Model-guided analysis of the role of OPI1 and RPD3 transcription factors in hexadecanol overproduction strategies

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Project goals:

To explore the effect of transcription factor knockouts on lipid metabolism in the context of fatty alcohol overproduction to design beneficial strain engineering strategies.

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Abstract:

Obtaining a complete understanding of the lipid metabolic network has wide reaching implications in biofuel and biochemical production, one of them being fatty alcohols, where engineering the lipid network can produce higher yields of target biochemical. However, the strong regulation of lipid metabolism makes it difficult to engineer strategies for overproduction. Various studies regarding hexadecanol overproduction in yeast that explored the knockouts of transcription factors OPI1 and RPD3 report seemingly contrasting results about the effects of these knockouts on hexadecanol yield[1,2]. We employed a mathematical model-guided approach to study the flux control coefficients within lipid metabolism under different the transcription factor (TF) knockouts of OPI1 and RPD3. Our model-based analysis shows that knockout of these transcription factors results in the loss of a dynamic regulatory feature originally in place to conserve carbon flux in membrane lipid biosynthesis. As a result, upstream overproduction strategies coupled with the TF knockouts, as employed in the studies, result in an uncontrolled amount of flux being channeled towards membrane lipid biosynthesis, reducing the yield of fatty acid-derived chemicals. Our analysis demonstrates that mitigation strategies, such as downregulation of membrane biosynthesis, when applied in tandem with TF knockouts can be a useful method to harness the full benefit of these knockouts for overproduction of fatty acid-derived biochemicals such as fatty alcohols.

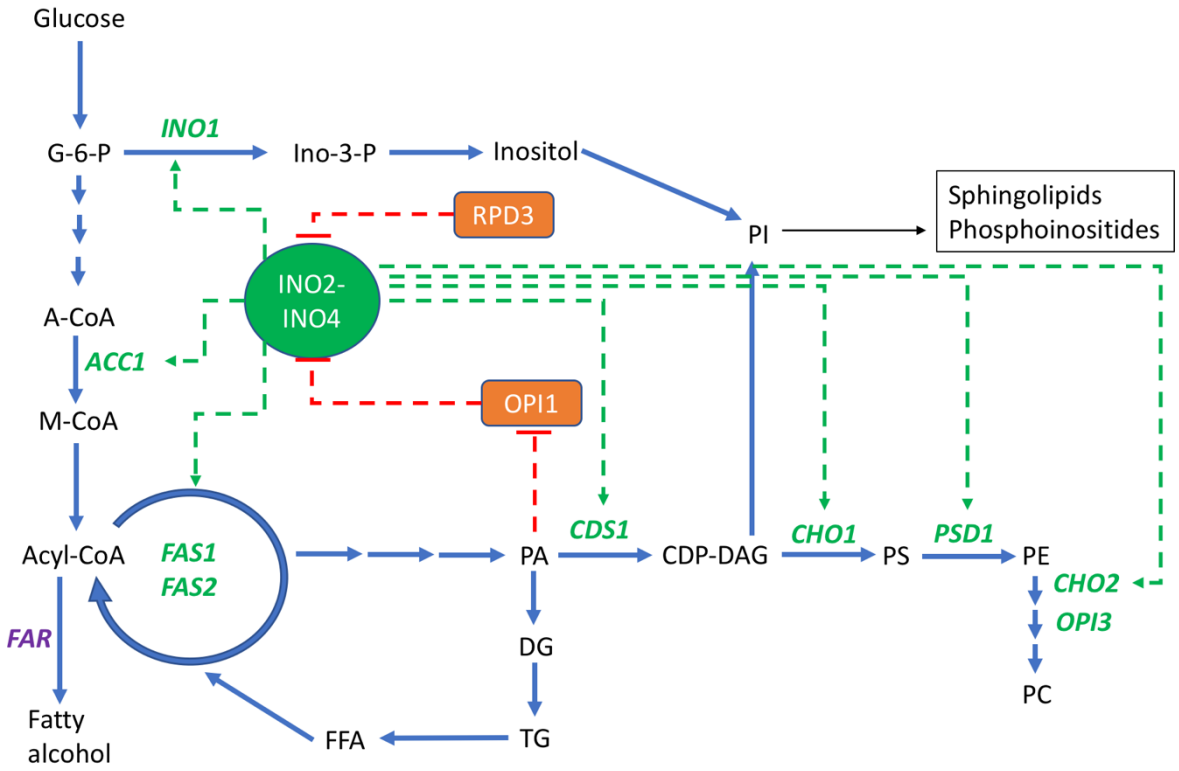

Figure 1: Map of the lipid metabolic network displaying the role of transcription factors OPI1 and RPD3 on the various biosynthetic genes in fatty acid chain elongation and membrane lipid biosynthesis reactions.

References:

1. d'Espaux L, Ghosh A, Runguphan W, et al. Engineering high-level production of fatty alcohols by Saccharomyces cerevisiae from lignocellulosic feedstocks. *Metab Eng*. 2017;42(April):115-125. doi:10.1016/j.ymben.2017.06.004.
2. Feng X, Lian J, Zhao H. Metabolic engineering of Saccharomyces cerevisiae to improve 1-hexadecanol production. *Metab Eng*. 2015;27:10-19. doi:10.1016/j.ymben.2014.10.001.

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