Plasmalogen Structure and Function in Health and Disease

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Plasmalogens constitute a distinct subclass of glycerophospholipids defined by the presence of a vinyl ether bond at the sn-1 position of the glycerol backbone, replacing the ester linkage typical of most phospholipids. Together with an ester-linked fatty acid at the sn-2 position and a polar head group, most commonly ethanolamine, this unique architecture confers specialized biophysical and chemical properties. The vinyl ether linkage is particularly susceptible to oxidative attack, allowing plasmalogens to function as preferential scavengers of reactive oxygen species and thereby protect other membrane lipids from oxidative damage. In addition, their enrichment in polyunsaturated fatty acids at the sn-2 position position places plasmalogens as important reservoirs for bioactive lipid mediators and enables them to influence membrane microdomain organization, curvature stress, and lateral mobility. Through these structural features, plasmalogens contribute to key cellular processes, including membrane fusion, vesicle formation, neurotransmitter release, and innate immune signaling.

Because the initial steps of plasmalogen biosynthesis occur in peroxisomes, defects in peroxisomal biogenesis, such as those seen in Zellweger spectrum disorders and rhizomelic chondrodysplasia punctata, result in profound plasmalogen deficiency, contributing to the severe neurological, skeletal, and metabolic abnormalities characteristic of these conditions. Beyond classical peroxisomal disorders, reduced plasmalogen levels have also been documented in more prevalent neurological and metabolic diseases, including Alzheimer disease, Parkinson disease, multiple sclerosis, type 2 diabetes, and obesity. These observations suggest that disrupted plasmalogen homeostasis may represent a common consequence of cellular stress, membrane dysfunction, or altered lipid remodeling pathways.

In response to these widespread deficiencies, plasmalogen replacement therapy has emerged as a potential therapeutic strategy aimed at restoring depleted plasmalogen pools. This approach involves supplementation with plasmalogens or their metabolic precursors to reconstitute membrane composition, normalize lipid signaling, and enhance resistance to oxidative stress. While this strategy is being actively explored in both rare peroxisomal disorders and more common neurodegenerative or metabolic diseases, its clinical efficacy remains under active investigation.

Short lecture presented on Thursday January 22, 2026 at the CSIC Network on Rare Diseases, RER-CSIC, Madrid (Virtual).

Slide 12. Phospholipid Composition of Plasmalogen-Deficient Cells.

Slide 13. Eicosanoid Production by Plasmalogen-deficient Cells.

Slide 14. Phagocytosis in Plasmalogen-deficient Macrophages.

Slide 15. Phagocytosis in Plasmalogen-deficient Macrophages ("Replacement Therapy").

Slide 16. Plasmalogens in Innate Immune Cells.

Slide 17. Acknowledgments.

As requested, a comprehensive list of significant papers from our laboratory follows.

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