PRESS RELEASE

Breaking bad: How breaks in folded, active DNA promote leukaemia in response to cancer therapy

Mainz, 13 June 2019. *Cancer is one of the most prevalent diseases worldwide, with the World Health Organisation estimating 18.1 million new cases in 2018. The predominant method for fighting cancer is still chemotherapy – introducing a toxic substance to the body that preferentially kills cancer cells. When effective, this is literally a lifesaver but chemotherapy can also cause severe complications. One of the worst is the development of a second cancer, usually leukaemia, arising from toxic damage to the DNA of cells in the bone marrow. New research published in* Molecular Cell *from the group of Vassilis Roukos at the Institute of Molecular Biology (IMB) in Mainz unveils how these treatment-related cancers can arise.*

When treating cancer, one of the most successful strategies is to damage the DNA of the cancer cell to the point that the cell can no longer function. So-called topoisomerase poisons are anticancer drugs that work by blocking cellular enzymes called topoisomerases. These enzymes make temporary cuts in the DNA to help it unwind whenever it needs to be copied or read. When these enzymes are blocked by topoisomerase poisons, they stall on the DNA molecule leading to DNA damage that kills cancer cells. This strategy has its drawbacks however, as healthy cells may also be affected. Unintentional DNA breaks in healthy cells produce unstable DNA ends which may then fuse inappropriately with ends from different breaks, linking up parts of the genome that are normally separated. These DNA rearrangements (translocations) can disrupt gene regulation, possibly leading to the development of a second, therapy-induced cancer.

Previous studies showed that therapy-induced cancers typically involve these types of DNA rearrangements. Moreover, they very often involve the same gene regions fusing together, producing rearrangements which promote leukaemia. However, it was unclear why these particular leukaemia-promoting fusions predominate after treatment with topoisomerase poisons. The pattern suggested that there was something unique about these regions and the genes therein, which makes them more likely to be rearranged.

In their work published in the latest issue of *Molecular Cell*, Dr Vassilis Roukos and his group at IMB in Mainz, together with the lab of Argyris Papantonis (Center for Molecular Medicine Cologne) and the lab of Nicola Crosetto (Karolinska Institute, Stockholm), combined cutting-edge genomics and single-cell imaging methods to solve this puzzle. They found that certain sites may be more susceptible to DNA rearrangements after cancer treatment because they are fragile and more liable to break.

Inside a cell, DNA is not arrayed in one long string, but is folded up on itself in loops and coils. These structures help compact DNA into the tiny size needed to fit into a nucleus. The two strands of DNA are routinely separated and straightened, making way for enzymes that copy or read the genetic code. Much like with a telephone cord, straightening one section of DNA forces extra twists into nearby regions. The neighbouring DNA becomes contorted, placing a large mechanical strain on the genome. This strain is relieved by the action of topoisomerases that cut the DNA, allowing it to unwind.

Dr Roukos and his team found that highly active genes tend to be close to regions of DNA folding, which may need more mechanical stress relief. It is their location that makes these genes more susceptible to DNA breaks caused by topoisomerase poisons. Indeed, the researchers showed that genes which translocate most often in certain types of leukaemias are both highly active and located close to regions that define how DNA is folded.

As Dr Roukos explains: “Genes that frequently fuse tend to be active and are located close to regions which shape how chromosomes fold. These regions are quite fragile and prone to breaking, producing rearrangements which disrupt genetic function and promote abnormal, rapid cell growth, driving the development of leukaemia. Together with the specific gene deregulation that these rearrangements promote, this finding may explain why treatment with topoisomerase poisons is associated with specific genomic rearrangements and leukaemias.” Overall, this study highlights how gene activity and the arrangement of DNA within the nucleus can have a profound impact on events that trigger genomic instability to promote cancer.

Further details

The paper in which this research is presented can be found at https://www.cell.com/molecular-cell/fulltext/S1097-2765(19)30387-9.

Vassilis Roukos is a Group Leader at IMB. Further information about research in the Roukos lab can be found at www.imb.de/research/roukos.

About the Institute of Molecular Biology gGmbH

The Institute of Molecular Biology gGmbH (IMB) is a centre of excellence in the life sciences that was established in 2011 on the campus of Johannes Gutenberg University Mainz (JGU). Research at IMB focuses on three cutting-edge areas: epigenetics, developmental biology, and genome stability. The Institute is a prime example of successful collaboration between a private foundation and government: The Boehringer Ingelheim Foundation has committed 154 million euros to be disbursed from 2009 until 2027 to cover the operating costs of research at IMB. The State of Rhineland-Palatinate has provided approximately 50 million euros for the construction of a state-of-the-art building and will give further 52 million in core funding from 2020 until 2027. For more information about IMB, please visit: www.imb.de.

Boehringer Ingelheim Foundation

The Boehringer Ingelheim Foundation is an independent, non-profit organization committed to the promotion of the medical, biological, chemical, and pharmaceutical sciences. It was established in 1977 by Hubertus Liebrecht (1931–1991), a member of the shareholder family of the company Boehringer Ingelheim. With the Perspectives Programme “Plus 3” and the Exploration Grants, the foundation supports independent junior group leaders. It also endows the internationally renowned Heinrich Wieland Prize as well as awards for up-and-coming scientists. In addition, the Foundation is donating a total of 154 million euros from 2009 to 2027 to the University of Mainz for the Institute of Molecular Biology (IMB). Since 2013, the Foundation has been providing a further 50 million euros for the development of the life sciences at the University of Mainz. www.bistiftung.de

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