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Transforming Lipoxygenases: PE-Specific Enzymes in Disguise

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In this issue of *Cell*, Wenzel et al. solve a long-standing mystery regarding how damage to cell membranes occurs during ferroptosis, an iron-dependent form of regulated cell death. They found that lipoxygenases are like Transformer toys, being converted from one enzyme type to another in the presence of the protein PEBP1.

Cells are bounded by greasy lipid molecules that act as a barrier to water, separating different compartments of the cell, as well as separating the outside world from the inside of the cell (Agmon and Stockwell, 2017). The most common class of membrane lipids is built from a combination of two kinds of molecules: a polar head group that contains the element phosphorus and one or more fatty acid tails that contain a long string of carbon atoms. Once constructed, these lipids are referred to as phospholipids. The fatty acid part of the phospholipid can be saturated (meaning that there are no carbon-carbon double bonds), monounsaturated (meaning that there is one carbon-carbon double bond), or polyunsaturated (meaning that there is more than one carbon-carbon double bond); only the latter species is sensitive to reacting with oxygen in a chemical reaction referred to as peroxidation (Gaschler and Stockwell, 2017).

It has been previously established that cell death by ferroptosis is a result of such lipid peroxidation (Yang et al., 2016; Yang and Stockwell, 2016). In this chemical reaction, oxygen is added to polyunsaturated tails of phospholipids in cell membranes, creating new types of molecules known as lipid hydroperoxides, as well as other derivative species that may interfere with the assembly and structure of cellular lipid membranes. In some cases, this process can be catalyzed by a class of enzymes known as lipoxygenases. While the physiological functions of lipoxygenases are numerous, they are perhaps best known for their role in generating leukotrienes, which are carbon-rich lipid signaling molecules that play important roles in inflammatory signaling, such as regulating the release of histamine and activating other immune responses (Haeggstrom and Funk, 2011). Recently, several research groups discovered a central role for these enzymes in promoting ferroptosis; for example, cells became resistant to this form of cell death as a result of lipoxygenase gene knockdown (Friedmann Angeli et al., 2014; Kagan et al., 2017; Yang et al., 2016).

However, an important question regarding lipoxygenases functioning in ferroptosis remained unanswered until now. Lipoxygenases are known to act on free polyunsaturated fatty acids, not on polyunsaturated fatty acids that have been incorporated into more complex membrane phospholipids. Nonetheless, it has been found that the peroxidation in ferroptosis occurs directly on membrane phospholipids. How lipid peroxidation occurs on phospholipids through the action of lipoxygenases during ferroptosis has remained a mystery.

Moreover, out of many different types of membrane phospholipids, one in particular—phosphatidylethanolamine (PE) —is predominantly peroxidized during ferroptosis (Kagan et al., 2017). How this specific phospholipid species is selected for peroxidation by lipoxygenases has been another key question. Once peroxidized PE molecules are formed, they act as death signals that navigate cells toward ferroptosis and subsequent cell death. Therefore, unraveling the puzzle of how they are generated is crucial in understanding one of the pivotal mechanisms of this form of cell death and the strategies for controlling it. This is particularly important because ferroptotic cell death has been implicated in several human diseases, such as acute kidney injury (Linkermann et al., 2014), other degenerative disorders (Li et al., 2017), and several forms of cancer (Yang and Stockwell, 2016). Therefore, better insight into the mechanisms driving this form of cell death may provide the key to the development of a new class of therapeutics.

Using an interdisciplinary approach combining biochemical methods, computational modeling, and fluorescence microscopy, Wenzel et al. (2017, this issue of *Cell*) found that a protein previously studied only in the context of protein kinase cascades, PEBP1, can unexpectedly associate with lipoxygenases such as 15LO1 and 15LO2 to change their substrate specificity, allowing them to directly react with the polyunsaturated tails of phospholipids already incorporated into cell membranes. Like the Transformer toys that are robots in disguise, these lipoxygenases are PE-phospholipid-specific enzymes in disguise. The binding of PEBP1 allows these lipoxygenases to acquire specificity for the PE phospholipids that are key to ferroptosis (Figure 1).

This discovery was facilitated using global redox phospholipidomics, with which the authors evaluated the phospholipid composition of cells by comparing the overall abundance of oxidized PE relative to other oxidized phospholipid

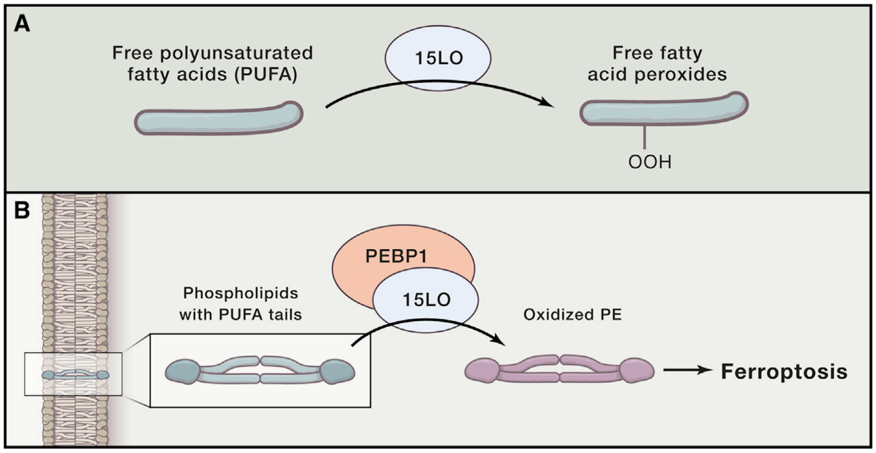

Figure 1. PEBP1 Associates with Lipoxygenases and Allows Them to Generate a Specific Lipid Peroxide that Promotes Ferroptosis

(A) The unbound enzyme acts on free fatty acids.

(B) Bound to PEBP1, lipoxygenases acquire the ability to convert membrane phosphatidylethanolamine (PE) to its oxidized form, leading to ferroptotic cell death.

species in cells either with or without PEBP1-15LO complexes. These findings solved two mysteries in one fell swoop and illuminated a new key regulator of ferroptosis in a major advance for this nascent field.

Wenzel et al. (2017) further highlighted the relevance of this work to human health and disease by identifying evidence of PEBP1-15LO-complex-driven lipid peroxidation in the context of asthma, acute kidney injury, and traumatic brain injury, demonstrating that these disease states are at least partially caused by PEBP1-15LO activity and resulting ferroptotic cell death.

This discovery opens the door for further efforts to examine the suitability of the PEBP1-15LO complex as a drug target. For example, small molecules disrupting either 15-lipoxygenases, PEBP1, or the interaction between the two proteins could act as inhibitors of PE peroxidation and ferroptotic cell death, which in turn can potentially be used clinically to treat patients with numerous degenerative diseases.

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