The long and winding road towards autophagy

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Our interest in the changes induced by several agents on the architecture of lipid bilayers started when, as a PhD student, I observed the 'fusion', i.e. lysis and reassembly, of small unilamellar vesicles in the presence of detergents. Then followed our model of (true) membrane fusion promoted by phospholipase C, and the involvement of diacylglycerol-driven non-lamellar phases in the fusion mechanism. In the last decade our interest has focused on ceramide, a molecule deceptively similar in structure to diacylglycerol, although endowed with vastly different properties. More recently we have applied our experience to the study of the role of lipids in the growth of the autophagosome, a cellular structure occurring at the early stages of autophagy. We have been able to describe how lipid geometry and bilayer curvature modulate autophagosomal elongation mediated by proteins of the Atg8 family. We have also quantified the binding of cardiolipin to LC3 and other Atg8 homologues, and described the negative effect of cardiolipin oxidation in these initial steps of autophagy. Ceramides are also important modulators of autophagy. In collaboration with G. Velasco (UCM, Madrid) we have demonstrated that the dihydroceramide/ceramide ratio mediates the cytotoxic autophagy of cancer cells via autolysosome destabilization. Our current studies include the interaction with Atg3 proteins with lipid membranes, and the lipidation reaction occurring between Atg8 and phospholipids.