

# Synthesis of membrane phospholipids influences redox metabolism to promote cell growth and survival

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Phospholipids are major components of cellular membranes that compartmentalize metabolic pathways. Alteration in membrane phospholipid composition has been linked to a variety of diseases, including cancer, liver diseases, cardiovascular diseases, and neurodegenerative disorders. However, mechanisms underlying the role of phospholipids in pathogenesis are poorly understood. Our recent studies demonstrate that methylation of phosphatidylethanolamine (PE) for the synthesis of phosphatidylcholine is the major consumer of the biological methyl donor S-adenosylmethionine (SAM) and thus acts as a methyl sink to facilitate SAM turnover for the synthesis of cysteine and glutathione<sup>1</sup>. These findings revealed an unforeseen function of phospholipid synthesis in controlling cellular redox balance. Under nutrient starvation or during the oxidative phase of yeast metabolic cycle, I found that the synthesis of phospholipids is transcriptionally activated by shuttling the transcriptional repressor Opi1 out of the nucleus. It is likely that phospholipid synthesis that influences cellular metabolism might be employed as a cellular strategy to defend oxidative stress. Indeed, the *opi1Δ* mutant exhibits increased cellular levels of a crucial cofactor involved in redox reactions, nicotinamide adenine dinucleotide (NAD<sup>+</sup>), and an antioxidant, glutathione, as well as elevated resistance to oxidative stress induced by hydrogen peroxide. Overall, our findings suggest that phospholipid biosynthesis has an underappreciated role in redox metabolism to maintain physiological fitness, which can be pathological bases for many diseases where phospholipid synthesis is perturbed.

1. Ye C, Sutter BM, Wang Y, Kuang Z, Tu BP. A Metabolic Function for Phospholipid and Histone Methylation. *Molecular cell*. 2017;66(2):180-193 e188.