New molecule fights oxidative stress, may lead to therapies for cancer and Alzheimer's

October 1 2014, by Paige Blankenbuehler

Your body has an invisible enemy. One that it creates all on it's own called oxidative stress, long thought of as an underlying cause of some of humanity's most insidious diseases – cancer, Alzheimer's, Parkinson's Disease, cardiovascular disease and diabetes.

Every day, our bodies are exposed to harmful free radicals known as reactive oxygen species as a result of our environment.

But, when something goes wrong with this energy extraction process, cells become inundated with reactive oxygen compounds that cause oxidative stress. The search for drugs to treat the problem have been ongoing, and with a complicated problem like oxidative stress, it's all about finding the right combination.

Recent research by Bond Life Sciences Center investigator and Biochemistry Department Professor, Mark Hannink, provides a new approach for addressing the problem of oxidative stress and a starting point on developing a drug in pill form.

Mark Hannink and Kimberly Jasmer, a Ph.D. student in his lab, recently helped characterize a new molecule (called HPP-4382) that provides a novel way to treat oxidative stress. Their research was done in a partnership with High Point Pharmaceuticals, LLC, of North Carolina, where this new molecule was developed.

Oxidative stress can cause damage to the building blocks of a cell,

resulting in excessive cell proliferation in the case of cancer or cell death in the case of neurodegenerative diseases like Parkinson's.

Often, the majority of stressors are actually created inside our own cells as a byproduct of how our cells extract energy from the food that we eat and the air that we breathe.

Understanding oxidative stress

Most simply, oxidative stress is an imbalance that happens when the body uses oxygen to produce energy.

Superoxide, a "promiscuous and nonspecific" compound produced as a byproduct of this process, is a highly reactive molecule that can damage DNA and other cellular components, Hannink said.

The superoxide molecule is a "free radical." That means it's especially promiscuous and reacts with many different types of cellular molecules, leaving destruction in its wake, he said.

That damage can lead to a long list of problems, including cancer or neurodegenerative diseases like Parkinson's disease.

In response to oxidative stress, the cell produces protective "anti-oxidant" proteins, which help remove the harmful reactive oxygen species and minimize damage.

But a heavy anti-oxidant response could be dangerous, too. The bottom line: it's about maintaining a fine balance between "oxidants" and "anti-oxidants".

Search for right combination continues

A drug that corrects the imbalance of oxidative stress could one day have wide applicability.

Jasmer developed a test to measure how specific compounds altered gene expression. The genetic response to oxidative stress has both an "ON" switch and an "OFF" switch.

Using this test, Jasmer determined how each compound affected specific genetic switches and, in turn, how the response to oxidative stress is regulated.

This test helped identify which molecules might be promising candidates for treating oxidative stress, leading them to one in particular that seemed to have the desired properties: HPP-4382.

But creating effective drugs is a long process of trial and error. Once molecules have been identified that show efficacy in lab-based assays, scientists try different combinations to increase their potency and drug-like properties, and High Point is currently testing other molecules that behave like HPP-4382.

The compound serves as a good starting point for researchers who are interested in understanding how oxidative stress affects cellular processes, such as cell proliferation or cell death."Now we have a better understanding of what this compound is doing," Hannink said. "This compound can be used to test different ideas of how the balance between oxidants and anti-oxidants is achieved in healthy cells and how perturbation of this balance can lead to different diseases."

More information: The research, "Induction of Heme Oxygenase I (HMOX1) by HPP-4382: A Novel Modulator of Bach1 Activity" was published in *PLOS One*. www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0101044

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