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Future therapeutics: Drugs that stop free radicals at their source

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Go to any health food store and you're likely to see shelves crowded with antioxidants that promise to quell damage from free radicals, which are implicated in a myriad of human diseases and in the aging process itself. The problem is that antioxidants have failed to show benefits in several clinical trials and there is even some evidence they could be counterproductive.

Buck professor Martin Brand, PhD thinks that the current approaches to free radicals may fail because they apply a "sledgehammer" to a complex metabolic process that provides essential energy to our cells. "Rather than a sledgehammer that seeks to decrease the effects of free radicals, we've developed a scalpel that allows us to stop them from being produced in the first place," he said. The results of the research will be published online in *Cell Metabolism*.

Free radicals are produced in the mitochondria - the energy-converting organelles which are abundant in almost every type of human cell. Highly-reactive free radicals, which oxidize cell constituents (hence the use of antioxidants), are spun-off as a normal byproduct of cellular bioenergetics; it's a process that appears to go up when cells are stressed, something Brand says can occur with aging and disease.

A chain of electron transporters within the mitochondria is involved in the production of both free radicals and the chemical energy essential for life. The challenge has been to stop the free radicals without shutting down the cell's ability to release energy. Brand and his colleagues at the

Genomics Institute of the Novartis Research Foundation (GNF) did that by painstakingly screening 635,000 small molecules in GNF's academic library to single out the few that blocked free radical production at a specific site thought to be a major source of free radicals in the electron transport chain.

In this latest research, they demonstrated the potency and specificity of the successful molecules and tested their effects in cell culture, isolated hearts, and live models of disease. Brand says the compounds dramatically protected against reperfusion injury in a mouse heart model of ischemia. "Most of the lasting damage from heart attacks comes when blood flow is restored to the heart muscle," he said. "These compounds have great potential as therapeutic leads for drugs that could be given following a heart attack or after stents have been inserted to open blocked coronary blood vessels."

In addition, the molecules diminished oxidative damage in brain cells cultured in low levels of oxygen; they also diminished stem cell hyperplasia in the intestines of fruit flies. Brand says the study offers researchers a way to test the hypothesis that oxidative damage is specifically linked to disease. "For the first time we can test the effects of free radical damage in Alzheimer's, Parkinson's, cancer, type 2 diabetes, macular degeneration - you name it," he said. "It gives you a target, and a drug candidate to hit that target."

Given that the diseases Brand mentions are all associated with aging, he says the tool now gives researchers an opportunity to test the free radical theory of aging, which has dropped in popularity in the field, in large part because of the failure of antioxidant therapies. "We can start to answer questions that scientists have puzzled about for 50 years in terms of the specifics of oxidative damage," he said. "We now have a precise tool to find out if the theory is correct. We can go into a biological system, see specifically what free radicals do and take preliminary steps

to stop it."

More information: Martin D. Brand et al, Suppressors of Superoxide-H2O2 Production at Site IQ of Mitochondrial Complex I Protect against Stem Cell Hyperplasia and Ischemia-Reperfusion Injury, *Cell Metabolism* (2016). DOI: 10.1016/j.cmet.2016.08.012

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