



Published in final edited form as:

*Cancer Res.* 2022 January 15; 82(2): 187–194. doi:10.1158/0008-5472.CAN-21-3054.

## Myeloid-cell derived oxidized lipids and regulation of the tumor microenvironment

Kristin C. Hicks<sup>1</sup>, Yulia Y. Tyurina<sup>2</sup>, Valerian E. Kagan<sup>2</sup>, Dmitry I. Gabrilovich<sup>1,\*</sup>

<sup>1</sup>AstraZeneca, ICC, Early Oncology, R&D, Gaithersburg, MD, USA

<sup>2</sup>Departments of Environmental and Occupational Health, Chemistry, Pharmacology and Chemical Biology, Radiation Oncology, University of Pittsburgh, PA 15261, USA.

### Abstract

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

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 anti-tumor 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 utilize 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, utilizing 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 in the context of cancer, and thus the focus of this review, are PMN, MON, MΦ, and DC. Populations of PMN and MON consist

\*Address for correspondence: Dmitry Gabrilovich, AstraZeneca, One Medimmune Way, Gaithersburg, MD, 20878 USA. Dmitry.gabrilovich@astrazeneca.com, Phone: 484 4349896.

Conflict of interests statement

Authors declare no conflict of interest

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, morphology), they also have distinct transcriptomics, biochemical and functional traits with the most distinguishing feature of MDSC being the immune suppressive activity (3). Based on 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 NK cells, M-MDSCs secrete immunosuppressive cytokines (IL-10, IL-6, TGF $\beta$ ) and nitric oxide (NO) as well as express checkpoint inhibitors, while PMN-MDSC utilize reactive oxygen species (ROS), peroxynitrite (PNT), arginase I, and prostaglandin E2 (PGE2) (3). The prevalence of MDSCs has been closely associated with poor patient prognosis and response to therapy in a variety of tumor types (6).

M $\Phi$  have a broad role in host defense and maintenance of tissue homeostasis (7). Based on their origin, M $\Phi$  can be classified into two major groups: tissue resident macrophages derived from embryonic progenitors or bone marrow derived M $\Phi$  differentiated from MON. Additionally, M $\Phi$  can be polarized *in vitro* to a classically activated M1 phenotype when incubated with interferon  $\gamma$  or lipopolysaccharide or alternatively activated M2 phenotype when incubated with IL-4 and IL-13 (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 anti-tumor functions (reviewed in (2)). In recent years, evidence has emerged that M $\Phi$  in cancer can be distinguished as classical (non-suppressive) and pathologically activated (suppressive) (10), similar to what was observed for MDSC. These suppressive M $\Phi$  may include multiple subsets and utilize mechanisms that may be shared by M1 and M2 M $\Phi$ . For instance, both arginase I and NO, a distinct feature of M2 and M1 M $\Phi$ , respectively, were directly implicated in the immune suppressive 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 anti-tumor 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) (16). cDC1 are considered the major cross-presenting cells promoting antitumor responses, whereas monocyte-derived DC are implicated in inhibition of immune responses (16).

## Outline of the metabolism of oxidized lipids

Lipids are small amphiphilic molecules containing a non-polar 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) which 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 (Figure 1). GPLs are further classified based on 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 KEGG’s pathway for the biosynthesis of unsaturated FA lists a total of 30 PUFA (20). Combined with ~15 other possible SUFA and MUFA, each class of GPLs can encompass  $>2 \times 10^3$  individual species. In some types of GLP (eg, 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 GLP species including not only intact GLP but also metabolites, act as signaling 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 which catalyze the release of free PUFA from the *sn*-2 position thus making them available for the oxygenation by cyclooxygenases (COX), lipoxygenases (LOX) and isoforms of cytochrome P450 (CYP450) (21). These reactions represent the canonical mechanisms for the formation of several classes of well-known lipid mediators with multiple regulatory functions. Based on 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 (Figure 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 utilizes a GLP subclass called plasmalogens. Plasmalogens (pGLP) can contain two different types of bonds: a vinyl ether linkage at the *sn-1* position of the glycerophospholipid backbone and an ester-bond at the *sn-2* position (similar to diacyl-GLPs (25)) (Figure 1). In the context of signaling, the important property of pGLP is the vulnerability of their vinyl ether bond to cleavage by hypochlorous acid (HClO) generated by myeloperoxidase (MPO) and peroxynitrite (ONOO-) massively produced by MDSC and MΦ (21) (Figure 2). In pro-inflammatory conditions, elevated levels of HClO or ONOO- 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. Dis-coordinated 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 (DAGs) and triacylglycerols (TAGs) as well as in cholesterol esters (CE). These covalent derivatives of FA are highly hydrophobic and usually excluded from biomembranes to produce separate intracellular organizations, lipid droplets (LD). (Figure 1). Recent studies demonstrated that LD 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 utilized 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 which will be discussed below. Once shuttled into the mitochondria, the carnitine is removed by carnitine palmitoyl transferase 2 (CPT2). FA 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 since 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) (31). The lipids transported from the microenvironment promoted immune suppression 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*) (32). While 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 immune suppressive 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 to 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 (38). (Figure 2). 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 which was not mediated by its direct effect on tumor cells (40). PGE2 is a product of lipid oxygenation initiated when AA is metabolized by cyclooxygenase 2 (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 immune suppressive 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 immune suppressive activity.

### **Macrophages.**

It has long been appreciated that metabolism is involved in M $\Phi$  polarization. M1-like M $\Phi$  preferentially use glycolysis, have a broken TCA cycle, and generate lipids via fatty acid synthesis. Conversely, M2-like M $\Phi$  have an intact TCA cycle and rely on FAO to fuel OXPHOS for energy production (29,47,48). In fact, the polarization of M $\Phi$  can be altered by modifying the metabolic pathways being utilized. A recent study found that unsaturated FA or LD polarized bone-marrow derived cells into immune suppressive M2-like M $\Phi$ . 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 M $\Phi$  from tumor bearing mice or cultured with tumor cells had increased lipid accumulation and utilized scavenger receptors CD36 and LOX-1 to transport FA from the lipid rich TME (50-52). FA undergo lipolysis mediated by lysosomal acid lipase to support OXPHOS and M2 activation which is reversed by inhibition of these lipases (51). Additionally, 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 protumor 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 M $\Phi$  biology. Inducible nitric oxide synthase (iNOS)/NO $^{\bullet}$ , a characteristic of M1 M $\Phi$ , conferred M $\Phi$  resistance to ferroptosis by inhibiting pro-ferroptotic lipid peroxidation (55). This study and another showed that exposure of M2 M $\Phi$  to NO $^{\bullet}$  protected them from ferroptosis and that GPX4 expression was not required for survival of M2 (alternatively activated) M $\Phi$  if sufficient amounts of NO $^{\bullet}$  were generated (55,56). These studies suggest that induction of ferroptosis can alter the M $\Phi$  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 M $\Phi$  activation with potent tumoricidal activities (57).

### **Dendritic cells.**

Early studies showed that PUFA reduced expression of DC co-stimulatory molecules and pro-inflammatory 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 cancer patients 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 utilizes two major pathways: cytosolic and vacuolar (63). The latter, includes processing peptides and formation of peptide-MHC Class I complexes in lysosomes/late endosomes. LD 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 heat shock protein 70 (HSP70) preventing it from transporting peptide-MHC Class I complexes to the cell surface (64,65) (Figure 2).

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 DC (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 up-regulation 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 accumulate oxidized lipids after generating them by utilizing 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 (71) (Figure 2).

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 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, amongst other changes, had significantly higher OXPHOS and FAO. Additionally, 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. While inhibition of the FAO with etomoxir was shown to inhibit immune suppression 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). Due to 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 PGE<sub>2</sub>, has also been examined as a potential target for cancer 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 which 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 up-regulated on immune suppressive myeloid cells, but 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 don't proliferate limiting tumor expansion and supporting tumor remission. On the other hand, dormant tumors cells are more resistant to chemo- or radiation therapies. 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 which 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.

Due to 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 utilized a reporter construct that allowed for the identification of non-cycling or cycling persister cells that remained after chemotherapy. It



found that although both, non-cycling and cycling persister cells, shifted their metabolism to FAO relative to untreated cells, cycling cells had higher FA metabolism than non-cycling cells (87). While the authors called these cells persister cells, a non-cycling 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-MDSC were able to reactivate proliferation of dormant tumor cells (26) (Figure 2). 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 pro-inflammatory 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 up-regulation of fibroblast growth factor 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 immune suppression 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.

## Acknowledgment

This work was partially supported by NIH grants CA165065, CA243142 to VEK.

## References

1. Pathria P, Louis TL, Varner JA. Targeting Tumor-Associated Macrophages in Cancer. Trends Immunol 2019;40:310–27 [PubMed: 30890304]

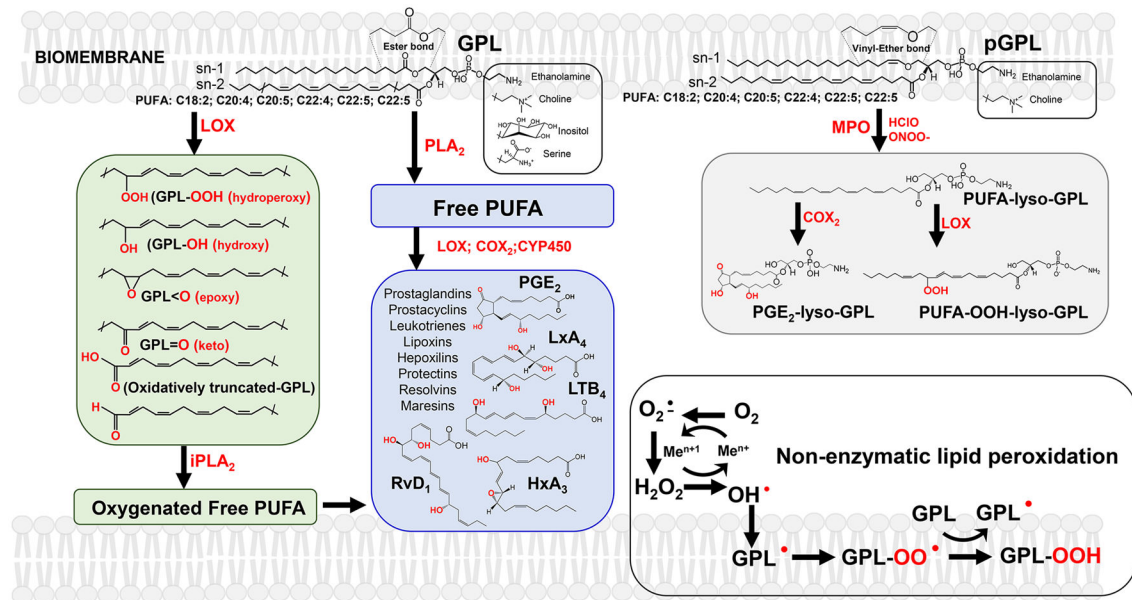
2. Pinto ML, Rios E, Duraes C, Ribeiro R, Machado JC, Mantovani A, et al. The Two Faces of Tumor-Associated Macrophages and Their Clinical Significance in Colorectal Cancer. *Frontiers in Immunology* 2019;10:1875 [PubMed: 31481956]
3. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. *Nat Rev Immunol* 2021;21:485–98 [PubMed: 33526920]
4. Zhou J, Nefedova Y, Lei A, Gabrilovich D. Neutrophils and PMN-MDSC: Their biological role and interaction with stromal cells. *Semin Immunol* 2018;35:19–28 [PubMed: 29254756]
5. Binnewies M, Roberts EW, Kersten K, Chan V, Fearon DF, Merad M, et al. Understanding the tumor immune microenvironment (TIME) for effective therapy. *Nat Med* 2018;24:541–50 [PubMed: 29686425]
6. Solito S, Marigo I, Pinton L, Damuzzo V, Mandruzzato S, Bronte V. Myeloid-derived suppressor cell heterogeneity in human cancers. *Ann N Y Acad Sci* 2014;1319:47–65 [PubMed: 24965257]
7. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity* 2010;32:593–604 [PubMed: 20510870]
8. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 2004;25:677–86 [PubMed: 15530839]
9. Mills CD, Kincaid K, Alt JM, Heilman MJ, Hill AM. M-1/M-2 macrophages and the Th1/Th2 paradigm. *J Immunol* 2000;164:6166–73 [PubMed: 10843666]
10. Kwak T, Wang F, Deng H, Condamine T, Kumar V, Perego M, et al. Distinct Populations of Immune-Suppressive Macrophages Differentiate from Monocytic Myeloid-Derived Suppressor Cells in Cancer. *Cell reports* 2020;33:108571 [PubMed: 33378668]
11. Wagner J, Rapsomaniki MA, Chevrier S, Anzeneder T, Langwieder C, Dykgers A, et al. A Single-Cell Atlas of the Tumor and Immune Ecosystem of Human Breast Cancer. *Cell* 2019;177:1330–45 e18 [PubMed: 30982598]
12. Tsutsui S, Yasuda K, Suzuki K, Tahara K, Higashi H, Era S. Macrophage infiltration and its prognostic implications in breast cancer: the relationship with VEGF expression and microvessel density. *Oncol Rep* 2005;14:425–31 [PubMed: 16012726]
13. Yahaya MAF, Lila MAM, Ismail S, Zainol M, Afizan N. Tumour-Associated Macrophages (TAMs) in Colon Cancer and How to Reeducate Them. *J Immunol Res* 2019;2019:2368249 [PubMed: 30931335]
14. Bottcher JP, Reis e Sousa C. The Role of Type 1 Conventional Dendritic Cells in Cancer Immunity. *Trends Cancer* 2018;4:784–92 [PubMed: 30352680]
15. Gardner A, Ruffell B. Dendritic Cells and Cancer Immunity. *Trends Immunol* 2016;37:855–65 [PubMed: 27793569]
16. Veglia F, Gabrilovich DI. Dendritic cells in cancer: the role revisited. *Curr Opin Immunol* 2017;45:43–51 [PubMed: 28192720]
17. Deamer D The Role of Lipid Membranes in Life's Origin. *Life (Basel)* 2017;7
18. Segre D, Ben-Eli D, Deamer DW, Lancet D. The lipid world. *Orig Life Evol Biosph* 2001;31:119–45 [PubMed: 11296516]
19. Tyurina YY, Tyurin VA, Anthonymuthu T, Amoscato AA, Sparvero LJ, Nesterova AM, et al. "Redox lipidomics technology: Looking for a needle in a haystack". *Chem Phys Lipids* 2019;221:93–107 [PubMed: 30928338]
20. Kanehisa M, Goto S. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Res* 2000;28:27–30 [PubMed: 10592173]
21. Tyurina YY, St Croix CM, Watkins SC, Watson AM, Epperly MW, Anthonymuthu TS, et al. Redox (phospho)lipidomics of signaling in inflammation and programmed cell death. *J Leukoc Biol* 2019;106:57–81 [PubMed: 31071242]
22. Dennis EA, Norris PC. Eicosanoid storm in infection and inflammation. *Nat Rev Immunol* 2015;15:511–23 [PubMed: 26139350]
23. Spickett CM. Formation of Oxidatively Modified Lipids as the Basis for a Cellular Epilipidome. *Front Endocrinol (Lausanne)* 2020;11:602771 [PubMed: 33408694]

24. Ni Z, Goracci L, Cruciani G, Fedorova M. Computational solutions in redox lipidomics - Current strategies and future perspectives. *Free Radic Biol Med* 2019;144:110–23 [PubMed: 31035005]
25. Broniec A, Klosinski R, Pawlak A, Wrona-Krol M, Thompson D, Sarna T. Interactions of plasmalogens and their diacyl analogs with singlet oxygen in selected model systems. *Free Radic Biol Med* 2011;50:892–8 [PubMed: 21236336]
26. Perego M, Tyurin VA, Tyurina YY, Yellets J, Nacarelli T, Lin C, et al. Reactivation of dormant tumor cells by modified lipids derived from stress-activated neutrophils. *Science translational medicine* 2020;12
27. Bacci M, Lorito N, Smiriglia A, Morandi A. Fat and Furious: Lipid Metabolism in Antitumoral Therapy Response and Resistance. *Trends in cancer* 2021;7:198–213 [PubMed: 33281098]
28. Mohammadyani D, Tyurin VA, O'Brien M, Sadovsky Y, Gabrilovich DI, Klein-Seetharaman J, et al. Molecular speciation and dynamics of oxidized triacylglycerols in lipid droplets: Mass spectrometry and coarse-grained simulations. *Free Radic Biol Med* 2014;76:53–60 [PubMed: 25110833]
29. O'Neill LA, Kishton RJ, Rathmell J. A guide to immunometabolism for immunologists. *Nat Rev Immunol* 2016;16:553–65 [PubMed: 27396447]
30. Hossain F, Al-Khami AA, Wyczechowska D, Hernandez C, Zheng L, Reiss K, et al. Inhibition of Fatty Acid Oxidation Modulates Immunosuppressive Functions of Myeloid-Derived Suppressor Cells and Enhances Cancer Therapies. *Cancer Immunol Res* 2015;3:1236–47 [PubMed: 26025381]
31. Al-Khami AA, Zheng L, Del Valle L, Hossain F, Wyczechowska D, Zabaleta J, et al. Exogenous lipid uptake induces metabolic and functional reprogramming of tumor-associated myeloid-derived suppressor cells. *Oncoimmunology* 2017;6:e1344804 [PubMed: 29123954]
32. Condamine T, Dominguez GA, Youn JI, Kossenkov AV, Mony S, Alicea-Torres K, et al. Lectin-type oxidized LDL receptor-1 distinguishes population of human polymorphonuclear myeloid-derived suppressor cells in cancer patients. *Sci Immunol* 2016;1
33. Chai E, Zhang L, Li C. LOX-1+ PMN-MDSC enhances immune suppression which promotes glioblastoma multiforme progression. *Cancer Manag Res* 2019;11:7307–15 [PubMed: 31447588]
34. Kim HR, Park SM, Seo SU, Jung I, Yoon HI, Gabrilovich DI, et al. The Ratio of Peripheral Regulatory T Cells to Lox-1(+) Polymorphonuclear Myeloid-derived Suppressor Cells Predicts the Early Response to Anti-PD-1 Therapy in Patients with Non-Small Cell Lung Cancer. *American journal of respiratory and critical care medicine* 2019;199:243–6 [PubMed: 30339766]
35. Si Y, Merz SF, Jansen P, Wang B, Bruderek K, Altenhoff P, et al. Multidimensional imaging provides evidence for down-regulation of T cell effector function by MDSC in human cancer tissue. *Sci Immunol* 2019;4
36. Cassetta L, Bruderek K, Skrzeczynska-Moncznik J, Osiecka O, Hu X, Rundgren IM, et al. Differential expansion of circulating human MDSC subsets in patients with cancer, infection and inflammation. *J Immunother Cancer* 2020;8
37. Dominguez GA, Polo AT, Roop J, Campisi AJ, Somer RA, Perzin AD, et al. Detecting Prostate Cancer Using Pattern Recognition Neural Networks With Flow Cytometry-Based Immunophenotyping in At-Risk Men. *Biomark Insights* 2020;15:1177271920913320 [PubMed: 32341637]
38. Veglia F, Tyurin VA, Blasi M, De Leo A, Kossenkov AV, Donthireddy L, et al. Fatty acid transport protein 2 reprograms neutrophils in cancer. *Nature* 2019;569:73–8 [PubMed: 30996346]
39. Adeshakin AO, Liu W, Adeshakin FO, Afolabi LO, Zhang M, Zhang G, et al. Regulation of ROS in myeloid-derived suppressor cells through targeting fatty acid transport protein 2 enhanced anti-PD-L1 tumor immunotherapy. *Cell Immunol* 2021;362:104286 [PubMed: 33524739]
40. Alicea GM, Rebecca VW, Goldman AR, Fane ME, Douglass SM, Behera R, et al. Changes in Aged Fibroblast Lipid Metabolism Induce Age-Dependent Melanoma Cell Resistance to Targeted Therapy via the Fatty Acid Transporter FATP2. *Cancer Discov* 2020;10:1282–95 [PubMed: 32499221]
41. Sinha P, Clements VK, Fulton AM, Ostrand-Rosenberg S. Prostaglandin E2 promotes tumor progression by inducing myeloid-derived suppressor cells. *Cancer Res* 2007;67:4507–13 [PubMed: 17483367]

42. Rodriguez PC, Hernandez CP, Quiceno D, Dubinett SM, Zabaleta J, Ochoa JB, et al. Arginase I in myeloid suppressor cells is induced by COX-2 in lung carcinoma. *J Exp Med* 2005;202:931–9 [PubMed: 16186186]
43. He YM, Li X, Perego M, Nefedova Y, Kossenkov AV, Jensen EA, et al. Transitory presence of myeloid-derived suppressor cells in neonates is critical for control of inflammation. *Nat Med* 2018;24:224–31 [PubMed: 29334374]
44. Liu Y, Perego M, Xiao Q, He Y, Fu S, He J, et al. Lactoferrin-induced myeloid-derived suppressor cell therapy attenuates pathologic inflammatory conditions in newborn mice. *J Clin Invest* 2019;129:4261–75 [PubMed: 31483289]
45. Nagaraj S, Nelson A, Youn JI, Cheng P, Quiceno D, Gabrilovich DI. Antigen-specific CD4(+) T cells regulate function of myeloid-derived suppressor cells in cancer via retrograde MHC class II signaling. *Cancer Research* 2012;72:928–38 [PubMed: 22237629]
46. Prima V, Kaliberova LN, Kaliberov S, Curiel DT, Kusmartsev S. COX2/mPGES1/PGE2 pathway regulates PD-L1 expression in tumor-associated macrophages and myeloid-derived suppressor cells. *Proc Natl Acad Sci U S A* 2017;114:1117–22 [PubMed: 28096371]
47. Jha AK, Huang SC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, et al. Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. *Immunity* 2015;42:419–30 [PubMed: 25786174]
48. Remmerie A, Scott CL. Macrophages and lipid metabolism. *Cell Immunol* 2018;330:27–42 [PubMed: 29429624]
49. Wu H, Han Y, Rodriguez Sillke Y, Deng H, Siddiqui S, Treese C, et al. Lipid droplet-dependent fatty acid metabolism controls the immune suppressive phenotype of tumor-associated macrophages. *EMBO Mol Med* 2019;11:e10698 [PubMed: 31602788]
50. Kume N, Moriwaki H, Kataoka H, Minami M, Murase T, Sawamura T, et al. Inducible expression of LOX-1, a novel receptor for oxidized LDL, in macrophages and vascular smooth muscle cells. *Ann N Y Acad Sci* 2000;902:323–7 [PubMed: 10865857]
51. Huang SC, Everts B, Ivanova Y, O'Sullivan D, Nascimento M, Smith AM, et al. Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages. *Nat Immunol* 2014;15:846–55 [PubMed: 25086775]
52. Su P, Wang Q, Bi E, Ma X, Liu L, Yang M, et al. Enhanced Lipid Accumulation and Metabolism Are Required for the Differentiation and Activation of Tumor-Associated Macrophages. *Cancer Res* 2020;80:1438–50 [PubMed: 32015091]
53. Stockwell BR, Friedmann Angeli JP, Bayir H, Bush AI, Conrad M, Dixon SJ, et al. Ferroptosis: A Regulated Cell Death Nexus Linking Metabolism, Redox Biology, and Disease. *Cell* 2017;171:273–85 [PubMed: 28985560]
54. Pizzimenti S, Ciamporocero E, Daga M, Pettazzoni P, Arcaro A, Cetrangolo G, et al. Interaction of aldehydes derived from lipid peroxidation and membrane proteins. *Front Physiol* 2013;4:242 [PubMed: 24027536]
55. Kapralov AA, Yang Q, Dar HH, Tyurina YY, Anthonymuthu TS, Kim R, et al. Redox lipid reprogramming commands susceptibility of macrophages and microglia to ferroptotic death. *Nature chemical biology* 2020;16:278–90 [PubMed: 32080625]
56. Piattini F, Matsushita M, Muri J, Bretscher P, Feng X, Freigang S, et al. Differential sensitivity of inflammatory macrophages and alternatively activated macrophages to ferroptosis. *Eur J Immunol* 2021
57. Gu Z, Liu T, Liu C, Yang Y, Tang J, Song H, et al. Ferroptosis-Strengthened Metabolic and Inflammatory Regulation of Tumor-Associated Macrophages Provokes Potent Tumoricidal Activities. *Nano Lett* 2021;21:6471–9 [PubMed: 34292757]
58. Zeyda M, Saemann MD, Stuhlmeier KM, Mascher DG, Nowotny PN, Zlabinger GJ, et al. Polyunsaturated fatty acids block dendritic cell activation and function independently of NF-kappaB activation. *J Biol Chem* 2005;280:14293–301 [PubMed: 15684433]
59. Weatherill AR, Lee JY, Zhao L, Lemay DG, Youn HS, Hwang DH. Saturated and polyunsaturated fatty acids reciprocally modulate dendritic cell functions mediated through TLR4. *J Immunol* 2005;174:5390–7 [PubMed: 15843537]

60. Zapata-Gonzalez F, Rueda F, Petriz J, Domingo P, Villarroya F, Diaz-Delfin J, et al. Human dendritic cell activities are modulated by the omega-3 fatty acid, docosahexaenoic acid, mainly through PPAR( $\gamma$ ):RXR heterodimers: comparison with other polyunsaturated fatty acids. *J Leukoc Biol* 2008;84:1172–82 [PubMed: 18632990]
61. Kong W, Yen JH, Vassiliou E, Adhikary S, Toscano MG, Ganea D. Docosahexaenoic acid prevents dendritic cell maturation and in vitro and in vivo expression of the IL-12 cytokine family. *Lipids Health Dis* 2010;9:12 [PubMed: 20122166]
62. Herber DL, Cao W, Nefedova Y, Novitskiy SV, Nagaraj S, Tyurin VA, et al. Lipid accumulation and dendritic cell dysfunction in cancer. *Nat Med* 2010;16:880–6 [PubMed: 20622859]
63. Joffre OP, Segura E, Savina A, Amigorena S. Cross-presentation by dendritic cells. *Nat Rev Immunol* 2012;12:557–69 [PubMed: 22790179]
64. Veglia F, Tyurin VA, Mohammadyani D, Blasi M, Duperret EK, Donthireddy L, et al. Lipid bodies containing oxidatively truncated lipids block antigen cross-presentation by dendritic cells in cancer. *Nature communications* 2017;8:2122
65. Ramakrishnan R, Tyurin VA, Veglia F, Condamine T, Amoscato A, Mohammadyani D, et al. Oxidized lipids block antigen cross-presentation by dendritic cells in cancer. *J Immunol* 2014;192:2920–31 [PubMed: 24554775]
66. Perrin-Cocon L, Diaz O, Andre P, Lotteau V. Modified lipoproteins provide lipids that modulate dendritic cell immune function. *Biochimie* 2012
67. Gardner JK, Mamotte CD, McGonigle T, Dye DE, Jackaman C, Nelson DJ. Lipid-laden partially-activated plasmacytoid and CD4(–)CD8 $\alpha$ (+) dendritic cells accumulate in tissues in elderly mice. *Immunity & ageing : I & A* 2014;11:11 [PubMed: 25089147]
68. Gardner JK, Mamotte CD, Patel P, Yeoh TL, Jackaman C, Nelson DJ. Mesothelioma tumor cells modulate dendritic cell lipid content, phenotype and function. *PLoS one* 2015;10:e0123563 [PubMed: 25886502]
69. Peng X, He Y, Huang J, Tao Y, Liu S. Metabolism of Dendritic Cells in Tumor Microenvironment: For Immunotherapy. *Frontiers in immunology* 2021;12:613492 [PubMed: 33732237]
70. Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, Chopra S, Perales-Puchalt A, Song M, et al. ER Stress Sensor XBP1 Controls Anti-tumor Immunity by Disrupting Dendritic Cell Homeostasis. *Cell* 2015;161:1527–38 [PubMed: 26073941]
71. Ugolini A, Tyurin VA, Tyurina YY, Tcyganov EN, Donthireddy L, Kagan VE, et al. Polymorphonuclear myeloid-derived suppressor cells limit antigen cross-presentation by dendritic cells in cancer. *JCI insight* 2020;5
72. Muntjewerff EM, Meesters LD, van den Bogaart G. Antigen Cross-Presentation by Macrophages. *Frontiers in immunology* 2020;11:1276 [PubMed: 32733446]
73. Malinarich F, Duan K, Hamid RA, Bijin A, Lin WX, Poidinger M, et al. High mitochondrial respiration and glycolytic capacity represent a metabolic phenotype of human tolerogenic dendritic cells. *J Immunol* 2015;194:5174–86 [PubMed: 25917094]
74. Ferreira GB, Vanherwegen AS, Eelen G, Gutierrez ACF, Van Lommel L, Marchal K, et al. Vitamin D3 Induces Tolerance in Human Dendritic Cells by Activation of Intracellular Metabolic Pathways. *Cell Rep* 2015;10:711–25 [PubMed: 25660022]
75. Svajger U, Obermajer N, Jeras M. Dendritic cells treated with resveratrol during differentiation from monocytes gain substantial tolerogenic properties upon activation. *Immunology* 2010;129:525–35 [PubMed: 20002210]
76. Ceccarelli SM, Chomienne O, Gubler M, Arduini A. Carnitine palmitoyltransferase (CPT) modulators: a medicinal chemistry perspective on 35 years of research. *J Med Chem* 2011;54:3109–52 [PubMed: 21504156]
77. Veltman JD, Lambers ME, van Nimwegen M, Hendriks RW, Hoogsteden HC, Aerts JG, et al. COX-2 inhibition improves immunotherapy and is associated with decreased numbers of myeloid-derived suppressor cells in mesothelioma. Celecoxib influences MDSC function. *BMC cancer* 2010;10:464 [PubMed: 20804550]
78. Chen J, Shen P, Zhang XC, Zhao MD, Zhang XG, Yang L. Efficacy and safety profile of celecoxib for treating advanced cancers: a meta-analysis of 11 randomized clinical trials. *Clin Ther* 2014;36:1253–63 [PubMed: 25016505]

79. Guo Q, Li Q, Wang J, Liu M, Wang Y, Chen Z, et al. A comprehensive evaluation of clinical efficacy and safety of celecoxib in combination with chemotherapy in metastatic or postoperative recurrent gastric cancer patients: A preliminary, three-center, clinical trial study. *Medicine (Baltimore)* 2019;98:e16234 [PubMed: 31277138]
80. Wang H, Franco F, Tsui YC, Xie X, Trefny MP, Zappasodi R, et al. CD36-mediated metabolic adaptation supports regulatory T cell survival and function in tumors. *Nat Immunol* 2020;21:298–308 [PubMed: 32066953]
81. Xu S, Chaudhary O, Rodriguez-Morales P, Sun X, Chen D, Zappasodi R, et al. Uptake of oxidized lipids by the scavenger receptor CD36 promotes lipid peroxidation and dysfunction in CD8(+) T cells in tumors. *Immunity* 2021;54:1561–77 e7 [PubMed: 34102100]
82. Jeanne A, Schneider C, Martiny L, Dedieu S. Original insights on thrombospondin-1-related antireceptor strategies in cancer. *Front Pharmacol* 2015;6:252 [PubMed: 26578962]
83. Recasens A, Munoz L. Targeting Cancer Cell Dormancy. *Trends Pharmacol Sci* 2019;40:128–41 [PubMed: 30612715]
84. Quesnel B Tumor dormancy and immunoescape. *APMIS* 2008;116:685–94 [PubMed: 18834412]
85. Viale A, Pettazzoni P, Lyssiotis CA, Ying H, Sanchez N, Marchesini M, et al. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature* 2014;514:628–32 [PubMed: 25119024]
86. Nakayama T, Sano T, Oshimo Y, Kawada C, Kasai M, Yamamoto S, et al. Enhanced lipid metabolism induces the sensitivity of dormant cancer cells to 5-aminolevulinic acid-based photodynamic therapy. *Sci Rep* 2021;11:7290 [PubMed: 33790399]
87. Oren Y, Tsabar M, Cuoco MS, Amir-Zilberstein L, Cabanos HF, Hutter JC, et al. Cycling cancer persister cells arise from lineages with distinct programs. *Nature* 2021
88. Panigrahy D, Edin ML, Lee CR, Huang S, Bielenberg DR, Butterfield CE, et al. Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *J Clin Invest* 2012;122:178–91 [PubMed: 22182838]
89. Sosnoski DM, Norgard RJ, Grove CD, Foster SJ, Mastro AM. Dormancy and growth of metastatic breast cancer cells in a bone-like microenvironment. *Clin Exp Metastasis* 2015;32:335–44 [PubMed: 25749879]



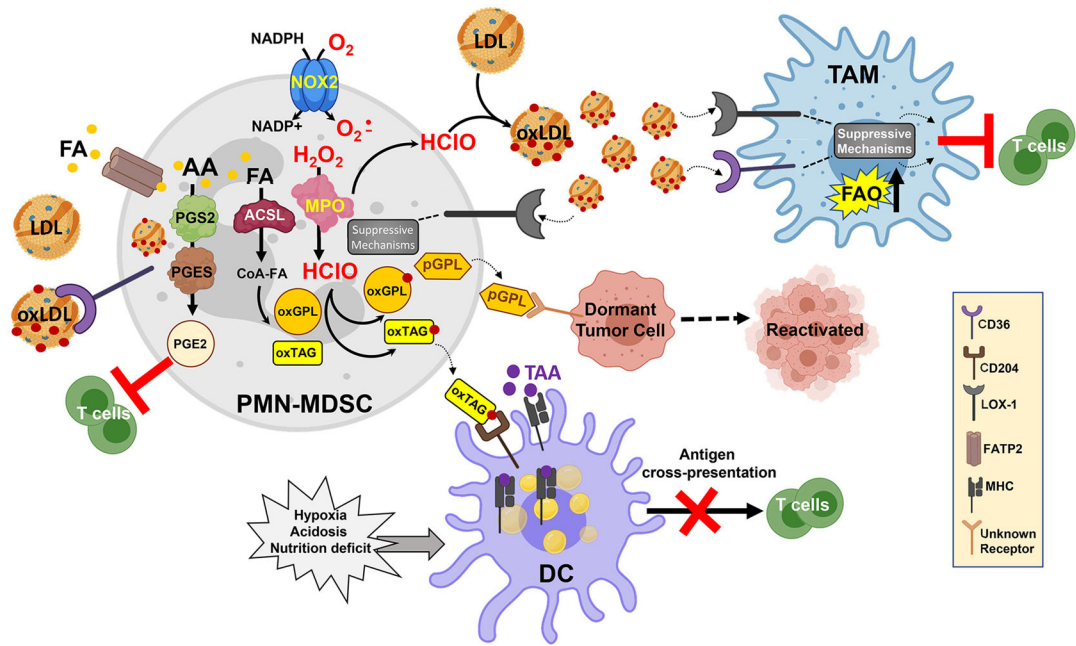
**Figure 1. The major metabolic pathways leading to the formation of signaling molecules from PUFA-GPL and pGPL.**

*Right upper panel (grey):* Cleavage of vinyl ether bond of pGPL by oxidants (eg, hypochlorous acid (HClO) generated by myeloperoxidase (MPO) or peroxynitrite (ONOO<sup>-</sup>) result in the production of unusual lyso-GPLs with the retained sn-2 PUFA oxidizable residues. These types of lyso-GPLs can be readily be used as substrates of cyclooxygenases (COX) 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 panel (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 panel (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 non-canonical pathway leading to the formation of free oxygenated PUFA acting as lipid mediators.

*Right lower panel (white):* non-enzymatic lipid peroxidation



**Figure 2. Effect of oxidized lipids of function of myeloid cells in cancer.**

Oxidative machinery of PMN-MDSC include MPO and superoxide produced by NADPH oxidase (NOX2) support 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 XBP1. In PMN-MDSC, accumulation of oxidized lipids result 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 up-regulation of arginase 1, NO production, secretion of immune suppressive cytokines.



**Table 1:**

## Targeting lipids in myeloid cells

Target Type	Target	Drug	Preclinical or Clinical	Effects	Potential Pitfall
<b>FAO rate limiting enzyme</b>	CPT1	Small molecule Etomoxir	Preclinical	<ul style="list-style-type: none"> <li>Reversed lipid-mediated polarization of M2-like MΦ 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
<b>Enzyme that transports FFA into LD</b>	DGAT1 DGAT2	Small molecule A922500 & PF-06424439	Preclinical	<ul style="list-style-type: none"> <li>Reversed lipid-mediated polarization of M2-like MΦ and had anti-tumor activity (49)</li> </ul>	
<b>Lipolysis inhibition</b>	Lipase	orlistat	Preclinical	<ul style="list-style-type: none"> <li>Reduced M2-like MΦ activation and survival (51)</li> </ul>	
<b>Enzyme involved in PGE2 generation</b>	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
<b>Lipid Receptors and Transporters</b>	CD36	Antibody blockade	Preclinical	<ul style="list-style-type: none"> <li>Antitumor efficacy (81)</li> <li>Potentiated anti-PD-1 anti-tumor efficacy (80)</li> <li>Effects on myeloid cells not examined</li> </ul>	High redundancy in these receptors may represent therapeutic challenge
			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 anti-tumor activity (38-40)</li> </ul>	