How to hijack degrading complexes to put cancer cells asleep

April 23 2018

Credit: Newcastle University

Newcastle and Dundee University researchers have uncovered an alternative path of how the breast cancer drug palbociclib drives malignant cells into cell death, senescence.

Palbociclib is a drug used for the treatment of advanced estrogen-

receptor-positive breast cancer. It induces cell cycle arrest and senescence, an irreversible resting state marking these 'out-of-order' cells to be cleared by the immune system.

Notably, the mechanistic details of how palbociclib drives cancer cells into senescence are largely unknown to date. Professor Matthias Trost at Newcastle University along with colleagues at Dundee University investigated the drug's mode of action in more detail and uncovered the proteasome, a cellular degradation machinery vital for the control of cell proliferation, as its yet unknown target.

Their discovery could potentially help expand palbociclib-based breast cancer treatments and identify patients that would profit most from this medication. The research is published today in *The EMBO Journal*.

Stalling proliferation

Palbociclib has been designed to thwart tumor growth by preventing key molecules of cell cycle progression from doing their job. Specifically, it inhibits cyclin-dependent kinase 4 (CDK4) and closely related CDK6; two factors that are essential to drive cells into DNA replication phase. However, recent observations indicate that palbociclib induces a more complete arrest than what can be achieved by blocking CDK4/6. Cells treated with palbociclib irreversibly withdraw from the cell division cycle and enter a state referred to as cellular senescence.

In this study, the researchers addressed in more detail why cells treated with palbociclib enter senescence. The researchers used a novel method called thermal proteome profiling to detect cellular changes induced by palbociclib. This technology is based on observing drug induced changes in the thermal stability of cellular proteins. The method will pick up proteins that either bind to the drug directly or change their activity in response to the drug.

With this approach the researchers identified that palbociclib induced substantial changes in the proteasome, the protein complex degrading unneeded or damaged proteins. More specifically, palbociclib dissociates the proteasomal component ECM29. Once freed, the proteasome degrades proteins required for cell cycle progression, thus driving cells into senescence.

"While it was known that palbociclib stalls proliferation by inhibiting CDK4/6, inducing proteasomal activity may be an additional mechanism that ensures the completeness of the cell cycle arrest," says Dr. Mikael Björklund, one of the lead authors of the study.

The importance for drug combinations

Proteasomal activity must be precisely regulated to direct cells through cell division, degrading the right proteins at the right time to help the cell progress to the next step in the division cycle. Anything that disturbs this tight regulation is likely to hinder proliferation. Accordingly, both activators and suppressors of proteasomal activity have been considered as treatment options for breast cancer.

The discovery that palbociclib can activate proteasomal activity is important when considering potential drug combinations to treat breast cancer.

"Our work suggests that proteasome inhibitors and palbociclib are a not a good combination, given that they act in opposite directions," says Professor Matthias Trost of the Institute of Cell and Molecular Biosciences at Newcastle University, who co-led the study.

The researchers also found that, at least for certain types of breast cancer, patients with low ECM29 levels had longer relapse-free survival times. "ECM29 possibly could be a biomarker for predicting the

responsiveness of patients to palbociclib. The drug would probably be more beneficial in patients with high ECM29 levels," says Trost.

More information: Teemu P Miettinen et al. Thermal proteome profiling of breast cancer cells reveals proteasomal activation by CDK4/6 inhibitor palbociclib, *The EMBO Journal* (2018). DOI: 10.15252/embj.201798359

Provided by Newcastle University