Fig. 8. Partial x-ray structure of cyt *c* illustrates the proximity of a candidate Tyr residue involved in peroxidase activation by CL. The upper panel shows the positions of the cyt *c* tyrosines (Y48, Y67, Y74, and Y94). Y67 is located in the closest proximity to the heme-iron (lower panel). Y67 acts as a donor of an electron for a porphyrin cation-radical generated as a reactive peroxidase intermediate. In the oxygenase half-reaction of the cyt *c* /CL peroxidase complex, Y67 radical acts as an electron acceptor from oxidizable CL.

Fig. 9. Externalization of CLs to the mitochondrial surface occurs during mitophagy whereas oxidation of CLs is necessary for the execution of apoptosis. In mitophagy CL is translocated by NDPK-D which binds to both the IMM and OMM, facilitating CL movement to the OM where it can bind and activate LC3-II which initiates autophagosome formation leading to mitophagy. In the figure the CL is colored blue, other lipids are brown and oxidized CL is colored red. In apoptosis CL forms a complex with cyt *c* converting it to a peroxidase, H_2O_2 is used as the oxidant of CL and the net result is the release of cyt *c* through the OMM and into the cytoplasm, as well as externalization of CL to the OMM resulting in apoptotic death.

Fig. 10. Intra- and Extracellular CLs are involved in the regulation of the immune responses. The left panel shows that mitochondrial externalized CLs are involved in the activation of NLRP3 inflammasomes, which in turn activates caspase-1; The middle panel shows that LPS (which contains lipid A) cross-links two TLR4-MD2 complexes to activate an inflammatory response. However, CL only binds to MD2, but cannot cross-links TLR4's; In the right panel, mitochondria with externalized CL have characteristics of bacteria. CD1d protein is able to bind and present mammalian or bacterial CL to CL-responsive $\gamma\delta$ T cells that exist in the spleen and liver of healthy mice. In response to CL these cells proliferate in a dose-dependent manner, and secrete the cytokines IFN-γ and RANTES.

Supplemental Table 1 Extraordinary CL variability detected in the heart of a Northern Red Snapper (*Lutjanus campechanus*) contrasting with bovine heart CL. The identity of detected CL species are listed under molecular species A)153 in fish heart, B) 22 in bovine heart. This does not include regioisomers). CN is the carbon number of all 4 acyl chains, DB is the number of double bonds on all 4 acyl chains, m/z is mass/charge of the detected ions.

Supplemental Figure 1 Workflow scheme for a typical lipidomic study. Lipidomics can be applied to variety of samples including tissues, cells, serum, etc. Lipids are extracted with organic solvents, dried with nitrogen and then re-dissolved in a small volume. MS analysis is done by two methods, direct infusion or LC-MS. High resolution MS such as Orbitrap™ is frequently used to identify the complex lipid mixtures. Fragmentation analysis by MS/MS is used for structural identification. The data files acquired from the MS can be analyzed and quantified using software programs such as Lipidsearch™, SIEVE™ and Xcalibur™.