Many small differences contribute to a large variation

March 6 2018, by Fabio Bergamin

A drug can affect people very differently. Credit: Colourbox

There is no single main reason why certain drugs affect people differently, but rather many small factors. ETH researchers demonstrated this with a model system. They believe that, in order to test the effectiveness of certain drugs, it is necessary to look at the biological system as a whole.

Drugs are not equally effective for everyone. To some extent, this is due

to the fact that people's bodies will take up a pharmaceutical substance to varying degrees. Little research has been done in the past to determine whether this is the main reason for the individual differences or one of many.

A group of researchers headed by Ruedi Aebersold, a professor of systems biology at ETH Zurich, has now shed some light on the subject in their report published in the journal *Cell Systems*. The researchers performed detailed measurements of proteins and metabolites in cell culture experiments and succeeded in showing that the differing effects between individuals could not be attributed to a single factor or a few factors. Instead, the researchers found that many small differences together are responsible for the large variation.

Tests with a cholesterol-lowering drug

In order to investigate the variable effects of drugs, the scientists analysed cholesterol regulation in four different human cell lines. They tested how the cells responded differently to various drugs that affect cholesterol levels. In cooperation with ETH professor Uwe Sauer, the researchers used methods from the fields of systems biology, proteomics and metabolomics to measure and compare the concentrations of a very large number of different proteins and metabolites in the cells at specific times.

It turned out that each of the cell lines responded differently to the drugs. "Contrary to what one might expect, the differences were not due to one cell line simply taking up more of a pharmaceutical substance than another, or that one cell lacked a central regulation mechanism found in another cell," says Peter Blattmann, a postdoc in Aebersold's group and first author of the study. Instead, the scientists were able to show that many enzymes and many of the complex biochemical pathways of a cell together contribute to the differences.

Oncological applications

"Our findings clearly show that simply measuring the amount of drug uptake is not sufficient to understand inter-individual differences in effectiveness, an approach that was typically taken in the past," says Blattmann. "Rather we have to adopt a holistic perspective, and, as we did in this study, use computer models to look also at other complex intracellular processes to understand why the drug response varies."

The individual differences are even more pronounced in cancer treatments than in cholesterol-lowering medications. Especially in the case of more advanced medications, there are treatments that only work for a very small group of patients. "The systems biology approach we took in our study might thus also make it possible to predict which patients respond well to a cancer drug and which will not," says Blattmann.

More information: Peter Blattmann et al. Systems Pharmacology Dissection of Cholesterol Regulation Reveals Determinants of Large Pharmacodynamic Variability between Cell Lines, *Cell Systems* (2017). DOI: 10.1016/j.cels.2017.11.002

Provided by ETH Zurich