(CL) oxidation. It is experimentally established that under oxidative stress cytochrome c, an electron carrier in the mitochondrial respiratory chain, exerts peroxidase activity and oxidizes CL.[146] Addition of H_2O_2 + cytochrome c to CL-containing liposomes induced membrane permeabilization for molecules up to 3 kDa. The requirement of unsaturated CL for the permeabilization suggests that cardiolipin oxidation plays a critical role in the formation of membrane defects induced by H_2O_2 + cytochrome c.[147] Besides membrane permeabilization, cardiolipin oxidation leads to respiratory chain enzymes inactivation, cellular dysfunction and eventually apoptotic cell death.[148] Micro- and submicro-molar concentrations of mitochondrially targeted rechargeable antioxidants fully protected CL from peroxidation in liposomes.[149] Previously, a similar effect was shown in isolated mitochondria.[44]

9.6 Conclusion

Mitochondria-targeted rechargeable antioxidants represent a novel class of prospective anti-aging drug candidates. The important advantages of these compounds include: (1) extremely low effective concentrations due to selective accumulation in mitochondria (over 10,000-fold concentration); (2) ability to quench excess mitochondrial reactive oxygen species and thereby prevent oxidative stress and pathologies related to it, including chronic inflammation; (3) ability to regenerate the antioxidant (reduced) form of their quinone residue by reduction of the oxidized form by the mitochondrial respiratory chain; and (4) to decrease the $\Delta\psi$ and thereby reduce the mROS production (mild uncoupling).

The experiments in animal models suggest that mitochondria-targeted rechargeable antioxidants might be a tool to increase health span and lifespan in humans by lowering chronic inflammation and quenching oxidative damage during acute oxidative stress.

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