Buck Institute Technology Summary

Modulating ROS Production at Specific Sites within Mitochondria

Buck Institute Case No. BI-407

Background

Aging and cellular damage have long been associated with the production of free radicals, or mitochondrial reactive oxygen species (ROS). This has spawned a highly successful antioxidant industry. However, antioxidants have varying and limited benefit as they act downstream to clean up ROS after production, rather than directly targeting the production of free radicals.

Work at the Buck and by others has shown that ROS production takes place at specific sites within mitochondria. Inherited mitochondrial diseases are often caused by mutations in, or dysfunction of, specific complexes. Furthermore, the pathophysiology of age-related diseases, from cancer and inflammation to diabetes and neurodegenerative disease has been linked to ROS production at specific sites. However the role of these sites and the ability to specifically target them therapeutically has been hampered by a lack of site-selective ROS inhibitors.

The Technology

Superoxide or H_2O_2 (ROS) production occurs when electrons escape from mitochondrial redox centers during normal oxidative phosphorylation as well as under pathological conditions. There are at least ten sites of ROS production within mitochondria (Fig. 1).

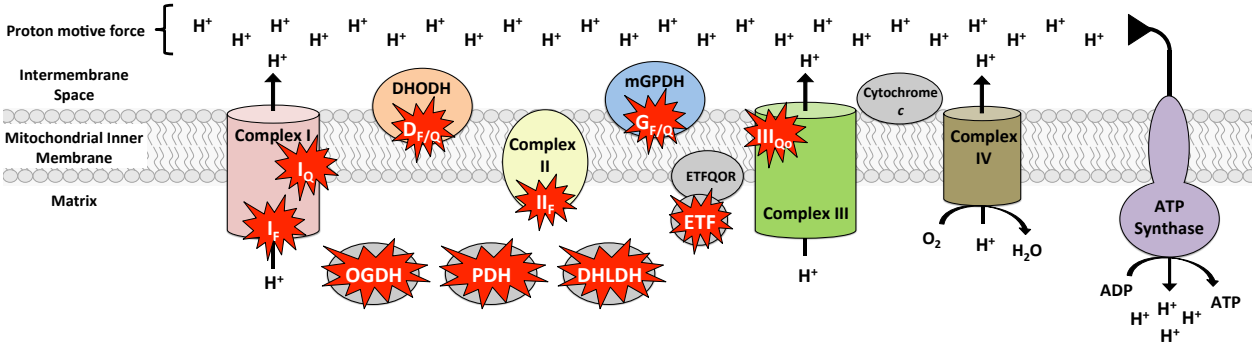

Figure 1 Mitochondrial ROS production has been identified at sites in complex I, II and III, in ubiquinone-linked oxidoreductases DHODH, mGPDH, and ETF/ETFQOR and within the matrix dehydrogenases OGDH, PDH, and DHLDH.

Researchers in the Brand lab at the Buck Institute have developed a panel of high-throughput assays capable of interrogating ROS production at each of these sites. These assays are designed to identify small molecules that inhibit ROS production selectively from each of these sites without compromising mitochondrial ATP production. Initial studies by Buck scientists have identified some inhibitors that specifically target defined sites of ROS production in isolated mitochondria (Fig. 2). The potential now exists for combining Buck's proprietary high-throughput assays with large compound libraries to identify more site-specific inhibitors.

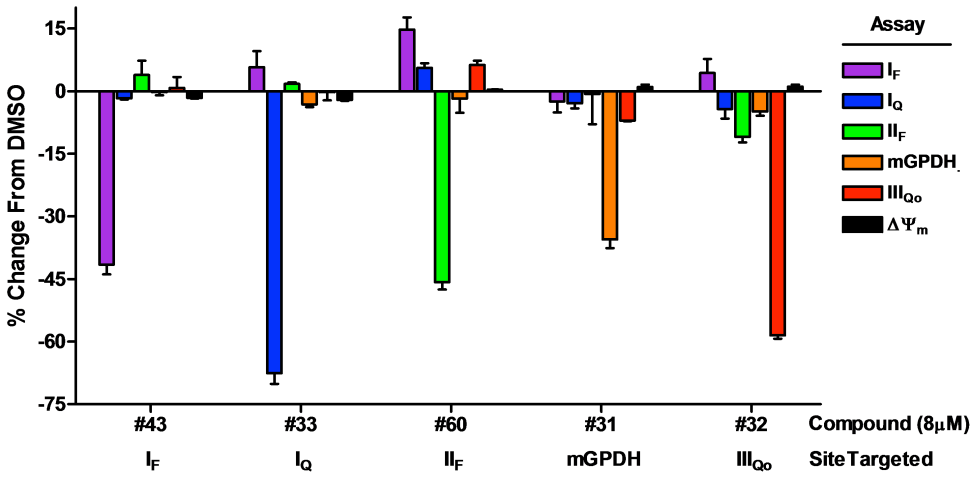

Figure 2. Site specificity and selectivity of leading ROS-inhibiting compounds.

Opportunity

It is becoming increasingly evident that mitochondrial function impacts not only rare diseases with specific mitochondrial complex defects, such as Leigh syndrome, but also common age-related diseases, including Type 2 diabetes and Parkinson's disease. Scientists at the Buck have developed compounds that target ROS production at specific mitochondrial sites, rather than antioxidants that simply scavenge free radicals after production. In addition to their utility as vital laboratory tools for interrogating mechanisms of oxidative stress, these novel mitochondrial modulators could potentially be used to treat rare mitochondrial genetic diseases and also have a broader reach in chronic metabolic and neurological diseases. The Buck seeks interested parties to partner this technology.

The Buck Institute is the only free-standing institute dedicated to aging and age-related research in the United States. We actively partner with industry to develop therapeutics, diagnostics or tools that make a difference. For more information on this or another technology or opportunity, please contact:

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