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Plant compound protects healthy cells from chemotherapy drugs

Chemotherapy drugs attack not only cancer cells but more generally rapidly dividing tissues. This can cause side effects ranging from hair loss to nausea to deadly infections. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered that the plant compound rocaglamide protects healthy cells from the toxic effects of chemotherapy drugs. This discovery may help reduce the side effects of cancer therapies.

Most chemotherapy drugs damage the DNA of dividing cells. These include not only cancer cells but also healthy cells such as blood, hair follicles, and cells of the mucous membranes of the stomach and gut. So far, researchers have identified only a few drugs that can directly prevent such adverse side effects on healthy tissues, but it has been unclear whether some of these drugs also protect cancer cells themselves from the effects of chemotherapy. This motivated Dr. Min Li-Weber and her team at the DKFZ to search for new compounds. "Rocaglamide was one of many plant substances that we examined," said study head Li-Weber. "This substance is extracted from herbs and has been used in Chinese medicine for many years as, for example, an anti-inflammatory agent."

To determine whether rocaglamide protects healthy cells from chemotherapy drugs, the researchers treated white blood cells from healthy donors with various chemotherapy drugs while adding various levels of rocaglamide. The result: "The more rocaglamide we used, the more white blood cells survived," reports Li-Weber. By contrast, the substance did not have any impact on the survival rate of the cancer cell lines used in the experiment.

How exactly does rocaglamide work? Could it somehow prevent DNA damage in healthy cells? To pursue these questions, the scientists compared the state of DNA in cells either with or without rocaglamide after adding a chemotherapy drug. "The damage was almost identical," says Michael Becker, first author of the publication. "This means on the one hand that rocaglamide does not directly prevent the effects of chemotherapy drugs. On the other hand, it also means that the compound itself does not cause any DNA damage."

In further tests, the scientists found that rocaglamide inhibits the production of the protein p53. This protein, which is also called a "guardian of the genome," is produced by cells that have undergone DNA damage. When p53 reaches a certain level, it induces "programmed cell death," making sure that the defective cell dies. "Rocaglamide prevents healthy cells that have had contact with a chemotherapy drug from producing the p53 protein and thus from activating programmed cell death," Becker explains. "Since p53 is absent or defective in the cancer cells of about half of all cancer types, rocaglamide had no impact on the cancer cells in our tests." Patients suffering from tumors that do not produce p53 may therefore benefit from rocaglamide, because in these cases, the substance protects only the healthy cells from the effects of chemotherapy.

However, what are the consequences if cells with damaged DNA do not die promptly? Could they give rise to new cancer cells? "Numerous experiments in other labs have shown that inhibiting p53 for a short time does not cause the cancer risk to rise," Becker reports. “Our next step is to determine whether this also holds true for rocaglamide." Becker already has a hypothesis, which remains to be tested, that might explain why p53 inhibitors do not increase a

person’s risk of developing cancer: "They might give cells more time to repair damage to their DNA."

Becker MS, Schmezer P, Breuer R, Haas SF, Essers MA, Krammer PH, Li-Weber M. (2014) The traditional Chinese medical compound Rocaglamide protects nonmalignant primary cells from DNA damage-induced toxicity by inhibition of p53 expression. Cell Death Dis. doi: 10.1038/cddis.2013.528

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) with its more than 2,500 employees is the largest biomedical research institute in Germany. At DKFZ, more than 1,000 scientists investigate how cancer develops, identify cancer risk factors and endeavor to find new strategies to prevent people from getting cancer. They develop novel approaches to make tumor diagnosis more precise and treatment of cancer patients more successful. The staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. Jointly with Heidelberg University Hospital, DKFZ has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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