

RESEARCH NEWS

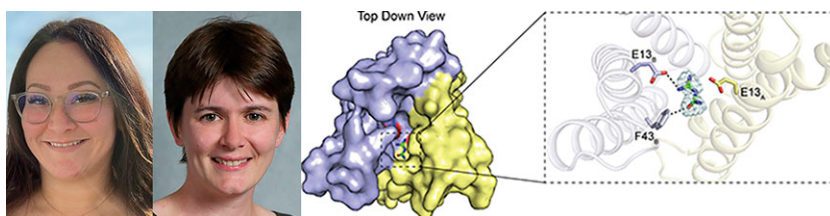
SMR transporters meet the challenge of metformin metabolites

Ben Short¹ 

JGP study (Lucero et al. <http://www.doi.org/10.1085/jgp.202313464>) shows that members of the SMR_{Gdx} subtype can export the degradation products of metformin, helping bacteria adapt to high environmental levels of the commonly prescribed diabetes medication.

The antidiabetic medication metformin is the most commonly prescribed drug in the world, with over 150 million patients taking typical daily doses of a gram or more. Because it is excreted in an unaltered form, high levels of metformin, along with its breakdown product guanylurea, can now be found in wastewater and, of increasing concern, in surface water as well (1). The presence of metformin is associated with changes in the composition of microbial communities in wastewater treatment plants, with some bacteria able to metabolize metformin as a carbon and nitrogen source (2). In this issue of *JGP*, Lucero et al. reveal that one way bacteria adapt to the presence of metformin in their environment is by co-opting a class of small multidrug resistance (SMR) proteins to export metformin metabolites from the cell, a finding that could aid the development of bioremediation methods to remove this compound from water supplies (3).

The ability of SMR proteins to transport molecules, including anthropogenic chemicals, out of cells can provide bacteria with significant fitness advantages. This is reflected in the frequent association of SMR-encoding genes with plasmids or other horizontal gene transfer (HGT) elements that allow them to spread rapidly across bacterial populations (4). SMR_{Qac} proteins, for example, are commonly associated with HGT elements because they export common antiseptics such as benzalkonium.



Rachael Lucero (left), Randy Stockbridge (center), and colleagues reveal that members of the SMR family that naturally export guanidinium from bacterial cells can also transport guanylurea and other breakdown products of the antidiabetic drug metformin. Bacteria in wastewater treatment plants appear to have co-opted these transporters to handle the high levels of metformin accumulating in their environment. The structure (right) shows how guanylurea (green sticks) binds to an SMR_{Gdx} protein (blue/yellow).

SMR_{Gdx} proteins, in contrast, originally evolved to export the physiological waste product guanidinium, but the reason why SMR_{Gdx}-encoding genes are often associated with HGT elements remains unclear. Recently, however, Randy Stockbridge and colleagues isolated a bacterial strain from a wastewater treatment plant that carried a plasmid encoding two SMR_{Gdx}-encoding genes along with several enzymes linked to metformin degradation.

“Given the structural similarities between metformin and guanidinium, we thought we should investigate whether metformin or its metabolites are also substrates of SMR_{Gdx} transporters,” says Stockbridge, a principal investigator at the University of Michigan.

Stockbridge and colleagues, including first author Rachael Lucero, tested four

SMR_{Gdx} homologs from different bacterial species. Two were genomically encoded and likely to carry out the ancient function of guanidinium export. The other two were plasmid encoded, potentially indicating a role in responding to newer selective pressures, such as metformin contamination. After purifying the different SMR_{Gdx} proteins and incorporating them into liposomes, Lucero et al. used solid-supported membrane electrophysiology to test their ability to transport metformin and its metabolites (3).

None of the SMR_{Gdx} proteins transported metformin itself, but all four efficiently transported the degradation product guanylurea at rates similar to those measured for the native substrate guanidinium. Some of the SMR_{Gdx} homologs transported additional metformin byproducts as well, whereas members of the SMR_{Qac} subtype

¹Science Writer, Rockefeller University Press, New York, NY, USA.

Correspondence to Ben Short: bshort@rockefeller.edu.

© 2024 Rockefeller University Press. This article is distributed under the terms of an Attribution–Noncommercial–Share Alike–No Mirror Sites license for the first six months after the publication date (see <http://www.rupress.org/terms/>). After six months it is available under a Creative Commons License (Attribution–Noncommercial–Share Alike 4.0 International license, as described at <https://creativecommons.org/licenses/by-nc-sa/4.0/>).

were unable to transport any metformin-related compounds.

Lucero et al. determined that the SMR_{Gdx} proteins exchange two protons for every guanylyurea, the same stoichiometry observed for guanidinium transport. The researchers then analyzed one of the SMR_{Gdx} homologs, Gdx-Clo, in more detail, obtaining an x-ray crystal structure of the transporter bound to guanylyurea. “We saw that guanylyurea slots into the same binding site as guanidinium,” Stockbridge explains.

Taken together, Lucero et al.’s results suggest that bacteria in wastewater

treatment plants have co-opted SMR_{Gdx} proteins to play a critical role in the degradation of metformin. “It’s amazing how bacteria have started to take genes they already have and assemble them into new operons to handle new chemical compounds in the environment,” Stockbridge says. “Now that we’ve established guanylyurea as a transport substrate, we can look to see where these genes are present and try to understand the processes that are occurring in bacterial populations.” This applies not only to wastewater treatment plants—where engineered bacteria could be used to

reduce metformin contamination—but also to the human gut microbiome, where bacteria can also be exposed to high levels of the drug.

References

1. Briones, R.M., et al. 2016. *Environ. Pollut.* <https://doi.org/10.1016/j.envpol.2016.07.040>
2. Martinez-Vaz, B.M., et al. 2022. *Front. Bioeng. Biotechnol.* <https://doi.org/10.3389/fbioe.2022.1086261>
3. Lucero, R.M., et al. 2024. *J. Gen. Physiol.* <https://doi.org/10.1085/jgp.202313464>
4. Pal, C., et al. 2015. *BMC Genomics.* <https://doi.org/10.1186/s12864-015-2153-5>