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Spotlight

Etherglycerophospholipids and ferroptosis: structure, regulation, and location

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Two pioneering studies by Zou *et al.* and Cui *et al.* have reported that the synthesis of etherglycerophospholipids (etherPLs) sensitizes cells to ferroptosis. The location and regulation of etherPLs suggest that: (i) lipid peroxidation in the inner leaflet of the plasma membrane might be of importance in ferroptosis, and (ii) different etherPLs may differently sensitize cells to ferroptosis.

Two recent studies have reported that the synthesis of etherPLs plays a key role in ferroptosis [1,2], which is a type of programmed cell death [3]. Specifically, ferroptosis entails the accumulation of lipid peroxides, which leads the cell to death [3]. Despite these two seminal studies, the way etherPLs may govern ferroptosis is still not clear [4]. Here we want to highlight that the association between the location and regulation of etherPLs is of special interest in future research on ferroptosis.

EtherPLs are composed of a glycerol backbone with an alkyl chain in the sn-1 position (i.e., with an ether bond). As shown in Figure 1A, this ether bond has two variants: plasmanyl (isolated ether) and plasmenyl (vinylether, a.k.a. plasmalogens). In the sn-2 position of the glycerol, etherPLs present an esterified fatty acid, commonly a polyunsaturated fatty acid (PUFA), which is prone to peroxidation. Finally, in the sn-3 position of the glycerol, etherPLs present a polar headgroup, the most common ones being phosphoethanolamine and phosphocholine. Consequently, the main structures of etherPLs are plasmanyls of choline (ePCs), plasmanyls of ethanolamine (ePEs), plasmenyls of choline (pPCs), and plasmenyls of ethanolamine (pPEs). Among these possibilities, pPEs are the most abundant.

Figure 1B shows that the regulation and location of etherPLs are associated [5]. Interestingly, pPEs in the plasma membrane are enriched in the inner leaflet [5,6]. As Honsho *et al.* have shown, the increase in pPEs in this location of the cell downregulates fatty acyl coenzyme A reductase 1 (Far-1). Far-1 activity is the initial step of the synthesis of all etherPLs, so an increase of pPEs in the inner leaflet of the plasma membrane would translate into a decrease of all etherPLs (Figure 1B) [7]. Less is known about other etherPLs. For example, to the best of our knowledge, it is not clear if ePEs, ePCs, and pPCs also localize in the inner leaflet of the plasma membrane.

In the context of ferroptosis and the synthesis of etherPLs, Zou *et al.* have reported that different enzymes involved in the synthesis of etherPLs sensitized cells to ferroptosis [Far-1 and alkylglyceronephosphate synthase (AGPS), Figure 1B] [1]. Interestingly, they reported that transmembrane protein 189 (TMEM189) did not affect the sensitivity to ferroptosis. In a new study, Cui *et al.* also reported the involvement in ferroptosis of different enzymes in the biosynthetic route of etherPLs [Far-1, glyceronephosphate O-acyltransferase (GNPAT), and AGPS, Figure 1B]. Cui *et al.* also found that pPEs downregulated Far-1, but ePEs did not [2]. Finally, in contrast to the results of Zou *et al.*, Cui *et al.* reported that that TMEM189 presented a protective role against ferroptosis by downregulating Far-1 [2]. In the light of the regulation of etherPLs, we discuss in the next two paragraphs that this contradiction may be apparent (Figure 1B,C).

First, let us consider a biological model with high basal levels of pPEs (Figure 1C). The downregulation of TMEM189 would significantly decrease the synthesis of pPEs. Subsequently, pPEs in the inner leaflet of the plasma membrane would decrease, which would upregulate Far-1 and increase the sum pPEs + ePEs. As pPEs and ePEs present a similar tendency to lipid peroxidation [1], the downregulation of TMEM189 when the basal amount of pPEs is high would translate into an increase in sensitivity to ferroptosis (Figure 1C). This would suggest a protective role of TMEM189 against ferroptosis, as Cui *et al.* described [2].

Second, let us consider a biological model with low basal levels of pPEs (Figure 1C). The downregulation of TMEM189 may not significantly change the amount of pPEs, which is already low. The activity of Far-1 and the sum of pPEs + ePEs may not change significantly. The downregulation of TMEM189 when the basal amount of pPEs is low would not translate into a significant change of sensitivity to ferroptosis (Figure 1C). This second model would be compatible with the observations by Zou *et al.* [1].

As highlighted before, there is a dearth of information about the location and regulation of ePEs, ePCs, and pPCs. Future studies could affect our interpretation in the previous two paragraphs. Nevertheless, in the light of current knowledge (Figure 1B), we suggest that future studies on ferroptosis may measure and compare among different models: (i) the ratio pPEs: ePEs as a surrogate of the activity of TMEM189, and (ii) the sum pPEs + ePEs as a surrogate of the contribution of all etherPLs to ferroptosis.

In addition, considering the ensemble of studies about ferroptosis and the location/regulation of pPEs, we suggest a special role in ferroptosis of lipid peroxidation in the inner leaflet of the plasma membrane.

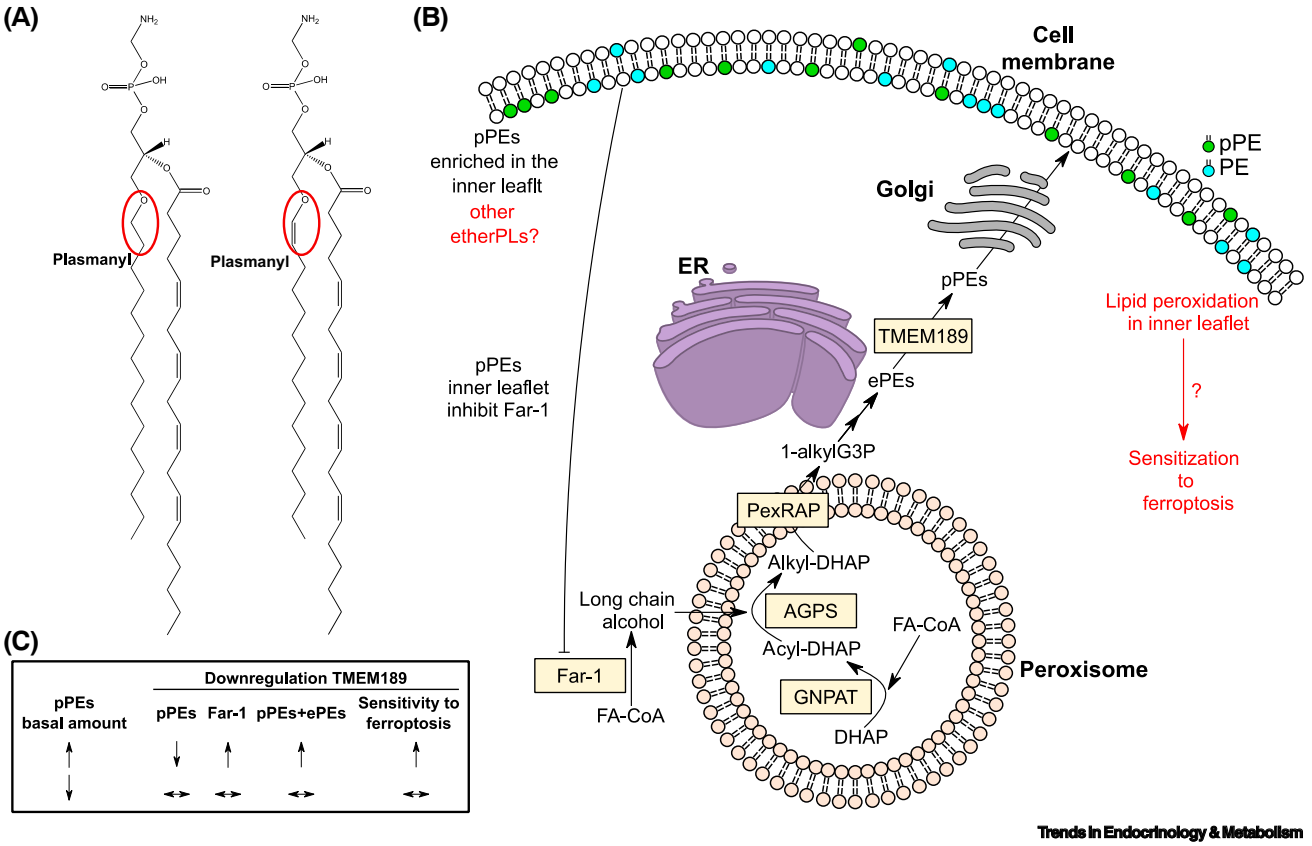

Figure 1. Structure and de novo synthesis of etherglycerophospholipids (etherPLs). (A) Structure of etherPLs. Examples of a plasmanyl glycerophospholipid of ethanolamine [ePE, specifically PE(O-16:0/20:4)] and a plasmenyl (plasmalogen) of a glycerophospholipid of ethanolamine [pPE, specifically PE(P-16:0/20:4)]. (B) Schematic view of cell biosynthesis, location, and regulation of etherPLs. Fatty acyl coenzyme A reductase (Far-1) reduces fatty acyls coenzyme A (FA-CoA, mainly palmitoyl and stearoyl CoA) to long chain alcohols. In the peroxisome, long chain alcohols are transferred to acyldihydroxyacetone phosphate (acyl-DHAP) by alkylglyceronephosphate synthase (AGPS) to yield alkyldihydroxyacetone phosphate (alkyl-DHAP). Acyl-DHAP in the peroxisome is provided by the acylation of dihydroxyacetone phosphate (DHAP) by glyceronephosphate O-acyltransferase (GNPAT). Alkyl-DHAP in the peroxisome is reduced to 1-alkyl-glycerol-3-phosphate (1-alkylG3P) by acyl/alkyldihydroxyacetone phosphate reductase (PexRAP). The maturation of alkylG3P into etherPLs is completed in the endoplasmic reticulum (ER). The main etherPLs are plasmenyls of ethanolamine (pPEs), which are synthesized from plasmanyls of ethanolamine (ePEs) by transmembrane protein 189 (TMEM189). pPEs are distributed to other cell membranes through the Golgi. In mammalian cells, pPEs present an enrichment in the inner leaflet of the plasma membrane and their content in this location downregulates Far-1, the initial step in the synthesis of all etherPLs. PEs also present an enrichment in the inner leaflet in the plasma membrane. We have highlighted in red the areas of research of special interest to unravel the role of etherPLs in ferroptosis. (C) Expected effect on ferroptosis of the downregulation of TMEM189 according to the basal levels of pPEs. Molecules, membranes, and organelles were created with ChemDraw 15.0.0.106 and processed with Inkscape 1.0.1.

In fact, previous studies about phosphatidylethanolamines (diacyl, PEs) also reinforce this suggestion: (i) PEs also present an enrichment in the inner leaflet of the plasma membrane of mammalian cells [6], and (ii) PEs with PUFAs are also key lipids in ferroptosis [8].

In contrast to the pro-ferroptotic role of the synthesis of etherPLs reported by Zou *et al.* and Cui *et al.* [1,2], Perez *et al.* have reported a protective effect of inhibiting AGPS in ferroptosis in *Caenorhabditis elegans* [9]. As pPEs have been primarily studied in mammalian cells, one can speculate that their location and regulation in non-mammalian cells is different. Further research may explain these contradictory results.

In conclusion, pPEs seem to be associated with ferroptosis sensitization through their location and regulation. In our opinion, the enrichment of pPEs (and PEs) in the inner leaflet of the plasma membrane suggests that this location is of importance for lipid peroxidation during ferroptosis. This could have consequences in a potential enhancement of ferroptosis in cancer treatment. For example, we have found that anthracyclins increase etherPEs with PUFAs in hepatocellular carcinoma (HCC) cells [10]. Consequently, one can speculate that one could sensitize HCC tumors to ferroptosis by using anthracyclins with liposomes containing ePEs or pPEs. However, the use of pPEs might be counterproductive by downregulating Far-1 and the total levels of ePEs and

pPEs. By contrast, ePEs may not have this effect. Further basic research about the deeds of all etherPLs in ferroptosis is warranted.

Declaration of interests

No interests are declared.

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