Protein researchers unravel the molecular dance of DNA repair

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Using state-of-the-art technology, scientists at the Novo Nordisk Foundation Center for Protein Research at the University of Copenhagen and their international collaborators have successfully obtained "molecular snapshots" of tens of thousands processes involved in DNA damage repair. On a daily basis this restoration keeps cells healthy and prevents the development of cancer. The results of this study will help unravel exactly how cells repair their broken DNA, how chemotherapy affects cells´ workings and will assist in the discovery of new drugs with fewer side effects.

"DNA repair is vital in keeping cells healthy," Associate Professor Chunaram Choudhary from the Novo Nordisk Foundation Center for Protein Research says.

"So unraveling the molecular details of how a cell communicates when its DNA is broken will help us understand how cells protect their genomes."

"We know, for example, that chemotherapy kills cancer cells by damaging their DNA," postdoc Petra Beli explains.

"This happens because the fast growing cancer cells are more sensitive to DNA damage than healthy cells. However, how exactly chemotherapy works on a cellular level is still a mystery. Once we understand the molecular consequences of chemotherapy on cancer cells, we could begin to work on ways to protect healthy cells during treatment of

patients with cancer."

Daily DNA damage threatens healthy cells

Everything from sun tanning to environmental factors and normal metabolic processes inside the cell damages the DNA of that cell every day. This in turn can lead to production of faulty proteins that - if not repaired - could go on to become the driver of cancer development.

To prevent these devastating effects, damaged DNA triggers an elaborate alarm system, which sets of a chain reaction in the cell, to slow processes, terminate others and wait, while legions of molecules go to work on the damaged DNA.

"Identification of proteins that are crucial for repairing broken DNA may help find new drug targets, and by using such very specific drugs it may also become possible to minimize the side effects, which occur when a drug hits too broadly in the body," Chunaram Choudhary continues.

Much remains to be learned

DNA repair has been studied intensely for years, but Associate professor Choudhary and his group at the Department of Proteomics along with his collaborators from University of Cambridge and Max Planck Institute are the first to unravel tens of thousands of molecular signaling events involved in this complex process.

"We first damaged the DNA of cells using radiation or chemical drugs and then used a technique called mass spectrometry, which is a way of precisely determining the identity of proteins and their chemical modifications," Petra Beli says.

"This allowed us to follow thousands of protein modifications that happened in the process of DNA repair, shedding new light on how the networks of biochemical signals are regulated and how the infrastructure of alerts works."

The data from the experiments is so extensive that it will require much further work by researchers to fully understand the significance and impact of these newly identified signaling pathways. The article Proteomic Investigations Reveal a Role for RNA Processing Factor THRAP3 in the DNA Damage Response is published online in the journal *Molecular Cell* on 15 March.

Provided by University of Copenhagen