Genetic function discovered that could offer new avenue to cancer therapies

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Researchers at Oregon State University have discovered a genetic function that helps one of the most important "tumor suppressor" genes to do its job and prevent cancer.

Finding ways to maintain or increase the effectiveness of this gene – called Grp1-associated scaffold protein, or Grasp – could offer an important new avenue for human cancer therapies, scientists said.

The findings were just published in *Photochemical and Photobiological Sciences*, a journal of the Royal Society of Chemistry, by researchers from OSU and Oregon Health & Science University. The work was supported by the National Institute of Environmental Health Sciences.

The Grasp gene was studied in the skin of mice in this research, but is actually expressed at the highest levels in the brain, heart and lung, studies have shown. It appears to play a fundamental role in the operation of the p53 tumor suppressor gene, which is a focus of much modern cancer research.

The p53 gene is involved in repair of DNA damage and, if the damage is too great, causing a mutated cell to die before it can cause further problems, up to and including cancer. Dysfunction of p53 genetic pathways have been linked to more than half of all known cancers - particularly skin, esophageal, colon, pancreatic, lung, ovarian, and head and neck cancers.

"DNA mutations occur constantly in our bodies just by ordinary stresses, something as simple as exposure to sunlight for a few seconds," said Mark Leid, professor of pharmacology and associate dean for research in the OSU College of Pharmacy, and one of the lead authors on this study.

"Just as constantly, the p53 gene and other tumor suppressors are activated to repair that damage," Leid said. "And in cases where the damage is too severe to be repaired, p53 will cause the apoptosis, or death of the mutated cell. Almost all of the time, when they are working right, these processes prevent the formation of cancers."

But the activity and function of p53 can sometimes decline or fail, Leid said, and allow development of cancer. Promising approaches to cancer therapy are now based on activating or stimulating the p53 protein to do its job.

The new study has found that the Grasp gene is significantly involved in maintaining the proper function of p53. When "Grasp" is not being adequately expressed, the p53 protein that has entered the cell nucleus to either repair or destroy the cell comes back out of the nucleus before its work is finished.

"It appears that a primary function of Grasp is to form sort of a halo around the nucleus of a damaged skin cell, and act as kind of a plug to keep the p53 cell inside the nucleus until its work is done," Leid said. "A drug that could enhance Grasp function might also help enhance the p53 function, and give us a different way to keep this important tumor suppressor working the way that it is supposed to.

"This could be important," he said.

OSU experts created laboratory mice that lacked the Grasp gene, and so

long as the mice were reared in a perfect environment, they developed normally. But when they were exposed to even a mild environmental stress – ultraviolet light similar to moderate sun exposure – they began to develop cellular abnormalities much more rapidly than ordinary mice. Most significantly, mutated skin cells did not die as they should have.

In normal mice, the same moderate light exposure caused a rapid increase in expression of the Grasp gene, allowing the p53 protein to stay in the nucleus and normal protective mechanisms to do their work.

Most current cancer therapies related to the p53 tumor suppression process are directed toward activating the p53 protein, Leid said. A therapy directed toward improving the Grasp gene function would be a different approach toward the same goal, he said, and might improve the efficacy of treatment.

More information: rp1-associated scaffold protein regulates skin homeostasis after ultraviolet irradiation, pubs.rsc.org/en/content/articl … p50351h#!divAbstract

Provided by Oregon State University