New study discovers cancer-relevant protein shield

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Credit: University of Copenhagen

Researchers from the Novo Nordisk Foundation Center for Protein Research have uncovered a new protein shield that aids in repairing damaged DNA in cells and affects resistance to drugs used for breast cancer treatment. The new study has just been published in the internationally acclaimed scientific journal *Cell*.

Breast cancer is one the most frequently occurring cancer in women worldwide, and hundreds of thousands of new cases are diagnosed with the disease every year. Around 5-10 percent of breast cancer is hereditary, meaning that a woman inherits faulty breast cancer-causing genes from her parents. For example, mutations in BRCA1 gene are found in many cases of hereditary breast cancer. These women are what we call BRCA positive. Basically, the BRCA proteins are involved in fixing broken DNA in a cell, and because BRCA mutant cells cannot accurately repair their DNA, it leads to the development of cancer. In fact, faulty DNA repair is the fundamental cause of most cancers.

The risk of developing aggressive forms of cancer in BRCA positive women is so high that some women even choose to have both breasts removed (mastectomy) as a preventative treatment. The most well-known case was when the actress Angelina Jolie chose to have both her breasts removed due to a BRCA-positive diagnosis. In Denmark, we conduct national screenings and offer genetic tests to discover the risk early and provide preventative treatment.

Researchers Discover New DNA Repairers

A research team, led by Chuna Choudhary and Jiri Lukas, at the Novo Nordisk Foundation Center for Protein Research at the Faculty of Health and Medical Sciences at the University of Copenhagen, used advanced technology (mass spectrometry) to uncover previously unknown proteins that are involved in repairing damages to the DNA. To do this, they genetically engineered human cells to "tag" key proteins that were already known to repair DNA and looked at other proteins that interact with them.

"This is very similar to using social media, such as Facebook, for finding out interactions of a person. By analyzing social network profile of a person we can find links to the individuals he/she interacts with, but who

are unknown to us". says Rajat Gupta, who is the first author of the study. This sophisticated analysis of "networks of DNA repair" allowed the researchers to get a detailed map of DNA repairing proteins and to discover new ones.

New Protein Shield affects Cancer Therapy

Breakthrough advances in the past years have led to highly promising drugs, called PARP inhibitors, that effectively cures BRCA positive cancers. Unfortunately, not all patients respond to the drug and many of those who do respond initially develop resistance to these drugs after a period of treatment. Researchers are therefore actively trying to understand the mechanisms that cause the resistance and to find new targets that can be used to treat these resistant cancers.

Importantly, the new research has discovered a previously unknown group of proteins, which they have called Shieldin. "We have gained new, unique insight into protein networks of the DNA repair process and identified a new "protein shield" that protects broken DNA ends and thereby helps in repairing damaged DNA. Shieldin also affects treatment responses to PARP inhibitor drugs, that are among the most advanced and effective therapy for BRCA positive cancers. The new findings may contribute in making decisions for treating cancer patients and to understand the mechanisms of resistance to PARP inhibitor drugs," says Professor Chuna Choudhary.

The next step will be to further understand details of protein networks, how exactly shieldin protects DNA, and how it impacts cancer resistance to PARP inhibitor. Researchers will also be interested to understand whether shieldin could be used as a new cancer drug target.

More information: Rajat Gupta et al. DNA Repair Network Analysis Reveals Shieldin as a Key Regulator of NHEJ and PARP Inhibitor

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