Moreover, PPAR α agonist activated CPT and thereby enhanced fatty acid catabolism in melanoma-specific CD8 $^+$ TILs, ultimately leading to delayed

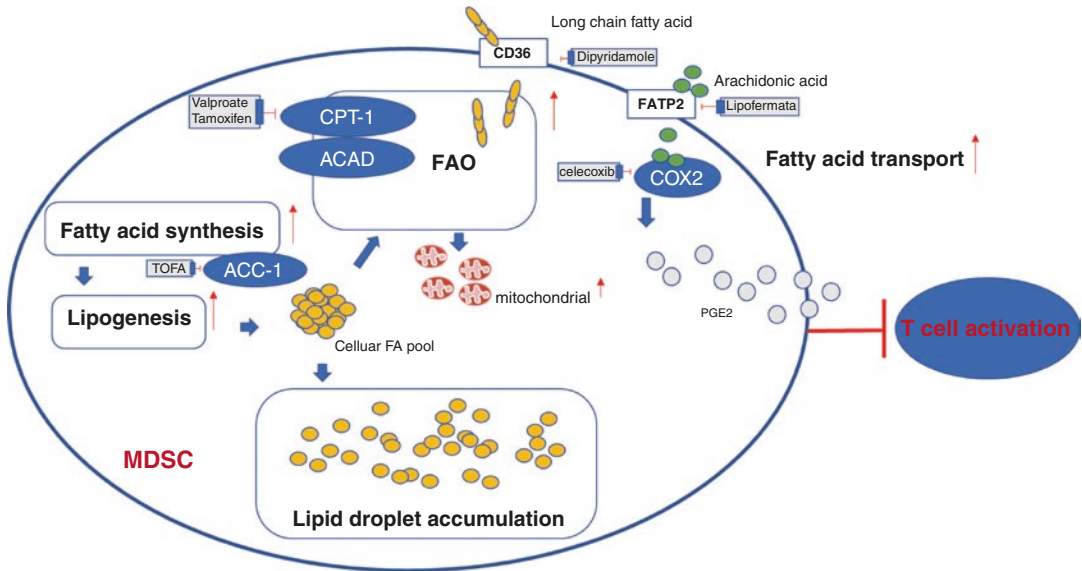


Fig. 7.3 lipid metabolism in MDSCs correlate with their suppressive function. (i) Fatty acid uptake, fatty acid beta oxidation (FAO), fatty acid synthesis, and lipogenesis increase in MDSCs and result in upregulation of immunosuppressive function. (ii) Lipid accumulation in MDSC leads to lipid droplet formation and associate with their immunosuppressive functions. (iii) Pharmacologic inhibition of fatty acid transport, FAO, and fatty acid synthesis

in MDSCs blocks immunosuppressive functions. *MDSC* Myeloid-derived suppressor cells, *FAO* Fatty acid beta oxidation, *FATP2* fatty acid transport protein 2, *COX2* cyclooxygenase 2, *PGE2* prostaglandin E2, *CPT-1* Carnitine palmitoyl transferase 1, *ACAD* acyl-CoA dehydrogenase, *ACC-1* Acetyl-CoA carboxylase, *TOFA* 5-tetradecyloxy-2 furoic acid

tumor progression [66]. These studies indicate targeting PPAR pathways as a promising strategy for rebalancing lipid metabolism in MDSCs. Further research supported cross-regulation between PPARs and LXRs pathways to increase atherosclerosis susceptibility and elucidated that activation of this regulatory network has additive effects in controlling ATP binding cassette transporter A1 (ABCA1) expression, thereby reversing cholesterol transport in macrophages [67, 68].

Changes in lipid metabolism can also influence cell differentiation and functions by epigenetic modifications. For example, the phospholipid derivative lysophosphatidic acid (LPA) activates a family of GPCRs named LPAR1–6 and leads to recruitment of HDAC1 coincides with decreased histone acetylation in the TRAIL death receptors promoter, which ultimately promotes survival of cancer cells [69]. Moreover, many DNA/histone-modifying enzymes often require cofactors and

substrates that are also critical intermediate metabolites. For example, increased FAO leads to elevation of acetyl-CoA, which served as a carrier of acyl groups by histone acetyltransferases to promote open chromatin state and activate transcription. Compared with other immune cells, evidence to support the direct link between metabolites or cofactors and epigenetic regulation in MDSCs is still lacking [70, 71].

Besides providing most of the acetyl groups on histones, fatty acids are also involved in another histone modification: histone acylation. Up till now, a variety of short and long-chain acyl groups have been identified covalently attached to a histone lysine residue, including propyl, butyryl, crotonyl, myristoyl, and palmitoyl. Each fatty acid modifying group confers distinct biochemical properties that influence subcellular localization, intracellular trafficking, and protein–lipid interactions. A compelling study to link lysine fatty acylation to immune response shows

the role of HDAC11 in the regulation of serine hydroxymethyltransferase 2 (SHMT2) defattyacylation in type I IFN-mediated signaling [72]. HDAC11, the only class IV HDAC member, has been rediscovered as a highly potent and efficient defattyacylase of lysine as compared to its deacetylase activity [72]. Of note, HDAC11 acts as a negative regulator of MDSCs expansion and function [73]. A better understanding of the mechanisms and functional consequences of reversible lysine fatty acylation may provide new insights into regulating lipid metabolic homeostasis. In the future, we expect to see the signaling pathway inhibitors, epigenetic inhibitors, and metabolite antagonists that specifically interfere with the above mentioned regulatory process being applied in combination to manipulate the fate of MDSCs and its function.

7.5 Issues of Translating MDSC Knowledge from Bench to Bed

Although several key discoveries made in mouse studies have been validated on human, there are still differences between human and murine MDSCs. For example, LOX-1, a low-density lipoprotein receptor, has been proposed as a candidate marker for human immunosuppressive PMN-MDSCs and numbers of LOX-1⁺ PMN-MDSCs correlate with cancer progression [74]. On the contrary, PMN-MDSCs from LOX-1 knockout mice did not exhibit differences in migration toward tumor tissue, nor in suppressive function against T cells compared to wild type PMN-MDSCs. Moreover, Arg-1 expression in M-MDSCs and TAMs are well documented in murine studies, whereas Arg-1 is constitutively expressed in human neutrophils and inducible in other monocytic cells under disease setting [75]. Another example of these differences could be the fact that mice lacks cholesteryl ester transfer protein (CETP), which transferring CE from HDL toward ApoB containing lipoproteins [76]. Consequently, mice

and human display a substantially different plasma lipoprotein profile. These species barriers might hinder the translation process from mouse studies to effective therapies targeting metabolisms of MDSCs.

Despite the success achieved in past years on studying lipid metabolism and mouse MDSCs, research on human MDSCs is still scarce and key questions regarding human MDSC biology remain largely unexplored. How chronic tumor microenvironment influence the generation process of human MDSCs? Through which mechanism are they recruited to the tumor microenvironments? Would it be possible to manipulate human MDSC generation or migration toward tumor microenvironment through altering lipid metabolism? To address these questions, novel research models and tools are required. For instance, severe immune-deficient mice engrafted with human CD34⁺ HSC develop multi-lineage human immune cells, which can serve as a unique platform to study human MDSC biology in vivo [77, 78]. These humanized mouse models can be further transplanted with tumor cells or tissues to dissect the factors of TME on both the generation and the recruitment of MDSCs [79, 80]. Moreover, liver humanization protocol has succeeded in addition to human immune system reconstitution to create a double humanized mouse. These complex yet highly clinically relevant models would provide an in vivo platform to investigate the metabolic and immune cross-talk among human MDSCs, tumor, and liver (Fig. 7.4). On average, 95% of new cancer drug candidates failed during clinical tests due to the inconsistency between murine and human immune systems [81] and lack of reliable preclinical animal models, which could accurately recapitulate patient tumor microenvironment [82]. Hence, it is critical to appreciate the differences between human and murine MDSCs in order to accelerate therapeutic development. With the advance of humanized mouse models, screening, and validation of MDSC targeted therapeutics would be easier and faster in the future.

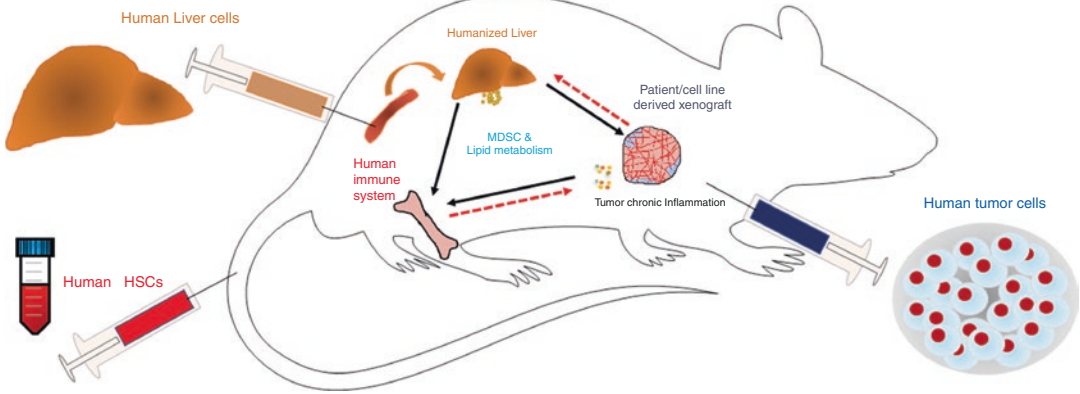


Fig. 7.4 Liver/Tumor/Immune humanized mouse models. To further investigate lipid metabolism in human tumor-associated MDSCs *in vivo*, we propose a liver, tumor, and immune system triple humanized mouse model. Human MDSC and immune system can be generated from human CD34⁺ HSC engrafted to severe immune-deficient mice. And the liver can be humanized by injecting human liver cells into spleen of a genetic engineered mouse strain with spontaneous or induced liver damage. This humanized mouse model can be fur-

ther transplanted with primary tumor cells or tissues from patients or tumor cell lines to create a triple humanized mouse model. With the availability of this triple humanized mouse model, we can decipher the factors involved in the generation and recruitment of MDSCs to tumor micro-environment and calibrate the balance between lipid catabolism and anabolism in MDSC function and tumor progression. *MDSC* Myeloid-derived suppressor cell, *HSC* hematopoietic stem cells

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