New knowledge about DNA repair can be turned into cancer inhibitors

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Researchers at the University of Copenhagen have discovered a molecular mechanism that reads so-called epigenetic information and boosts repair of lesions in our DNA. This knowledge can be used to develop new targeted cancer treatment in which 'inhibitor molecules' can prevent cancer cells from repairing themselves. The researchers have taken out a patent for their new knowledge and the results have just been published in *Nature*.

Professor Anja Groth and her research team at the University of Copenhagen are concerned with understanding the basic molecular mechanisms responsible for the development and maintenance of the more than 200 specific cell types in our body. Now, new groundbreaking results have made them take out a patent on their knowledge.

"We have shown how a cellular DNA repair protein is directed to lesions in DNA via modifications on histone proteins that are bound tightly to DNA. Cancer cells divide rapidly and experience a high load of DNA damage - without efficient repair systems these cells will die. Accordingly, cancer cells are highly dependent upon DNA repair mechanisms and this new molecular mechanism we have found constitutes an attractive target for cancer therapy."

Researchers design cancer inhibitors

In collaboration with Dinshaw Patel, at Memorial Sloan-Kettering Cancer Center in New York, the research group from BRIC has obtained a detailed crystal structure of the TONSL protein bound to the histone protein, which they show directs TONSL to DNA lesions. This structure tells researchers how the protein works and gives them the opportunity to design a molecule that can bind to TONSL and prevent it from locating the DNA damages. Such an inhibitor molecule may be used in the treatment of cancer because blocking of TONSL function could promote cancer cells to accumulate DNA damage and eventually die. The research team has now put together a team of experts in medicinal chemistry and rational drug design to develop small molecule inhibitors.

PHD student Giulia Saredi has been in charge of the functional cell biological experiments.

"When our cells divide, not only our DNA is copied but also so-called epigenetic information which is vital for the cells to maintain their identity and stay healthy. The epigenetic information is found in a structure called chromatin. We have discovered that the TONSL molecule recognizes a special chromatin signature which arises when the DNA is duplicated during cell division. TONSL is able to read this signature to boost the repair of damages in our DNA."

The researcher's discovery provides a new foundation to understanding how chromatin - the structure that organizes DNA in the nucleus - directs DNA repair processes within our cells. As basic researchers they chase the understanding of how our cells function and this has now generated a unique possibility for designing inhibitors that may be useful in cancer treatment.

"Basic research is our core competence and this discovery shows, once again, that society's investment in understanding basic biological processes is vital to open new avenues that can be explored for disease treatment. The possibility of exploiting our basic research findings for advancing cancer treatment in the future is an important driving force in our work," says Professor Anja Groth.

More information: H4K20me0 marks post-replicative chromatin and recruits the TONSL-MMS22L DNA repair complex, *Nature*, DOI: 10.1038/nature18312

Provided by University of Copenhagen

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