

# Myeloid Cell–Derived Oxidized Lipids and Regulation of the Tumor Microenvironment

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## ABSTRACT

Immunosuppressive myeloid cells play a major role in cancer by negatively regulating immune responses, promoting tumor progression, and limiting the efficacy of cancer immunotherapy. Immunosuppression is mediated by various mechanisms dependent upon the type of myeloid cell involved. In recent years, a more universal

mechanism of immunosuppressive activity of myeloid cells has emerged: Generation of oxidized lipids. Oxidized lipids accumulate in all types of myeloid cells and are often transferred between cells. In this review, we discuss mechanisms involved in the generation and biological role of myeloid cell–derived oxidized lipids in cancer.

## Introduction

Myeloid cells have long been recognized as one of the major regulators of tumor progression and metastasis. They are one of the major hurdles in generating a productive antitumor immune response and contribute to the limitation of cancer immunotherapy. Therefore, effectively targeting myeloid cells has become a key strategy in improving current therapies. The biology and role of myeloid cells in cancer have been discussed in many recent reviews (1–5). The myeloid lineage is a complex, closely connected network of cells with diverse functions. They use a large variety of molecules and mechanisms to regulate the immune system in cancer. These mechanisms depend on the specific type and state of activation of different myeloid cells. However, in recent years one common mechanism that myeloid cells exploit in cancer has emerged, using oxidized lipids. In this review, we will discuss the potential role of oxidized lipids in the function of different myeloid cells.

## Brief Overview of Myeloid Cells in Cancer

The myeloid compartment is comprised of several major groups of cells: Granulocytic represented by polymorphonuclear neutrophils (PMN), eosinophils, and basophils; monocytic represented by monocytes (MON) and macrophages (MΦ), dendritic cells (DC), and megakaryocytes. Of these, the most well-studied cells in the context of cancer, and thus the focus of this review, are PMN, MON, MΦ, and DC. Populations of PMN and MON consist of classically activated cells (evolved as major protectors of organisms from pathogens) and pathologically activated myeloid-derived suppressor cells (MDSC). Although MDSC share many features with classical PMN and MON (origin, phenotype, and morphology), they also have distinct tran-

scriptomics, biochemical, and functional traits with the most distinguishing feature of MDSC being the immunosuppressive activity (3). On the basis of the differentiation pathway (granulocytic and monocytic), MDSC are defined as either PMN-MDSC or M-MDSC. PMN-MDSC are the most abundant, representing >90% of all MDSC. To suppress the function of T, B, and natural killer cells, M-MDSCs secrete immunosuppressive cytokines (IL10, IL6, and TGFβ) and NO as well as express checkpoint inhibitors, whereas PMN-MDSC use reactive oxygen species (ROS), peroxynitrite (PNT), arginase I, and prostaglandin E2 (PGE2; ref. 3). The prevalence of MDSCs has been closely associated with poor patient prognosis and response to therapy in a variety of tumor types (6).

MΦ have a broad role in host defense and maintenance of tissue homeostasis (7). On the basis of their origin, MΦ can be classified into two major groups: Tissue resident macrophages derived from embryonic progenitors or bone marrow–derived MΦ differentiated from MON. In addition, MΦ can be polarized *in vitro* to a classically activated M1 phenotype when incubated with interferon γ or lipopolysaccharide or alternatively activated M2 phenotype when incubated with IL4 and IL13 (8, 9). In cancer, M1/M2 polarization of tumor-associated macrophages (TAM) is difficult to capture, reflecting the dynamic nature of TAM polarization and complexity of signals from the tumor microenvironment. Nonetheless, TAM can be polarized to have either pro- or antitumor functions (reviewed in ref. 2). In recent years, evidence has emerged that MΦ in cancer can be distinguished as classical (nonsuppressive) and pathologically activated (suppressive; ref. 10), similar to what was observed for MDSC. These suppressive MΦ may include multiple subsets and use mechanisms that may be shared by M1 and M2 MΦ. For instance, both arginase I and NO, a distinct feature of M2 and M1 MΦ, respectively, were directly implicated in the immunosuppressive activity of TAM. To identify the multiple subsets of TAM, single-cell RNA sequencing and spectral cytometry have been used, but the functional characterization of each population is still largely lacking (11). Corresponding to the divergent polarization of TAM, the presence of TAM has been correlated to both shorter relapse-free survival and overall survival (12) as well as better outcomes in the same types of cancer (13).

DC differentiate from specialized progenitors and function as professional antigen presenting cells that endocytose, process, and present antigens to T cells to generate cytotoxic antigen-specific responses. These processes are critical for the induction of an antitumor immune response and success of cancer immunotherapy (14, 15). DC can be broadly classified into classical DC (cDC), of which, two subsets cDC1 and cDC2 are defined, plasmacytoid DC, and monocyte-derived DC (inflammatory DC; ref. 16). cDC1s are considered the

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major cross-presenting cells promoting antitumor responses, whereas monocyte-derived DCs are implicated in inhibition of immune responses (16).

## Outline of the Metabolism of Oxidized Lipids

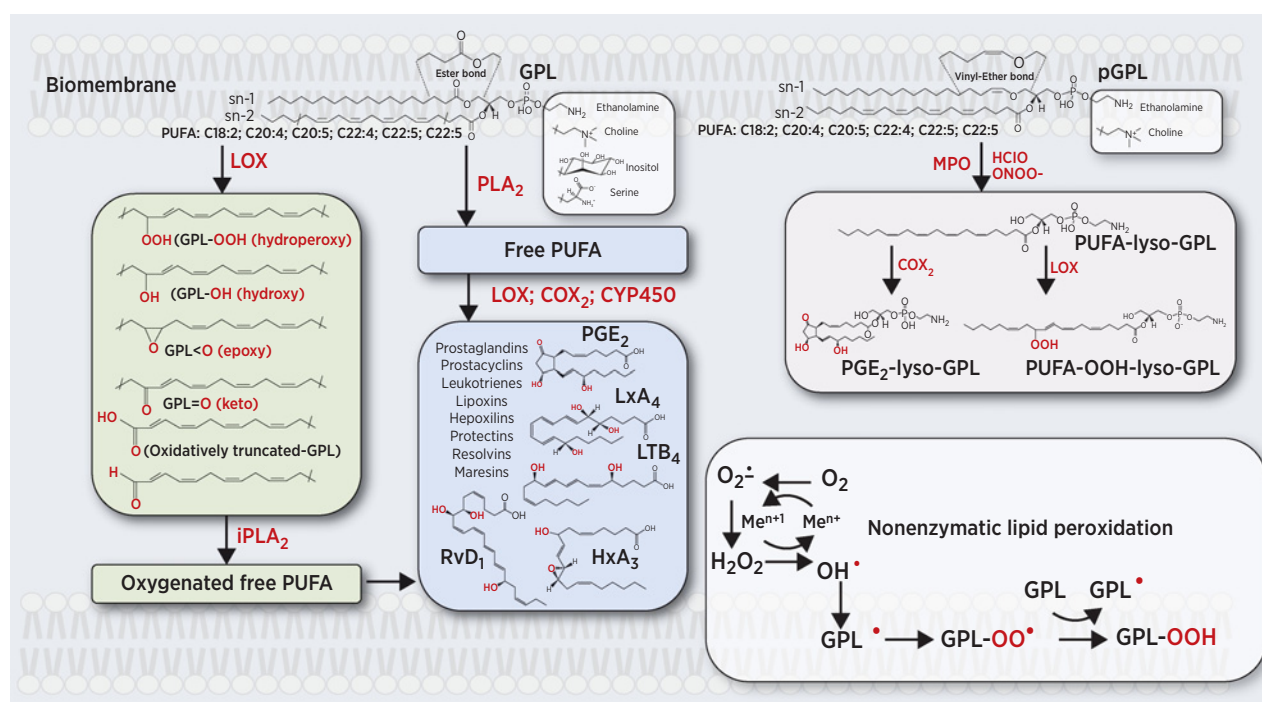
Lipids are small amphiphilic molecules containing a nonpolar hydrocarbon moiety and a polar head group. If the length of the hydrocarbon chain is 10 or more carbons, lipids can assemble into monolayers (at the air-water interface), micelles in solution, and vesicles having bilayer membranes. Lipids are indispensable in forming biomembranes (17). Lipids also self-organize into supramolecular structures allowing for the creation of microenvironments that can contain proteins, nucleic acids and/or small molecules (18).

The requirement of context-specific properties of biomembranes, maintenance of their parameters within a relatively narrow range of fluidity/rigidity and optimized regulation of the membrane-embedded protein machinery, defined the selection of several major classes of lipids. Among them, the most important and common in membranes are phospholipids (PL) that are composed of fatty acid(s) (FA), an alcohol, a phosphate and a polar group. Glycerophospholipids (GPL) are the major class of PL in which one or two FA are attached at the *sn*-1, *sn*-2 positions of the glycerol backbone through an ester or ether

bond and a polar group occupies the *sn*-3 position via a phosphodiester bond (Fig. 1). GPLs are further classified on the basis of the nature of their polar groups: choline, ethanolamine, serine, inositol, etc. (19).

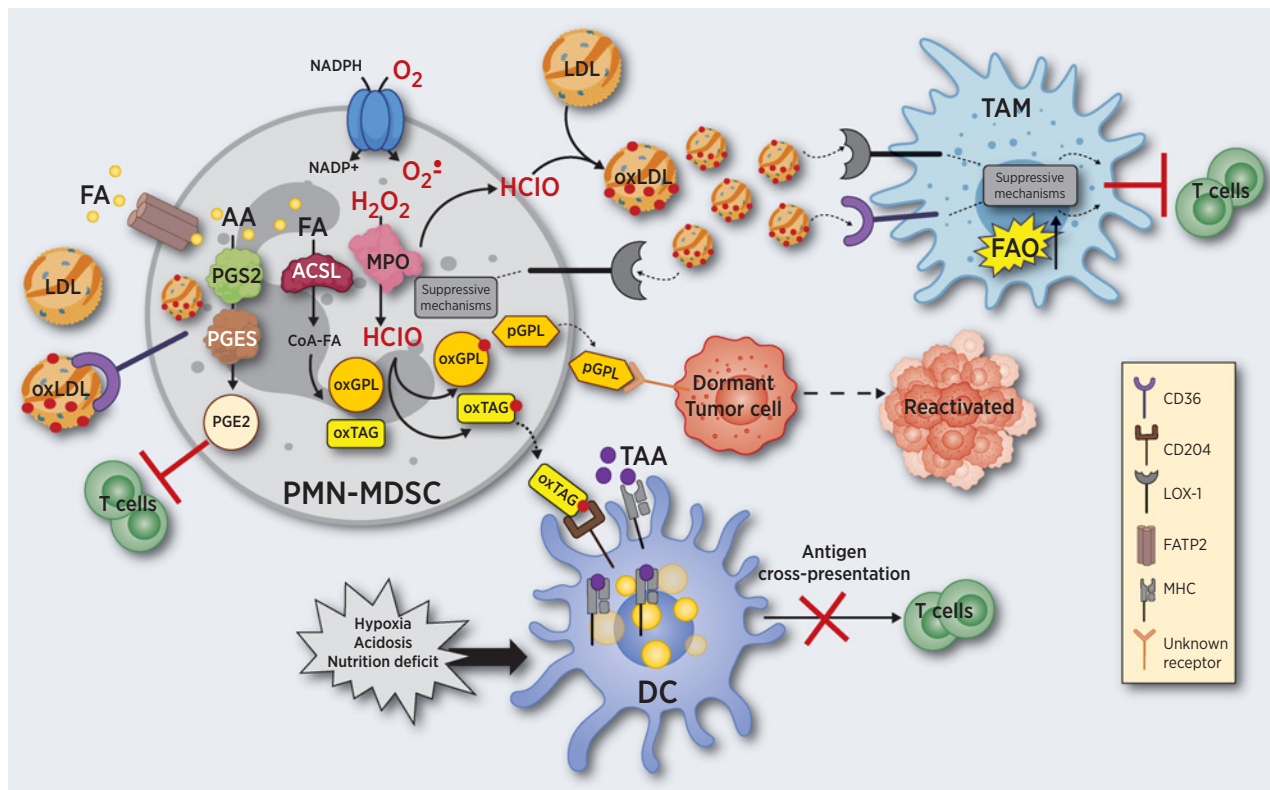
FA are classified as saturated FA (SUFA), monounsaturated FA (MUFA) or polyunsaturated FA (PUFA) with the latter two containing one or more double bonds, respectively. SUFA and MUFA residues are usually localized at both *sn*-1 and *sn*-2 positions, whereas PUFA preferably occupy the *sn*-2 position. In eukaryotic cells, long-chain PUFA are usually synthesized from saturated FA by two major classes of enzymes, elongases that add an ethylene group and desaturases that insert a double bond in the FA. In mammalian cells, these enzymes can "build" the myriads of individual molecular species by differing the number and position of up-to 6 double bonds. There are two major families of PUFA in which the double bonds are localized starting from the 3<sup>rd</sup> ( $\omega$ -3) or the 6<sup>th</sup> ( $\omega$ -6) carbon atom, counting from the PUFA terminal methyl group. The Kyoto Encyclopedia of Genes and Genomes pathway for the biosynthesis of unsaturated FA lists a total of 30 PUFA (20). Combined with approximately 15 other possible SUFA and MUFA, each class of GPLs can encompass  $>2 \times 10^3$  individual species. In some types of GPL (e.g., mitochondrial cardiolipins), this number may be much greater reaching in excess of  $4 \times 10^6$  different species.

It has become clear that the large number of different GPL species, including not only intact GPL but also metabolites, act as signaling



**Figure 1.**

The major metabolic pathways leading to the formation of signaling molecules from PUFA-GPL and pGPL. Top right (gray), cleavage of vinyl ether bond of pGPL by oxidants (e.g., hypochlorous acid (HClO) generated by myeloperoxidase (MPO) or peroxynitrite (ONOO<sup>-</sup>)) results in the production of unusual lyso-GPLs with the retained *sn*-2 PUFA oxidizable residues. These types of lyso-GPLs can be readily used as substrates of COXs and lipoxygenases (LOX) to yield respective hydroperoxy-lyso-GPLs and their secondary oxygenated derivatives (including PGE<sub>2</sub>-lyso-GPLs) with multiple signaling functions. Middle (blue), canonical PLA<sub>2</sub> catalyzed release of free PUFA from the *sn*-2 position of GPLs and subsequent oxygenation of liberated free PUFA by COX, LOX, and isoforms of cytochrome P450 (CYP450). Among these oxygenated molecules formed are prostaglandins, prostacyclins, leukotrienes, lipoxins, hepxilins, protectins, resolvins, maresins. Left (green), LOX-catalyzed oxidation of GPL yields hydroperoxy-, hydroxy-, keto-, epoxy- and oxidatively truncated GPL species with signaling functions. Hydrolysis of these peroxidized GPL by Ca<sup>2+</sup>-independent PLA<sub>2</sub> (iPLA<sub>2</sub>) represents a noncanonical pathway leading to the formation of free oxygenated PUFA acting as lipid mediators. Bottom right (white), nonenzymatic lipid peroxidation



**Figure 2.**

Effect of oxidized lipids of function of myeloid cells in cancer. Oxidative machinery of PMN-MDSC, which includes MPO and superoxide produced by NADPH oxidase (NOX2), supports the generation of a large variety of oxidized lipids. Oxidized fatty acids (oxFA) undergo esterification to triglycerides (TAG) and various phospholipids (PL). oxTAG can be transferred to DC where they undergo degradation and oxidatively truncated FA are then incorporated into LD. Electrophilic LD bind HSP70 and prevent the transfer to the cell surface of peptide-MHC class I complexes formed in lysosomes and endosomes during vacuolar pathway of cross-presentation, thus inhibiting cross-present tumor antigens by DC. Formation of LD containing oxFA can also be mediated by activation of ER stress and spliced XBPI. In PMN-MDSC, accumulation of oxidized lipids results in increased biosynthesis of PGE2 and plasmalogens, leading to enhanced suppressive activity of these cells. Plasmalogens promote reactivation of dormant tumor cells. Oxidized LDL signal in PMN-MDSC and TAM via several receptors to potentiate suppressive activity of these cells, which include upregulation of arginase 1, NO production, and secretion of immunosuppressive cytokines.

molecules. Two metabolic mechanisms—(i) hydrolysis by different phospholipases, (ii) oxygenation reactions—and their combination represent the major pathways leading to the production of lipid signals.

Lipid mediators are the products of sequential hydrolysis of PUFA-GLP by type 2 phospholipases that catalyze the release of free PUFA from the *sn*-2 position thus making them available for the oxygenation by COXs, lipoxygenases (LOX), and isoforms of cytochrome P450 (CYP450; ref. 21). These reactions represent the canonical mechanisms for the formation of several classes of well-known lipid mediators with multiple regulatory functions. On the basis of their carbon chain length, they are represented by octadecanoids, eicosanoids, docosanoids, and docosahexanoids, the oxygenated derivatives of PUFA with 18, 20, and 22 carbons (22). Among these oxygenated molecules are prostaglandins, prostacyclins, leukotrienes, lipoxins, hepoxilins, protectins, resolvins, maresins—lipid signals that function to recruit myeloid cells and have pro- and anti-inflammatory effects.

Lately, it has become apparent that an alternative mechanism may generate the same lipid mediators. This process may be executed enzymatically, whereby Fe-containing proteins, LOX and peroxidases, directly attack GLP PUFA residues and generate their peroxidation products. These peroxidized GLPs include thousands of oxidatively modified molecules with oxygen-containing functional groups such as hydroperoxy-, hydroxy-, epoxy-, and keto- that are positioned on the

GLP FA residues (Fig. 1). Similar to free PUFA-based lipid mediators, the peroxidized GLP may act through specific receptors or signal via covalent modification of protein targets. The latter mechanism is based on the formation of oxidatively truncated highly electrophilic peroxidation products capable of attacking the nucleophilic sites in target proteins (23, 24).

One additional way to metabolically generate lipid signals uses a GLP subclass called plasmalogens. Plasmalogens (pGPL) can contain two different types of bonds: A vinyl ether linkage at the *sn*-1 position of the GPL backbone and an ester-bond at the *sn*-2 position (similar to diacyl-GLPs; Fig. 1; ref. 25). In the context of signaling, the important property of pGPL is the vulnerability of their vinyl ether bond to cleavage by hypochlorous acid (HClO) generated by myeloperoxidase (MPO) and peroxynitrite (ONOO<sup>-</sup>) massively produced by MDSC and MΦ (Fig. 2; ref. 21). In proinflammatory conditions, elevated levels of HClO or ONOO<sup>-</sup> can lead to the production of unusual lyso-GLPs with the retained *sn*-2 PUFA oxidizable residues. These special lyso-GLPs can be readily used as substrates of COX and LOX to yield respective hydroperoxy-GLPs with potentially multiple signaling functions (21). As an example, massive production of *sn*-2-PUFA-lyso-phosphatidylethanolamines occurs during PMN MPO attack causing awakening of dormant cancer cells, as discussed below (26).

In addition to membrane GLPs, there are several classes of non-amphiphilic lipid molecules, neutral lipids. Their formation is frequently associated with the aberrant metabolism of FAs. Disordinated FA metabolism in hypoxia or in suppressed beta-oxidation, leads to the accumulation of free FA and severe lipotoxicity. As a response, cells attempt to insulate-free FA by integrating them into esterified forms, diacylglycerols (DAG) and triacylglycerols (TAG) as well as in cholesterol esters. These covalent derivatives of FA are highly hydrophobic and usually excluded from biomembranes to produce separate intracellular organizations, lipid droplets (LD; Fig. 1). Recent studies demonstrated that LDs represent highly specialized organelles with active metabolism and signaling functions (27). This new understanding of the functional LD importance has been developed in parallel to the appreciation of the presence of readily “peroxidizable” PUFA-residues in DAGs and TAGs. Indeed, PUFA de-esterification/re-esterification into these neutral lipids can serve as interesting sources of signaling lipid mediators. Peroxidation of PUFA-containing DAG/TAG molecules and formation of their oxidatively truncated electrophilic derivatives forming covalent adducts with proteins may be also used for intracellular insulation and hiding of the proteins in the hydrophobic core of LDs (28).

Lipids can also be used as a source of energy via fatty acid oxidation (FAO). FAO begins with the activation of the FA through enzymatic conjugation with acyl-CoA. Then the FA must translocate into the mitochondria with short-chain FA less than six carbons diffusing passively and longer FA needing to be first conjugated to carnitine via carnitine palmitoyl transferase 1 (CPT1). The reaction is a rate-limiting step in FAO and can be inhibited with the drug etomoxir that will be discussed below. Once shuttled into the mitochondria, the carnitine is removed by carnitine palmitoyl transferase 2 (CPT2). FAs are then broken down by beta-oxidation to yield large amounts of acetyl-CoA, NADH, and FADH2 that is shuttled into the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) to generate ATP (29).

## Role of Oxidized Lipids in Myeloid Cell Dysfunction in Cancer

### MDSC

Lipid metabolism has been directly implicated in MDSC-suppressive activity. Tumor-infiltrated MDSC upregulated FA uptake and FAO relative to peripheral MDSC. This altered metabolism promoted the suppressive activity of MDSC because blockade of FAO decreased immunosuppression (30). A subsequent study explored the mechanism by which tumor-infiltrating MDSC increased lipid uptake. They demonstrated that the tumor-derived G-CSF and GM-CSF induced upregulation of a variety of lipid transport receptors, including CD36, macrophage scavenger receptor 1 (MSR1)/CD204 and fatty acid transporters 1 and 6 (FATP1 and 6; ref. 31). The lipids transported from the microenvironment-promoted immunosuppression by MDSC, which was reversed by CD36 deletion (31).

Additional receptors/transporters have been reported to be involved in lipid uptake by MDSC. For instance, PMN-MDSC overexpressed oxidized low-density lipoprotein (LDL) receptor 1 (*OLR1/LOX-1*; ref. 32). Although the impact of LOX-1 expression on lipid metabolism and suppressive activity of PMN-MDSC is not yet fully explored, LOX-1 was shown to be selectively expressed on human PMN-MDSC as opposed to classical PMN and associated with an immunosuppressive gene signature in PMN-MDSC. ER stress was shown to be the major inducer of LOX-1 expression in PMN-MDSC (32, 33). A number of studies correlated LOX-1 positive PMN-MDSC and

negative clinical outcomes in cancer and proposed that LOX-1 is a potential biomarker of PMN-MDSC (34–37).

Along the same lines, another study established that in contrast with classical PMN, PMN-MDSC expressed FATP2, a transporter for long chain fatty acids. Experiments with targeted deletion in neutrophils of *Slc27a2* gene that encodes FATP2 abrogated the suppressive activity of PMN-MDSC (38). Increased uptake of arachidonic acid (AA) and production of PGE2 were implicated in FATP2-mediated suppression by PMN-MDSC (Fig. 2; ref. 38). Inhibition of FATP2 with the small-molecule lipofermata reduced suppressive activity of MDSC and demonstrated potent antitumor activity (38, 39). In another study, lipofermata reduced melanoma tumor growth in aged mice that was not mediated by its direct effect on tumor cells (40). PGE2 is a product of lipid oxygenation initiated when AA is metabolized by COX2. Generation of PGE2 has been shown to not only promote MDSC development, but also mediate their suppressive activity (41, 42). PGE2 was directly implicated in MDSC immunosuppressive activity not only in cancer but also in newborns (43–46). Overall, these studies provide a link between lipid metabolism and lipid uptake by MDSC to the immunosuppressive activity.

### Macrophages

It has long been appreciated that metabolism is involved in MΦ polarization. M1-like MΦ preferentially use glycolysis, have a broken TCA cycle, and generate lipids via fatty acid synthesis. Conversely, M2-like MΦ have an intact TCA cycle and rely on FAO to fuel OXPHOS for energy production (29, 47, 48). In fact, the polarization of MΦ can be altered by modifying the metabolic pathways being used. A recent study found that unsaturated FA or LD polarized bone marrow-derived cells into immunosuppressive M2-like MΦ. This polarization could be reversed with etomoxir, the FAO inhibitor, or inhibition of diacylglycerol-O-acyltransferase (DGAT) the enzyme responsible for the import of FFA into LD (49).

Similar studies demonstrated that MΦ from tumor-bearing mice or cultured with tumor cells had increased lipid accumulation and used scavenger receptors CD36 and LOX-1 to transport FA from the lipid-rich TME (50–52). FA undergoes lipolysis mediated by lysosomal acid lipase to support OXPHOS and M2 activation that is reversed by inhibition of these lipases (51). In addition, inhibition of FAO with etomoxir or CD36 deletion in TAMs decreased tumor growth and M2 polarization (52). Together, these studies demonstrate that lipid metabolism and uptake can alter the polarization and enhance pro-tumor functions of TAM.

Ferroptosis is a redox-driven cell death program (53), which includes iron-dependent generation of (phospho)lipid hydroperoxides and failure of their reduction to alcohols by glutathione peroxidase 4 (GPX4). The decay of hydroperoxy lipids to oxidatively truncated reactive electrophilic species affects yet to be identified, critical protein targets, leading to the cell death (54). Recent studies implicated ferroptosis in regulation of MΦ biology. Inducible NO synthase (iNOS)/NO•, a characteristic of M1 MΦ, conferred MΦ resistance to ferroptosis by inhibiting pro-ferroptotic lipid peroxidation (55). This study and another showed that exposure of M2 MΦ to NO• protected them from ferroptosis and that GPX4 expression was not required for survival of M2 (alternatively activated) MΦ if sufficient amounts of NO• were generated (55, 56). These studies suggest that induction of ferroptosis can alter the MΦ polarization. Along the same lines, induction of ferroptosis in TAM resulted in a metabolic switch from mitochondrial OXPHOS to glycolysis, which induced pro-inflammatory signaling pathways, enabling MΦ activation with potent tumoricidal activities (57).

**Table 1.** Targeting lipids in myeloid cells.

Target type	Target	Drug	Preclinical or clinical	Effects	Potential Pitfall
FAO rate limiting enzyme	CPT1	Small-molecule etomoxir	Preclinical	<ul style="list-style-type: none"> <li>Reversed lipid-mediated polarization of M2-like M<math>\Phi</math> and reduced tumor growth (52)</li> <li>Reduced suppressive activity of MDSC and reduced tumor growth (30)</li> </ul>	Not specific to metabolism of myeloid cells
			Clinical	<ul style="list-style-type: none"> <li>Examined for treatment of congestive heart failure (76)</li> </ul>	Terminated due to toxicity
Enzyme that transports FFA into LD	DGAT1/DGAT2	Small-molecule A922500 & PF-06424439	Preclinical	<ul style="list-style-type: none"> <li>Reversed lipid-mediated polarization of M2-like M<math>\Phi</math> and had antitumor activity (49)</li> </ul>	
Lipolysis inhibition	Lipase	orlistat	Preclinical	<ul style="list-style-type: none"> <li>Reduced M2-like M<math>\Phi</math> activation and survival (51)</li> </ul>	
Enzyme involved in PGE2 generation	COX-2	Small-molecule celecoxib	Preclinical	<ul style="list-style-type: none"> <li>Reduced number and function of MDSC and potentiated immunotherapy (77)</li> </ul>	
			Clinical	<ul style="list-style-type: none"> <li>Beneficial for treatment of advanced cancer (78, 79)</li> </ul>	Potential cardiovascular effects
Lipid receptors and transporters	CD36	Antibody blockade	Preclinical	<ul style="list-style-type: none"> <li>Antitumor efficacy (81)</li> <li>Potentiated anti-PD-1 antitumor efficacy (80)</li> <li>Effects on myeloid cells not examined</li> </ul>	High redundancy in these receptors may represent therapeutic challenge
		Thrombospondin mimetic peptides	Clinical	<ul style="list-style-type: none"> <li>No efficacy observed (82)</li> </ul>	
	CD204	Antibody blockade	Preclinical	<ul style="list-style-type: none"> <li>Reversed defective DC presentation (62)</li> </ul>	
	LOX-1	MEDI6570	Clinical	<ul style="list-style-type: none"> <li>Being examined for treatment of cardiovascular disease (EudraCT Number: 2020-000840-75)</li> </ul>	
	FATP2	Small-molecule lipofermata	Preclinical	<ul style="list-style-type: none"> <li>Reduced MDSC-suppressive activity and had potent antitumor activity (38-40)</li> </ul>	

### DCs

Early studies showed that PUFA reduced expression of DC costimulatory molecules and proinflammatory cytokine production in response to different stimuli (58, 59). Two subsequent studies identified that PPAR $\gamma$  was involved in the PUFA, docosahexaenoic acid (DHA), mediated suppression of DC activation (60, 61). Along the same lines, accumulation of lipids was found in DC of tumor-bearing mice and patients with cancer and was associated with defective cross-presentation by these cells (62). The scavenger receptor, Msr1/CD204, was implicated in lipid uptake by DC and blockade of CD204 abrogated the accumulation of lipids from tumor explant supernatant (62). A later study demonstrated that the nature of lipids rather than the amount is critical for negative regulation DC function. Accumulation of oxidatively truncated lipids was directly implicated in blockade of cross-presentation by DC. DC cross-presentation uses two major pathways: Cytosolic and vacuolar (63). The latter includes processing peptides and formation of peptide-MHC Class I complexes in lysosomes/late endosomes. LDs containing oxidatively truncated lipids were implicated in blocking the vacuolar pathway of cross-presentation. The mechanism of this phenomenon involved LD containing oxidatively truncated lipids binding to chaperon HSP70 preventing it from transporting peptide-MHC Class I complexes to the cell surface (Fig. 2; refs. 64, 65).

Although an important role of lipid accumulation in DC dysfunction is established (66-69), the exact mechanism by which oxidized lipids can be accumulated by DC is not clear. DC lack the potent machinery of lipid oxidation, but it was proposed that the tumor-derived changes to DC allowed for them to generate oxidized lipids (70). Tumor-associated DCs (tDC) have significantly higher levels of the ER stress mediator XBP1, which was correlated with increased expression of genes involved in triglyceride biosynthesis, suggesting an increased ability to produce lipids. The increased lipid accumulation and upregulation of ROS allowed for lipid peroxidation to occur in tDC. Consistent with previous reports, this led to a reduction in antigen presentation via MHC complexes (70). However, this mechanism operated only in tumor site, whereas defective DC function was observed in peripheral lymphoid organs as well. A recent study demonstrated another mechanism. PMN-MDSC accumulates oxidized lipids after generating them by using MPO and superoxide produced by NADPH oxidase. PMN-MDSC can then transfer the oxidized lipids to DC, impairing the ability of DC to cross-present (Fig. 2; ref. 71).

Although cross-presenting activity of M $\Phi$  was long considered to be inferior to that of DC, recent studies indicated that M $\Phi$ , including TAM, were able to cross-present antigens. Interestingly, it appears that the vacuolar pathway is predominant mechanism of cross-presentation in these cells (72). Therefore, similar to what was

described above for DC, oxidatively truncated lipids also may substantially inhibit cross-presentation by TAM.

Lipid metabolism has also been implicated in promoting DC dysfunction. Examining the metabolic difference between immunogenic and tolerogenic DC revealed that tolerogenic DC, among other changes, had significantly higher OXPHOS and FAO. In addition, inhibition of FAO with etomoxir prevented the function of tolerogenic DC and partially restored T-cell stimulatory capacity (73). Similarly, resveratrol and vitamin D3 were also shown to promote OXPHOS and tolerogenic DCs (74, 75). Overall, these studies demonstrate that increased lipid metabolism and accumulation of oxidized lipids have profound ability to inhibit the function of DC.

## Targeting Oxidized Lipids from Myeloid Cells

Studies described above implicated lipid metabolism in regulation of myeloid cell function in cancer; thus, targeting it could provide therapeutic benefit for patients. The challenge is in the selection of targets. A summary of the preclinical and clinical attempts at targeting lipids from myeloid cells is shown in **Table 1**. As we discussed above, several studies implicated FAO in dysfunction of myeloid cells in cancer. Although inhibition of the FAO with etomoxir was shown to inhibit immunosuppression in preclinical models (30, 52), this drug is not specific to myeloid cells creating the potential for toxic side effects. In fact, a clinical trial with etomoxir for the treatment of congestive heart failure was terminated due to toxicity (76). Because of the fact that the enzymes in FAO are required for normal metabolism, careful drug design and dosing as well as targeted delivery is probably needed to safely target this pathway.

COX-2, the enzyme involved in generating PGE2, has also been examined as a potential target for cancer-related therapy. Preclinically, the COX-2 inhibitor celecoxib reduced the number and function of MDSC and potentiated DC-based immunotherapy (77). An analysis of 11 clinical trials found that the COX-2 inhibitor celecoxib was beneficial for the treatment of advanced cancer, but patients had an increased risk of cardiovascular events that is common for COX-2 inhibitors (78, 79). Once again highlighting that a more precise approach to target lipid metabolism of myeloid cells is needed. Among them could be targeting of specific receptors involved in myeloid cell lipid uptake such as the scavenger receptors CD36, LOX-1 or CD204. Preclinically, antibody blockade of CD36 reduced tumor growth alone or in combination with anti-PD-1, although the involvement of MDSC was not examined in these studies (80, 81). Of note, there is high redundancy of these receptors, which may represent a therapeutic challenge. For instance, attempts at targeting CD36 indirectly with thrombospondin mimetic peptides have been unsuccessful (82). One possible direction is to focus on molecules that are selectively upregulated on immunosuppressive myeloid cells, and studies of this nature are currently ongoing.

## Myeloid Cell-Derived Oxidized Lipids in Regulation of Dormant Tumor Cells

Tumor cells that have entered a reversible cell-cycle arrest are considered dormant (83). Tumor cell dormancy can occur for a variety of reasons, including an adaptation to environmental insults, the effect of oncogenes, and as a consequence of cancer treatment (83). Tumor dormancy has a positive and negative impact on tumor progression. On one hand, dormant tumor cells do not proliferate limiting tumor

expansion and supporting tumor remission. On the other hand, dormant tumor cells are more resistant to chemo- or radiotherapies. Furthermore, these cells are capable of evading immune surveillance making them resistant to immunotherapies (84). If reactivated, dormant tumor cells quickly progress, resulting in tumor recurrence that can happen many years after the start of the remission. One of the biggest challenges is, understanding the mechanism of reactivation of dormant tumor cells.

Because of the rarity of dormant tumor cells and the challenges identifying them in patients, few studies have delved into the altered metabolism of these cells. One study found that dormant cells relied on mitochondrial respiration rather than glycolysis for cellular energetics (85). Another study revealed that dormant tumor cells had increased expression of genes related to lipid metabolism (86). A recent study used a reporter construct that allowed for the identification of noncycling or cycling-persisters cells that remained after chemotherapy. It found that although both, noncycling and cycling-persisters cells, shifted their metabolism to FAO relative to untreated cells, cycling cells had higher FA metabolism than noncycling cells (87). Although the authors called these cells persisters cells, a noncycling tumor cell could probably be considered dormant. Thus, these studies suggest that FAO plays a role in the dormancy and reactivation of tumor cells.

Studies have indicated that lipid moieties can cause dormant tumor cell reactivation. A decade ago, one study showed that the lipid mediator, epoxyeicosatrienoic acid, caused escape from tumor dormancy in several tumor models (88). Similarly, in a 3D bone-like microenvironment, PGE2 induced dormant breast cancer reactivation (89). Neither of these studies investigated the impact of immune cells on the reactivation with lipid moieties. Recently, we demonstrated that PMN-MDSCs were able to reactivate proliferation of dormant tumor cells (**Fig. 2**; ref. 26). Importantly, neutrophils from tumor-free mice or healthy donors as well as other myeloid cells were not able to reactivate dormant tumor cells. Only after exposure to stress *in vivo* or stress hormones *in vitro*, neutrophils acquired the ability to induce exit of tumor cells from dormancy (26). This effect was mediated by release of proinflammatory S100A8/A9 proteins, leading to elevated MPO activity and accumulation of oxidized lipids, plasmalogens, in neutrophils. Direct experiments demonstrated that oxidatively modified by MPO phosphatidylethanolamine, plasmalogens were able to activate proliferation of dormant tumor cells via upregulation of the FGF pathway (26). These findings provide one possible mechanism for tumor recurrence. Patients in remission, who have undetectable dormant tumor cells, are encountering stress throughout their daily lives. If neutrophils in the vicinity of dormant tumor cells are exposed to stress hormones, they can release oxidized lipids that in turn induce exit of tumor cells from the state of dormancy.

## Conclusion

The importance of lipid metabolism in tumorigenesis has been shown to be crucial for tumor growth and survival. The impact of lipid metabolism and oxidatively modified lipids from myeloid cells on immunosuppression and tumor cell dormancy is an emerging field of study. The vast number of lipid signaling moieties as well as the different receptors and signaling pathways involved complicates understanding of these processes. Yet, this also provides a well of potential drug targets to improve response to chemotherapy or immunotherapy. The challenge is in identifying the nature of oxidized lipid species and particular receptors to target that are uniquely

upregulated in the tumor and that do not have crucial roles in normal lipid metabolism.

### Authors' Disclosures

No disclosures were reported.

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