Peridinin is a Potent Probe for the Role of Bilayer Lipid Peroxidation in Pathogenesis

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Deficiencies of antilipoperoxidant proteins have been associated with many human diseases, suggesting that lipid peroxidation may contribute broadly to pathogenesis. However, experimental evidence for such a role remains limited in most cases, as does the clinical impact that has been achieved by targeting inhibition of this process. The absence of chemical antilipoperoxidants that are potent and selective has made it challenging to overcome these important limitations.

Enabled by the efficient and flexible building block-based synthesis of a series of polyene natural products found in microorganisms that thrive in environments of extreme oxidative stress, here we report that the structurally atypical carotenoid peridinin is an exceptionally potent inhibitor of bilayer lipid peroxidation. Peridinin is effective in model liposomes at concentrations an order of magnitude lower than the gold standard antilipoperoxidants astaxanthin and α-tocopherol. Rationalizing its potency, solid state NMR experiments with a synthesized isotopologue revealed that peridinin uniquely resides completely inside the hydrophobic core of POPC lipid bilayers. Employing this potent chemical probe in primary human endothelial cells yielded advanced evidence for the role of bilayer lipid peroxidation in promoting monocyte-endothelial adhesion, a key step in the pathogenesis of atherosclerosis. Thus, peridinin has potential to clarify the still largely enigmatic role(s) played by lipid peroxidation in a wide range of human diseases and possibly serve as a starting point for the development of small molecule therapeutics that target this process.