Mouse study highlights potential therapeutic for one of the major chronic diseases of aging

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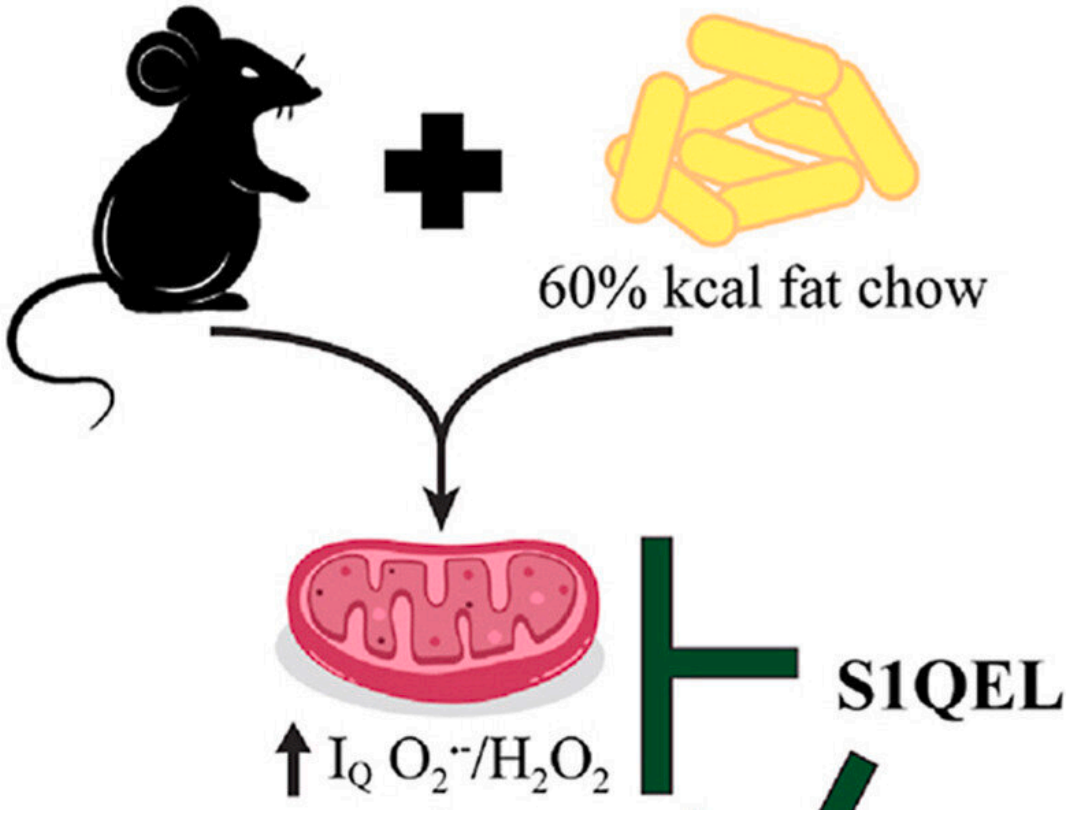

Graphical abstract. Credit: *Free Radical Biology and Medicine* (2023). DOI: 10.1016/j.freeradbiomed.2023.05.022

Mopping up free radicals with antioxidants was the rage in the 1970s;

people were taking large, sometimes massive doses of various general antioxidants, including vitamins and minerals, to try to remove harmful byproducts of energy metabolism. The method was supposed to blunt the effects of aging and stave off chronic disease.

The strategy didn't work, and in some cases, it caused harm because untargeted antioxidants also compromised beneficial cellular signaling pathways. Over time, this area of research went on the shelf as mitochondrial theories of disease and aging fell into disfavor.

But research at the Buck offers a new way to deal with free radicals: rather than mop them up, take a pill that selectively keeps them from being produced in the first place. Building on this work, collaborative research between the Buck and Calico Labs, recently published in *Free Radical Biology and Medicine* shows that specifically inhibiting free radical production at a particular mitochondrial site prevents and treats metabolic syndrome in mice, by preventing and reversing insulin resistance.

"We think that mitochondrial radical production drives many chronic diseases of aging, and that blocking the production of free radicals is a viable disease-treating and anti-aging intervention," said Martin Brand, Ph.D., Buck Professor Emeritus and senior investigator of the study.

"We've found a way to selectively keep problematic free radicals in check without compromising normal energy production in the mitochondria. These compounds act like a cork in a wine bottle. They plug a specific site so that it doesn't produce free radicals, without hindering the mitochondria's critical function of energy metabolism. We look forward to continuing this groundbreaking area of research."

The orally bioavailable compound that has been developed, S1QEL1.719 (a new "S1QEL"—Suppressor of site I_Q Electron Leak), was given both

prophylactically and therapeutically to mice fed a high-fat diet that causes metabolic syndrome. Treatment decreased fat accumulation, strongly protected against decreased glucose tolerance and prevented or reversed the increase in fasting insulin levels by protecting against the development of insulin resistance.

Acting on mitochondrial complex I highlights potential interventions for other conditions

S1QEL1s act on site I_Q in mitochondrial complex I. (The mitochondrial electron transport chain consists of four protein complexes integrated into the inner mitochondrial membrane. Together they carry out a multi-step process, oxidative phosphorylation, through which cells derive 90% of their energy.)

First author and Buck staff scientist Mark Watson, Ph.D., says current literature strongly implicates complex I in a number of different diseases, from metabolic syndrome to Alzheimer's, fatty liver disease, and noise-induced hearing loss, as well as the underlying aging process itself.

"S1QELs don't sequester oxidants or radicals. Rather, they specifically inhibit radical production at the I_Q site on complex I without interfering with other sites," Watson said. "So the normal redox signaling that we require in our cells will continue. S1QELs just modulate that one site. They are very clean, very specific, and do not disrupt mitochondrial functioning like inhibitors of mitochondria do."

Brand says the data shows that free radical production from complex I is an essential driver of insulin resistance and metabolic syndrome, a major disease of poor lifestyle choices and of aging. He says this feature is a strong reason to revisit the mitochondrial theory of aging. "These

compounds fine-tune mitochondrial production of free radicals," he said. "And it's really interesting; just inhibiting this specific site improves the whole redox environment and prevents metabolic disease, and that is amazing."

More information: Mark A. Watson et al, Suppression of superoxide/hydrogen peroxide production at mitochondrial site IQ decreases fat accumulation, improves glucose tolerance and normalizes fasting insulin concentration in mice fed a high-fat diet, *Free Radical Biology and Medicine* (2023). DOI: 10.1016/j.freeradbiomed.2023.05.022

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