Fatty-acid induced lipotoxicity in yeast operates through distinct mechanisms

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Triglycerides (TG) and phospholipids share common precursors, i.e. phosphatidic acid and diglycerides in the endoplasmic reticulum. In addition to providing a biophysically rather inert storage pool for fatty acids, TG synthesis plays an important role to buffer excess intracellular FA. Inability to incorporate exogenous oleic acid (OA) into TG in a mutant lacking the required acyltransferases results in dysregulation of lipid synthesis, massive proliferation of intracellular membranes and, ultimately, cell death. The unfolded protein response is highly upregulated and caboxypeptidase Y trafficking from the endoplasmic reticulum to the vacuole is severly impaired, upon exposure of these mutants to OA. FA-induced toxicity is specific to oleate and much less pronounced with palmitoleate, and not detectable with C16:0 and C18:0 saturated fatty acids. Such fatty acids, however, become highly toxic in a mutant lacking the Δ9-fatty acid desaturase, suggesting a pivotal role of FA desaturation for establishing a balanced ratio of saturated to unsaturated fatty acids, in membrane lipids. The importance of a tightly controlled flux of fatty acids is also evident from recent findings that demonstrate the importance of TG breakdown in controlling cell cycle progression. Potential executors of fatty acid toxicity will be discussed.

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