Fat-regulating Pah1 PA Phosphatase: Roles and Regulation in Lipid Homeostasis

George M. Carman

Rutgers University, Rutgers Center for Lipid Research, New Brunswick, New Jersey U.S.A.
gcarman@rutgers.edu

Phosphatidic acid (PA) phosphatase is an evolutionarily conserved enzyme that plays a major role in lipid homeostasis by controlling the cellular levels of its substrate, PA, and its product, diacylglycerol. These lipids are essential intermediates for the synthesis of triacylglycerol and membrane phospholipids; they also function in lipid signaling, vesicular trafficking, lipid droplet formation, and phospholipid synthesis gene expression. The importance of PA phosphatase to lipid homeostasis and cell physiology is exemplified in yeast, mice, and humans by a plethora of cellular defects and lipid-based diseases associated with loss or overexpression of the enzyme activity. In this lecture, the focus is on the mode of action and regulation of PA phosphatase in *Saccharomyces cerevisiae*, the organism from which the *PAH1* gene/Pah1 enzyme was discovered. Pah1 translocates from the cytosol (inactive form) to the nuclear/endoplasmic reticulum membrane (active form) through phosphorylation and dephosphorylation. Pah1 phosphorylation, which favors a cytosolic location, is mediated by multiple protein kinases (e.g., protein kinases A and C, cyclin dependent protein kinases Pho85 and Cdc28, and casein kinases I and II) whereas dephosphorylation, which favors a membrane location, is catalyzed on the membrane surface by the Nem1-Spo7 protein phosphatase complex. Posttranslational modifications of Pah1 also affect its catalytic activity and susceptibility to degradation by the proteasome. Nem1 and Spo7 are also subject to phosphorylations by protein kinases A and C. Overall, the phosphorylations of Pah1/Nem1-Spo7 phosphatase components promote phospholipid synthesis and attenuate the synthesis of triacylglycerol. (Supported by National Institutes of Health grants GM028140 and GM050679).