CQB Day

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"Healthy Life": interaction of polyphenols with lipid bilayers and their effects in human cells

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This work concerns the transversal project of the CQB thematic line: "Healthy Life: Molecular Interventions and Regulation Mechanisms". Biologically active plant phytochemicals have a broad range of pharmacological effects including anticarcinogenic, antimicrobial, antioxidant, and anti-inflammatory activity. [1] Notwithstanding the possibility of having a specific target, phytochemicals must interact and permeate through cell membranes in the body. Indeed, it was suggested that those molecules insert into the membranes and thereby may have a promiscuous activity by changing structural properties of lipid bilayers. [2] Some well-known phenolic acids such as caffeic (CA), rosmarinic (RA) and chlorogenic (CGA) acids, whose identification in plant extracts has been achieved by CQB research groups, were selected to be addressed in first place. All the phenolic acids studied have low lipophilicity and among them, RA was the only one with a partition to biological membrane models measurable by fluorescence spectroscopy, as opposed to CA and CGA. Cyclic voltammetry measurements using an electrode modified with a supported lipid bilayer, also indicated a higher affinity of RA to lipid membranes. In addition, oxidation/reduction of the phenolic acids displayed higher reversibility in the lipid milieu than in the aqueous bulk. Indeed, the reduced form of phenolic acids was unstable in aqueous solution. In particular, in DMEM/F-12 cell culture media, a colour change observed after incubation with each compound could be reverted by the addition of a reducing agent. The higher reversibility of phenolic acids oxidation/reduction, once they were inserted in the lipid membrane, may contribute to the stability of the compounds and prevent the formation of degradation products. Molecular dynamics (MD) simulations are being performed to probe the location and orientation of these and other selected compounds in lipid bilayers. The influence of the phenolic acids in the cytoskeleton

organization, both actin filaments and microtubules, of a human retinal pigment epithelial cell line (RPE1) was also investigated. All compounds induced concentration and time dependent effects, translated in structural alterations mainly at the cell periphery, and also in the perturbation of cell division. Moreover, it was not evident that these compounds induce apoptosis under the conditions tested. RA seemed to induce evident effects at earlier times and at lower concentrations, as compared to CA and CGA. This higher sensibility of RPE1 cells to RA correlates with the higher affinity of this compound to the lipid bilayer.

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References

[1] A. Stefanson and M. Bakovic, Nutrients 6 (2014) 3777-3801.

[2] H. I. Ingólfsson, P. Thakur, K. F. Herold, E. A. Hobart, N. B. Ramsey, X. Periole, D. H. de Jong, M. Zwama, D. Yilmaz, K. Hall, T. Maretzky, H. C. Hemmings, C. Blobel, S. J. Marrink, A. Koçer, J. T. Sack and O. S. Andersen, ACS Chem. Biol. 9 (2014) 1788-1798.