Joint press release of the German Cancer Consortium (DKTK) and Technische Universität München

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New method can predict side effects of anticancer drugs

Every new anticancer drug can improve patients' chances of survival. In some cases, however, these drugs can cause severe adverse side effects through mechanisms that are often unclear. An international team of researchers from Munich, Heidelberg, Sweden and Singapore has now succeeded in developing a new method that helps explain and even predict side effects that occur at cellular level.

Aside from their intended effects on cancer cells, anticancer drugs often cause severe and sometimes painful side effects including a loss of hair, nausea and immune system depression. Additionally, many patients suffer from a tingling of the hands or much more severe nervous problems, such as loss of their sense of touch. Others complain of heightened sensitivity to light (photosensitivity); any of these symptoms can severely affect a patient's quality of life. One reason for side effects lies in the mode of action of these drugs: Many of them attack not only quite specific proteins in cancer cells, their intended targets, but other proteins in healthy cells as well. While in some cases these secondary effects may boost the desired effect of a drug, the typical results are adverse side effects. Identifying the unintentional targets of a new drug in advance might make it possible to predict undesirable side effects. It would help clinicians estimate not only whether, but especially why and how they might occur.

A team of scientists from the company Cellzome in Heidelberg and the Swedish Karolinska Institute, collaborating with Professor Bernhard Küster of Technische Universität München at the DKTK partnering site in Munich, have now used a simple but sophisticated method to make such predictions. By heating leukemia cells to temperatures between 40°C and 70°C, the scientists were able to identify new target proteins of anticancer drugs. The heat caused cellular proteins to start "melting". "Each individual protein in a cell has a characteristic melting behavior, which we can measure," says Dr Mikhail Savitski, the first author of the study. "When we administer anticancer drugs into cells, the drugs bind to specific proteins and modify them. These changes also affect their melting behavior, which we can measure again."

Ideally, drugs should bind only to the specific proteins they are meant to target. However, in most cases they also bind to other proteins – usually not only molecules found in tumor cells, but in healthy ones as well. This is usually the cause of side effects. The scientists used protein mass spectroscopy to track these changes in the melting behavior of proteins in living cells. "We can thus exactly determine the effects of a drug," Küster says. "We hope to use this method in the future to explain or even predict many adverse effects." Küster is head of the participating research group at the DKTK partnering site of Technische Universität München.

In the current study, the researchers used the new method in an examination of a number of anticancer drugs. The list included vemurafenib, an agent that is used primarily to treat melanoma skin cancer. It was originally developed as an inhibitor of a cancer protein called B-Raf. However, in many patients it also causes painful photosensitivity that has an adverse effect on their quality of life. The new method allowed the scientists to discover a new,

unexpected target of this agent: an enzyme called ferrochelatase. This enzyme is required for the production of heme, the red pigment component of hemoglobin. When vemurafenib is administered in healthy cells, the ferrochelatase enzyme ceases to function – an effect which can be measured based on its melting behavior. This loss of function is known from another condition called cutaneous porphyria, an inherited metabolic disorder that leads to extreme and painful photosensitivity of the skin. Patients who suffer from this disorder exhibit the same defect in the enzyme. So the finding will have immediate clinical benefits, which gives Küster reason for hope: “Thanks to our results it should be possible to develop new agents that no longer bind to the ferrochelatase enzyme, which will relieve patients from the fear of photosensitivity as an adverse effect of anticancer drugs.”

Mikhail Savitski, Friedrich Reinhard, Holger Franken, Thilo Werner, Maria Fälth Savitski, Dirk Eberhard, Daniel Molina, Rozbeh Jafari, Rebecca Bakszt Dovega, Susan Klaeger, Bernhard Kuster, Pär Nordlund, Marcus Bantscheff, Gerard Drewes: Tracking cancer drugs in living cells by thermal profiling of the proteome. Science 2014. DOI 10.1126/science.1255784.

In the German Cancer Consortium (DKTK), the German Cancer Research Center (DKFZ) joins up with university hospitals all over Germany. Assembled around a core at the DKFZ in Heidelberg, the consortium unites twenty high-ranked institutes from seven partner sites: Berlin, Dresden, Essen/Dusseldorf, Frankfurt/Mainz, Freiburg, Munich and Tubingen, all specialized in research and treatment focused on oncological diseases. The DKTK was found to promote translational research, bringing together scientists, physicians and associates to work jointly toward the main goal of enhancing the translation of research from bench to bedside. New approaches in prevention, diagnostics and treatment will be applied to cancer in common translational centers at all partner sites. Patients will be recruited at all partner sites for innovative studies to be carried out by the consortium as a whole. All the data from this work will be collected in a universal system. The harmonization of techniques and methods used in laboratories will ensure identical standards for all researchers and physicians in the consortium. A joint infrastructure will make them available for communal research. With the school of oncology, the consortium is additionally dedicating itself to the education of new physicians and scientists. Talented young people will be trained in cancer medicine and translational cancer research in a common effort involving all members. The German Cancer Consortium is a joint initiative of the Federal Ministry of Education and Research, the participating German states, German Cancer Aid and the German Cancer Research Center. It is one of the six German Centers for Health Research (DZG).

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