Regulating the metabolic flow of fatty acids – a greasy line between life and death

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The lipidome of a yeast cell is composed of more than 250 lipid molecular species [1]. It remains an open question how de novo synthesized or exogenously supplemented fatty acids are specifically channeled into the various lipid classes, to establish a defined acyl-chain profile in membrane phospholipids that is required to maintain proper membrane function. Using stable isotope labeling with ^{13}C-glucose and mass-spectrometry we have developed a method to trace the fate of de novo-synthesized fatty acids into various lipid classes in growing yeast cells. The dynamic appearance of intermediate lipid species that harbor a combination of pre-existing and newly synthesized acyl chains follows distinct differences between lipid classes, challenging the general view of common precursor-product relationships. The potentially toxic consequences of a derailed fatty acid flux are evident from studies on acetyl-CoA carboxylase (Acc1), the initial and rate-limiting enzyme of fatty acid synthesis: Acc1 activity is essential to sustain oleic acid induced lipotoxicity, presumably to support fatty acid elongation that may be required to counteract detrimental oleic acid-induced alterations in membrane phospholipids. Increased oleic acid synthesis also exacerbates the pathogenesis of neurodegenerative disease [2], underscoring the importance of a balanced fatty acid composition in membrane lipids across species.

[1] Ejsing C.S., Sampaio J.L., Surendranath V., Duchoslav E., Ekroos K., Klemm R.W., Simons K., Shevchenko A. (2009) Global analysis of the yeast lipidome by quantitative shotgun mass spectrometry. *Proc Natl Acad Sci U S A*. 2009 Feb 17;106(7):2136-41. doi:

[2] Fanning S., et al. (2019) Lipidomic Analysis of α-Synuclein Neurotoxicity Identifies Stearoyl CoA Desaturase as a Target for Parkinson Treatment. *Mol Cell in press* pii: S1097-2765(18)30998-5. doi: 10.1016/j.molcel.2018.11.028. [Epub ahead of print]