Uncovering novel relationships between SLCs and cytotoxic drugs in human cells

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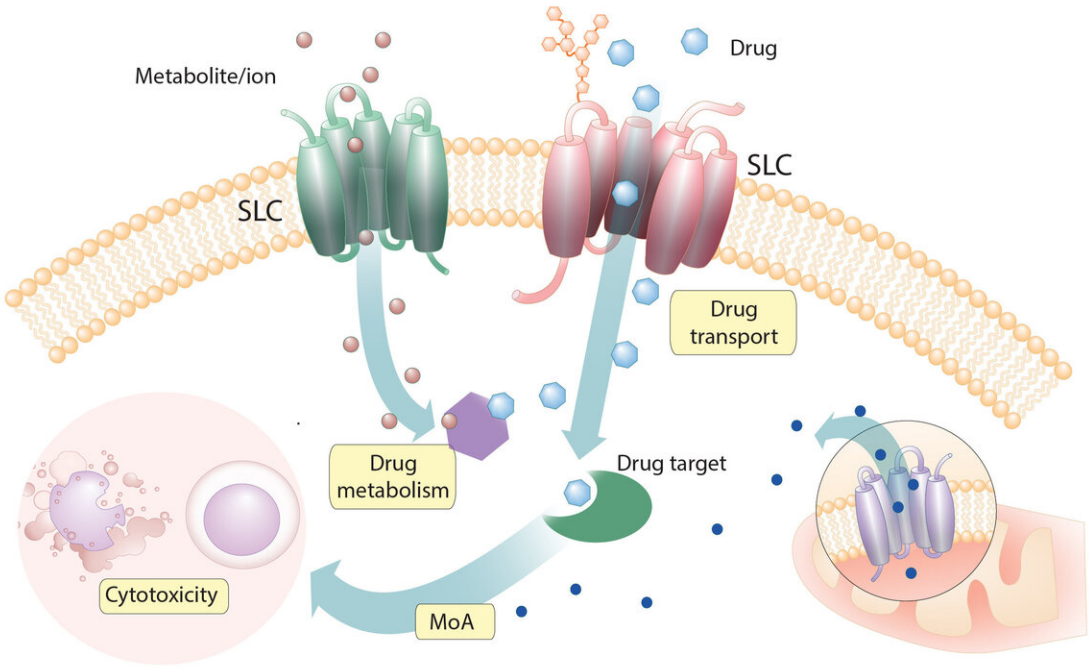

Solute Carriers (SLCs) affect the uptake, metabolism and mechanism of action (MoA) of cytotoxic drugs. Credit: © Enrico Girardi / CeMM

CeMM Researchers have studied how solute carriers (SLCs), a large family of membrane transport proteins, influence the activity and

potency of cytotoxic drugs. Their study in *Nature Chemical Biology* uncovers the dependency of most drugs studied on the function of at least one SLC. These findings shed new light on the biological roles of transporters, and open a path to the development of future precision therapies.

Solute carriers (SLCs) represent the largest family of transmembrane transporters in the human genome, with over 400 members arranged into 65 families. They play a key role in determining cellular metabolism and control essential physiological functions, including nutrient uptake, ion transport and waste removal. SLCs are vital for maintaining the stable internal state of the human body (known as homeostasis), but the presence of genetic variation (polymorphisms) in SLCs are associated with several diseases, including gout and diabetes, while gene mutations are associated with literally hundreds of disorders, including many metabolic deficiencies and orphan diseases.

Solute carriers have been shown to act as drug targets, as well as constitute paths for drug absorption into specific organs. However, despite of decades of studies, there is still a lack of systematic surveys of transporter-drug relationships in human cells. Uncovering how particular drugs enter human cells and how the cell metabolism affects them is key to gaining a better understanding of the side effects and limitations of current drugs and thus developing more effective drug therapies in the future.

Expanding on a previous study (Winter et al. *Nature Chemical Biology*, 10, pp 768-773, 2014), which uncovered how a single solute carrier (SLC35F2) is necessary in the uptake of the cytotoxic compound YM-155, Giulio Superti-Furga and his group at CeMM have now performed a more systematic investigation on the role of solute carriers in determining the activity of a large and diverse set of cytotoxic compounds. Their goal was to how SLC transporters would lose or a

affect the activity of a certain drug, and how often.

In their study, CeMM researchers built a CRISPR/Cas9-focused library specifically targeting 394 solute carriers and applied it to identify SLCs affecting the activity of a panel of 60 chemically diverse, mostly clinically approved, cytotoxic compounds. They determined that approximately 80% of the screened drug set shows a dependency with at least one solute carrier. To further validate these results, the scientists individually validated a subset of SLC-drug interactions and employed uptake assays and transcriptomics approaches to investigate how some of the SLCs affected drug uptake and activity. "The use of a custom-made, SLC-focused library was instrumental in allowing us to screen a large number of compounds, revealing hundreds of SLC-drug associations and providing many novel insights into SLC biology and drug mechanisms," says Enrico Girardi, CeMM senior postdoctoral fellow and first author of the study.

The present study is the result of a cross-disciplinary collaboration with researchers from the University of Vienna Pharmacoinformatics Research Group of Gerhard Ecker as well as the group of Stefan Kubicek at CeMM. It provides not only a strong validated argument to demonstrate the requirement of solute carriers in cellular uptake and drug activity, but also an experimentally validated set of SLC-drug associations for several clinically relevant compounds. The evidence provided by CeMM researchers opens a pathway to further investigations of the genetic determinants of drug activity and especially uptake in human cells.

"This study raises strong doubts that the generally accepted idea that most drugs can enter cells by simply diffusing through its membrane is correct and highlights the increasingly appreciated need to systematically studying the biological roles of solute carriers," says Giulio Superti-Furga, CeMM scientific director and last author of the study. Gaining

further insights into how the transporters affect the uptake and activity of drugs in tumors and tissues allows scientists to predict and counteract resistance mechanisms to design the most effective precision therapies. Furthermore, understanding the relationship between the expression of SLCs, cellular/organismal metabolism and nutrition is likely to allow the opening of novel therapeutic avenues in the future.

More information: A widespread role for SLC transmembrane transporters in resistance to cytotoxic drugs, *Nature Chemical Biology* (2020). DOI: 10.1038/s41589-020-0483-3 , nature.com/articles/s41589-020-0483-3

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