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Uncovering novel relationships between solute carrier transporters and cytotoxic drugs in human cells

Researchers at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences have studied how Solute Carriers (SLCs), a large family of membrane transport proteins, influence the activity and potency of cytotoxic drugs, such as those used in the treatment of leukemia and other cancers. Their study, published in the journal *Nature Chemical Biology*, uncovers the dependency of most drugs studied on the function of at least one SLC. In some cases, the drug required the transporter to enter into the cell, in other cases, it provided small molecules (metabolites), which are crucial to the drug's activity or the cell response to it. These findings shed new light onto the biological roles of transporters and open the path to the development of future precision therapies.

(Vienna, 9 March 2020) Solute carriers (SLCs) represent the largest family of transmembrane transporters in the human genome, with over 400 members arranged into 65 families. They have 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 a stable internal state of the human body (known as homeostasis), but the presence of genetic variation (polymorphisms) in SLCs are associated with several diseases, such as gout or 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. *Nat Chem Biol*, 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 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 survey on the "how often" and "how" SLC transporters would lose or affect the activity of a certain drug.

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, most of them 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's activity, but also an experimentally validated set of SLC-drug associations for several clinically relevant compounds. The evidence provided by CeMM researchers opens the 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.

Attached pictures:

1. Last author Giulio Superti-Furga and first author Enrico Girardi (© Klaus Pichler / CeMM)
2. Solute Carriers (SLCs) affect the uptake, metabolism and mechanism of action (MoA) of cytotoxic drugs (© Enrico Girardi / CeMM)

The study "A widespread role for SLC transmembrane transporters in resistance to cytotoxic drugs" was published in *Nature Chemical Biology* on 9 March 2020. DOI: 10.1038/s41589-020-0483-3

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Giulio Superti-Furga is CEO and Scientific Director of CeMM, and Professor of Medical Systems Biology at the Medical University of Vienna. He was trained as a molecular biologist at the University of Zurich, Genentech, IMP Vienna and EMBL Heidelberg. He obtained four grants from the European Research Council, is a member of five scientific academies, and has published more than 200 papers. CeMM, which he directs since 2005, is located in the middle of the large general hospital campus in Vienna, where, together with some 180 scientists and medical doctors, he is bringing the genomic and systems-views close to the clinical world to improve medical practice. For CeMM, he promoted a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. Recent interests include ways to create functional precision medicine approaches and the role of the human transportome in pathophysiology and drug discovery. He is the scientific coordinator of the Innovative Medicine Initiative consortium "RESOLUTE", dedicated to the deorphanization of SLC transporters.

The mission of **CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences** is to achieve maximum scientific innovation in molecular medicine to improve healthcare. At CeMM, an international and creative team of scientists and medical doctors pursues free-minded basic life science research in a large and vibrant hospital environment of outstanding medical tradition and practice. CeMM's research is based on post-genomic technologies and focuses on societally important diseases, such as immune disorders and infections, cancer and metabolic disorders. CeMM operates in a unique mode of super-cooperation, connecting biology with medicine, experiments with computation, discovery with translation, and science with society and the arts. The goal of CeMM is to pioneer the science that nurtures the precise, personalized, predictive and preventive medicine of the future. CeMM trains a modern blend of biomedical scientists and is located at the campus of the General Hospital and the Medical University of Vienna. www.cemm.oeaw.ac.at

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