MedicalXpress

'Epigenetic' concepts offer new approach to degenerative disease

April 28 2010

In studies on cancer, heart disease, neurological disorders and other degenerative conditions, some scientists are moving away from the "nature versus nurture" debate, and are finding you're not a creature of either genetics or environment, but both - with enormous implications for a new approach to health.

The new field of "epigenetics" is rapidly revealing how people, plants and animals do start with a certain genetic code at conception. But, the choice of which genes are "expressed," or activated, is strongly affected by environmental influences. The expression of genes can change quite rapidly over time, they can be influenced by external factors, those changes can be passed along to offspring, and they can literally hold the key to life and death.

According to Rod Dashwood, a professor of environmental and molecular toxicology at the Linus Pauling Institute at Oregon State University, epigenetics is a unifying theory in which many health problems, ranging from cancer to cardiovascular disease and neurological disorders, can all be caused at least in part by altered "histone modifications," and their effects on the reading of DNA in cells.

"We believe that many diseases which have aberrant gene expression at their root can be linked to how DNA is packaged, and the actions of enzymes such as histone deacetylases, or HDACs," Dashwood said. "As recently as 10 years ago we knew almost nothing about HDAC

dysregulation in cancer or other diseases, but it's now one of the most promising areas of health-related research."

In the case of cancer, tumor suppressor genes can cause cancer cells to die by acting as a brake on unrestrained cell growth. But too much of the HDAC enzyme can "switch off" tumor suppressor genes, even though the underlying DNA sequence of the cell - its genetic structure - has not been changed or mutated. If this happens, cells continue to replicate without restraint, which is a fundamental characteristic of cancer development.

The good news - for cancer and perhaps many other health problems - is that "HDAC inhibitors" can stop this degenerative process, and some of them have already been identified in common foods. Examples include sulforaphane in broccoli, indole-3-carbinol in cruciferous vegetables, and organosulfur compounds in vegetables like garlic and onions. Butyrate, a compound produced in the intestine when dietary fiber is fermented, is an HDAC inhibitor, and it provides one possible explanation for why higher intake of dietary fiber might help prevent cancer.

"Metabolism seems to be a key factor, too, generating the active HDAC inhibitor at the site of action," Dashwood said. "In cancer cells, tumor suppressors such as p21 and p53 often become epigenetically silenced. HDAC inhibitors can help turn them on again, and trick the cancer cell into committing suicide via apoptosis.

"We already know some of the things people can do to help prevent cancer with certain dietary or lifestyle approaches," Dashwood said. "Now we're hoping to more fully understand the molecular processes going on, including at the epigenetic level. This should open the door for new approaches to disease prevention or treatment through diet, as well as in complementing conventional drug therapies."

Dashwood, who is also head of LPI's Cancer Chemoprotection Program, will be presenting some of this research in a talk titled "Metabolism as a key to HDAC inhibition by dietary constituents," at the American Society for Biochemistry and Molecular Biology's annual meeting.

OSU scientists recently received an $8.5 million grant from the National Cancer Institute to explore these issues, making the LPI program one of the leaders in the nation on diet, epigenetics, and cancer prevention. The positive findings of laboratory research are already being converted to placebo-controlled human intervention trials on such health concerns as colon and prostate cancer, which are among the most common cancers in the United States.

OSU scientists have published a number of studies on these topics in professional journals such as Cancer Research, Cancer Prevention Research, Carcinogenesis, and Seminars in Cancer Biology. Among the most recent findings is that naturally occurring organoselenium compounds in the diet might prevent the progress of human prostate and colon cancer through an HDAC inhibition mechanism.

"Some therapeutic drugs already used for cancer treatment in the clinical setting probably work, at least in part, because they are acting as HDAC inhibitors," Dashwood said. "And what's most intriguing is that HDAC inhibition may affect many degenerative health issues, not just cancer. Heart disease, stroke, bipolar disorder, and even aging may all have links to HDAC/histone alterations.

"In the future, a single HDAC inhibitor conceptually could have benefits for more than one degenerative disease problem."

Provided by Federation of American Societies for Experimental Biology