

TARGETING BIOACTIVE MOLECULES TO MITOCHONDRIA

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Over the past few years myself and collaborators have developed antioxidants that selectively block mitochondrial oxidative damage. Among these molecules are derivatives of the natural antioxidants ubiquinone and Vitamin E. The antioxidant efficacy of these molecules was increased considerably by targeting them to mitochondria, which are the major source of oxidative stress in mammalian cells. This was achieved by covalent attachment of the antioxidant to a lipophilic cation. Due to the large mitochondrial membrane potential, these cations accumulate several hundred fold within mitochondria, protecting them from oxidative damage far more effectively than untargeted antioxidants.

To see if this approach could be used to prevent mitochondrial oxidative damage in human diseases, we determined whether these compounds could be directed to mitochondria within mice. Non-toxic doses of mitochondrially targeted antioxidants could be fed to animals safely and led to the accumulation of intact antioxidant by mitochondria in the heart, skeletal muscle, liver and brain. The targeted version of ubiquinone (MitoQ) was protective against pathologies in animals. This molecule has since then gone through phase II trials as a potential therapeutic agent that may be associated with mitochondrial oxidative damage. I will report on progress towards this goal and also on the development of other related molecules which may also have potential as mitochondrial antioxidants and modifying agents.