Genetic pathway critical to disease, aging found

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The same chemical reaction that causes iron to rust plays a similarly corrosive role in our bodies. Oxidative stress chips away at healthy cells and is a process, scientists know, that contributes to a host of diseases and conditions in humans ranging from Alzheimer's, heart disease and stroke to cancer and the inexorable process of aging.

Now, writing in the current edition (Feb. 21, 2008) of the journal *Nature*, a team of University of Wisconsin-Madison scientists reports the discovery of a gene expression pathway that exerts a sweeping influence over the process of oxidative stress.

The finding is important because at its foundation it represents a master pressure point for a host of medical conditions, and could one day enable the manipulation of genes or the development of novel drugs to thwart disease.

"Most of the genes this pathway controls are important for human disease," according to Richard A. Anderson of the UW School of Medicine and Public Health and senior author of the new Nature report. "This is a totally new and novel pathway that controls the synthesis of enzymes key for many human diseases."

Oxidative stress occurs when the body's ability to neutralize highly toxic chemicals known as free radicals is overtaxed. Free radicals can damage DNA and other molecules essential for the health of a cell.

A key enzyme in the new pathway, dubbed Star-PAP by its Wisconsin discoverers, functions as part of a complex that controls the expression of messenger RNA, all-important molecules that carry genetic information from the nucleus of a cell to the cytoplasm where proteins are made. Star-PAP is responsible for adding a critical biochemical tail onto messenger RNA. The tail, in kite-like fashion, is necessary for the stability of the messenger RNA molecules, can turn them on and off, and thus governs the production of certain key enzymes and proteins in the cell.

"The tail," Anderson explains, "is like a postage stamp that enables messenger RNA to exit the nucleus of the cell and enter the cytoplasm where the genetic message is translated into protein."

The Star-PAP enzyme regulates the production of a relatively small number of proteins and enzymes in cells, but those could have an influence far beyond oxidative stress, Anderson notes. However, the Wisconsin group found that the newfound pathway contains a genetic "on-off" switch for a key protein known as heme oxygenase-1, an agent that protects cells from oxidative stress.

"Star-PAP is a master switch that controls key aspects of oxidative stress in cells," says Anderson, a UW-Madison professor of pharmacology. "A wealth of the genes involved in oxidative stress also seems to be the direct targets for the Star-PAP pathway."

The discovery of a gene expression pathway and specific enzymes that exert broad influence on the process of oxidative stress has clear clinical relevance, Anderson says, because it could potentially be manipulated to mitigate the damage oxygen does to cells.

"Oxidative stress control pathways for us humans are pretty important because we live in an environment where oxygen is required to keep us

alive, but also stresses us because of oxidative damage to our cells," Anderson says.

Oxidation can damage DNA, mitochondria, cell membranes, and other mechanisms and structures essential to the cell. Such damage underpins disease, including in the parts of the body -- the heart, the lungs and the brain -- that are heavy users of oxygen.

"We'll be able to get at this new machinery and, hopefully, manipulate it," says Marvin Wickens, a UW-Madison biochemist who was not involved in the study. New drugs that modulate the enzyme and control its activity could potentially blunt the stress that leads to disease.

Although the discovery of a new genetic pathway in cells is important, much work remains to identify how the pathway influences human disease, Anderson says.

"We've discovered a novel pathway that controls expression of genes important to oxidative stress," he says. "It has really key implications for heart disease, stroke, and possibly for aging, but it is still not clear precisely what functions this pathway is regulating in the context of those conditions."

Source: University of Wisconsin-Madison