The effect of oxidation on the structure of a model lipid membrane

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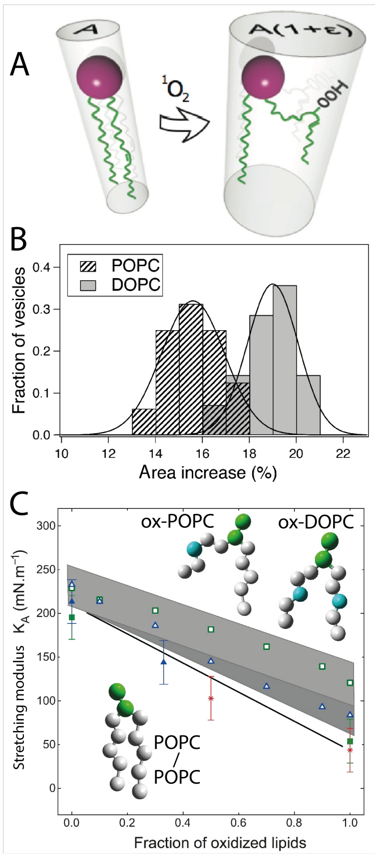
Oxidation is a natural outcome of life under oxygen. Oxidation targets are numerous in leaving organisms, amongst which are phospholipids, that build the passive matrix of cell membranes. Although a controlled amount of oxidized lipids is required for proper cell signaling, cell maturation and differentiation, and for cell apoptosis, the products of lipid oxidation, if uncontrolled, can have a deleterious effect on the functioning of the cell.



We have shown that phospholipid hydroperoxidation greatly modifies the average area per lipid (fig.A & B), as well as the mechanical stiffness of the membrane (fig. C)[1]. We have also shown that oxidation induces lipid phase separation in membranes made of lipid mixtures[2], and is also suspected to greatly modify the membrane permeability to different kinds of molecules[3], potentially altering the delicate balance required in healthy cells.

The present project aims at clarifying the influence of lipid oxidation on the structure of various model lipid membranes. Central to this project are the two following axes:

1. Pore formation: motivated by our preliminary findings[4] on the formation of pores in lipid bilayers containing hydroperoxidized lipids, the work will consist in exploring the dynamics of pore opening and closing when an electric potential is applied in the direction normal to the membrane (electroporation geometry); complementary experiments will concern the measurement of membrane permeability under an optical microscope.

2. Phase separation: the work will further explore the mechanisms of lateral lipid segregation induced by *in situ* oxidation of an initially homogeneously distributed membrane containing two or three kinds of lipid, including cholesterol, as a function of the lipid composition. Relation between phase separation and permeability will finally be established, for different types of bio-molecules (*e.g.* peptides) or nanoparticles.

Figure: A: Scheme of the lipid area increase following hydroperoxidation by reaction with a singlet oxygen $^1O_2$. **B:** Area increase as measured with POPC and DOPC bilayers. **C:** Membrane stiffness of DOPC and POPC bilayers as a function of oxidation level (experiments and numerical simulation).

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[1] G Weber *et al.*; “Lipid oxidation induces structural changes in biomimetic membranes“; *Soft Matter* (2014), **10**(24), 4241-4247.

[2] CK Haluska *et al.*; “Photo-activated phase separation in giant vesicles made from different lipid mixtures“; *Biochimica & Biophysica Acta-Biomembranes* (2012), **1818**(3), 666-672.

[3] IOL Bacellar *et al.*; “Permeability of DOPC bilayers under photoinduced oxidation: Sensitivity to photosensitizer“; *Biochimica & Biophysica Acta - Biomembranes* (2018), **1860**(11), 2366-2373.

[4] Biophysical Society, 61st Annual Meeting, February 11-15, 2017, New Orleans; “Voltage-Dependent Formation of Stable, Ion Conductive Pores in Suspended Lipid Bilayers from Oxidized Lipids“; AP Schroder *et al.*