Regulation and function of the PC deacylation-reacylation remodeling pathway (PC-DRP)

Sanket Anaokar[1], Alexiy Nikiforov[1], William King[1], Anton I. P. M. de Kroon[2] and Jana Patton-Vogt[1*]

[1]Duquesne University, Department of Biological Sciences, Pittsburgh, PA, USA
[2]Utrecht University, Institute of Biomembranes, Utrecht, The Netherlands

***Corresponding author:** pattonvogt@duq.edu

Phosphatidylcholine (PC), an abundant phospholipid in eukaryotic cellular membranes, is synthesized primarily by two well defined metabolic pathways in *Saccharomyces cerevisiae*. We recently characterized a novel glycerophosphocholine (GPC) acyltransferase, encoded by *GPC1*, that provides a third route for PC biosynthesis by catalyzing a step in the newly defined PC deacylation-reacylation remodeling pathway (PC-DRP) [1,2]. PC-DRP begins with the complete deacylation of PC by phospholipases of the B type, yielding GPC. Gpc1 acylates GPC to form lysophosphatidylcholine (LPC). LPC can subsequently be converted to PC by Ale1. Importantly, we report that Gpc1 activity, acting in the context of PC-DRP, affects the PC species profile. Loss of Gpc1 decreased the levels of mono-unsaturated PC species and increased those of di-unsaturated PC species, while Gpc1 overexpression had the opposite effects. Examination of *GPC1* message abundance indicated that *GPC1* expression is impacted by perturbation of other lipid biosynthetic pathways and as a function of inositol availability. Inositol starvation, which impacts several phospholipid biosynthetic genes and activates the Unfolded Protein Response (UPR), up-regulated *GPC1* expression at the mRNA and protein levels and, as expected, increased the levels of monounsaturated PC species. In addition, loss of *GPC1* resulted in decreased stationary phase viability in inositol-free media. Ongoing studies include an examination of other factors that might impact *GPC1* expression, and PC-DRP activity, including temperature alterations and drugs and mutations that perturb membrane function. Finally, while Gpc1 displays no homology to known acyltransferases, it has homologs in animals, plants and fungi. We have created a diploid knockout of the Gpc1 homolog (orf19.998) in *Candida albicans* and are in the process of examining the role of *ca*Gpc1 in PC metabolism in this pathogenic organism.

1. Glab B., Beganovic M., Anaokar S., Hao M. S., Rasmusson A. G., Patton-Vogt J., Banas A., Stymne S., and Lager I. (2016) Cloning of Glycerophosphocholine Acyltransferase (GPCAT) from Fungi and Plants. *J Biol Chem* **291**: 25066

2. Anaokar S., Kodali R., Jonik B., Renne M.F., Brouwers J.F.H.M., Lager I., de Kroon A.I.P.M., Patton-Vogt J. (2019) The glycerophosphocholine acyltransferase Gpc1 is part of a phosphatidylcholine (PC)-remodeling pathway that alters PC species in yeast. *J Biol Chem* **294**: 1189