New method to stop cells dividing could help fight cancer

January 18 2018

Researchers at Uppsala University, Karolinska Institutet, and the University of Oxford, have used a new strategy to shut down specific enzymes to stop cells from dividing. The method, published in *Cell Chemical Biology*, can be used as a strategy to fight cancer.

Turning off enzymes that are important for the survival of growing cells is a promising strategy to fight cancer. But to be able to shut down only one specific enzyme out of thousands in the body, drugs have to be tailored to exactly fit their target. This is particularly difficult for membrane proteins, since they only function when incorporated into the cell lipid envelope, and often cannot be studied in isolation.

In a new study published in *Cell Chemical Biology* researchers used a new strategy to find out how anticancer drugs bind to the membrane protein dehydroorotate dehydrogenase (DHODH), a new cancer target.

The Erik Marklund group at the Department of Chemistry, Uppsala Universty, has together with the groups of Sir David Lane and Sonia Lain at Karolinska Institutet used computer simulations together with native mass spectrometry, a technique where a protein is gently removed from its normal environment and accelerated into a vacuum chamber. By measuring the time it takes for the protein to fly through the chamber, it is possible to determine its exact weight. The researchers used this highly accurate 'molecular scale' to see how lipids (the building blocks of the cell membrane) and drugs bind to DHODH.

"To our surprise, we saw that one drug seemed to bind better to the enzyme when lipid-like molecules were present," says assistant professor Michael Landreh, Karolinska Institutet.

The team also found that DHODH binds a particular kind of lipid present in the cell's power plant, the mitochondrial respiratory chain complex.

"This means the enzyme might use special lipids to find its correct place on the membrane," Michael Landreh explains.

To understand why lipids can help a drug recognise its target, Erik Marklund and Joana Costeira-Paulo employed computer simulations to explore the structure and dynamics of free as well as membrane-bound DHODH.

"Our simulations show that the enzyme uses a few lipids as anchors in the membrane. When binding to these lipids, a small part of the enzyme folds into an adapter that allows the enzyme to lift its natural substrate out of the membrane. It seems that the drug, since it binds in the same place, takes advantage of the same mechanism," says Erik Marklund, Uppsala University.

"The study helps to explain why some drugs bind differently to isolated proteins and proteins that are inside cells. By studying the native structures and mechanisms for cancer targets, it may become possible to exploit their most distinct features to design new, more selective therapeutics," says Sir David Lane, Karolinska Institutet.

More information: Costeira-Paulo J, Gault J, Popova G, Ladds M.J.G.W., van Leeuwen IMM, Sarr M, Olsson A, Lane DP, Laín S, Marklund EG, and Landreh M (2018) Lipids shape the electron acceptor-binding site of the peripheral membrane protein dihydroorotate

dehydrogenase, *Cell Chemical Biology*, DOI: 10.1016/j.chembiol.2017.12.012

Provided by Uppsala University