Understanding the Biological Importance of Ether-Linked Lipids in Membrane and Organismal Aging

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Plasmalogens are a specialized class of phospholipids that are prevalent in the membranes of eukaryotes but whose biological function is not yet understood. The key structural difference in plasmalogens is the presence of a vinyl-ether bond as opposed to the ester bond used to link fatty acids in typical phospholipids. These ether-linked species are highly abundant in mammals, particularly in the brain where they comprise more than 40% of the phospholipids. In addition to having an association with many disease states including peroxisomal biogenesis disorders, Alzheimer's disease, and obesity, these lipids have been show to decrease with age as well as alter the properties of the membrane. Therefore, a characterization of these ether-linked lipids will allow us to better understand membrane structure in old animals as well as the biological importance of this lipid species in aging.

The presence of an ether bond in plasmalogens has been proposed to protect the membrane from damage by consuming reactive oxygen species and preventing damage to other cellular components. In fact, plasmalogen-deficient cells are highly susceptible to oxidative stress, and because plasmalogen abundance decreases with age, we hypothesize that these ether-linked lipids play an important role in stress response and organismal aging. However, explicit tests of the impact of plasmalogens on membrane maintenance and aging have not been completed, largely because of a lack of an adequate animal model for high-throughput studies. Recently, we have established biochemical tools that allow us to map membrane composition and dynamics in the model organism, *Caenorhabditis elegans.* Using these HPLC/MS-based methods, we have found that plasmalogens make up approximately 20% of the total phospholipid population in the nematode, similar to their abundance in humans. Additionally, the biosynthesis pathway for plasmalogens is conserved in the nematode, positioning us to begin to interrogate the biological importance of this unique lipid species *in vivo*. Indeed, in support of our hypothesis, we find that depletion of plasmalogens via RNAi results in animals that are sensitive to oxidative stress and have a shortened lifespan. Here, we seek to quantify how plasmalogen dynamics change with age and to establish the nematode as a model for defining a role for plasmalogens in aging.