Aspirin and resveratrol could prevent cancer by killing tetraploid cells, research shows

February 11 2014, by Marcia Malory

Coated aspirin tablets. Image: Wikimedia Commons.

(Medical Xpress)—Aspirin and resveratrol kill tetraploid cells in mice and humans, according to a study by Guido Kroemer of the Gustave Roussy Institute in Villejuif, France and his colleagues. Precancerous lesions often contain tetraploid cells; aspirin and resveratrol could help prevent cancer by eradicating these cells. The research appears in the *Proceedings of the National Academy of Sciences*.

Tetraploid cells contain four copies of each chromosome, rather than the usual two copies. Often, tetraploid cells die as soon as they form. If they don't die instantly, the body's immune system usually kills them. In the early stages of cancer, however, tetraploid cells can be abundant. Scientists have found abnormally large numbers of tetraploid cells in the beginning stages of bronchial, esophageal, gastric, breast, colorectal, cervical and prostate cancer. Inactivating tumor suppressors in

precancerous cells in mice leads to tetraploidization.

While scientists know that destroying tetraploid cells could protect against cancer, until now they haven't been able to find a substance that kills tetraploid cells without harming healthy cells. DNA-damaging agents don't hurt tetraploid cells. Some substances that inhibit enzymes needed for cell division do destroy tetraploid cells, but they also prevent normal cell division from taking place.

Kroemer and his team wanted to see if aspirin and resveratrol, both already known to play a role in cancer prevention, would eliminate tetraploid cells without damaging normal, diploid cells. They gave either aspirin or resveratrol, found in red wine, to mice genetically engineered for a predisposition to intestinal cancer. These genetically engineered mice had more tetraploid cells in their intestinal linings than normal mice. When the researchers gave the cancer-prone mice either resveratrol or aspirin, the number of cells in the mice decreased. The likelihood of the mice developing cancer also decreased.

When the team treated cloned tetraploid mouse Lewis lung cancer cells, mouse embryonic fibroblasts and human HCT1 16 colorectal carcinoma RKO cells with resveratrol, the tetraploid cells died but diploid cells of the same type survived. Other cytotoxic substances, such as cisplatin, quercetin and paraquat, were more effective at killing diploid HT1 16 parent cells than their tetraploid clones.

Both resveratrol and aspirin activate AMPK, an enzyme associated with cell homeostasis. Kroemer's team believes they cause AMPK overexpression, which leads to the selective destruction of tetraploid cells. Both diploid and tetraploid cells treated with resveratrol or aspirin experienced the same level of AMPK activation; however, only the tetraploid cells died. The researchers think tetraploid cells have a lower tolerance threshold for AMPK expression than diploid cells do.

More information: Resveratrol and aspirin eliminate tetraploid cells for anticancer chemoprevention, Delphine Lissa, *PNAS*, DOI: 10.1073/pnas.1318440111

Abstract

Tetraploidy constitutes a genomically metastable state that can lead to aneuploidy and genomic instability. Tetraploid cells are frequently found in preneoplastic lesions, including intestinal cancers arising due to the inactivation of the tumor suppressor adenomatous polyposis coli (APC). Using a phenotypic screen, we identified resveratrol as an agent that selectively reduces the fitness of tetraploid cells by slowing down their cell cycle progression and by stimulating the intrinsic pathway of apoptosis. Selective killing of tetraploid cells was observed for a series of additional agents that indirectly or directly stimulate AMP-activated protein kinase (AMPK) including salicylate, whose chemopreventive action has been established by epidemiological studies and clinical trials. Both resveratrol and salicylate reduced the formation of tetraploid or higher-order polyploid cells resulting from the culture of human colon carcinoma cell lines or primary mouse epithelial cells lacking tumor protein p53 (TP53, best known as p53) in the presence of antimitotic agents, as determined by cytofluorometric and videomicroscopic assays. Moreover, oral treatment with either resveratrol or aspirin, the prodrug of salicylate, repressed the accumulation of tetraploid intestinal epithelial cells in the ApcMin/+ mouse model of colon cancer. Collectively, our results suggest that the chemopreventive action of resveratrol and aspirin involves the elimination of tetraploid cancer cell precursors.

https://medicalxpress.com/news/2014-02-aspirin-resveratrol-cancer-tetraploid-cells.html