PRESS RELEASE

Dividing cells fix damaged DNA in nuclear PORTs

Mainz, 11 October 2019. *The research group lead by Professor Helle Ulrich at the Institute of Molecular Biology (IMB) in Mainz, Germany has made a breakthrough discovery in how cells repair damaged DNA during replication. In an article published today in* Molecular Cell*, they show that during and after DNA replication the damaged portions are repaired in specialised areas of the nucleus, which they named 'postreplicative repair territories', or PORTs. This discovery advances our understanding of how cells cope with damaged DNA during replication and provides a mechanistic basis on which new drug therapies could be designed in the future.*

DNA encodes the information necessary for cells to function and must be faithfully replicated every time a cell divides to ensure that the correct information is passed to both daughter cells. Replication of DNA is carried out by DNA polymerases, which 'read' the bases in the parent strand and insert complementary bases to synthesize a new, perfectly matching daughter strand. However, DNA is frequently damaged by everyday exposure to UV radiation, oxidative stress and mutagenic chemicals. These damaging agents can chemically modify bases in the DNA, creating what is known as a DNA lesion.

DNA lesions are very common, occurring more than 100,000 times per cell per day, and are a problem for DNA replication because the modified bases do not match any of the normal bases. If the lesions are not repaired to restore the original sequence the daughter cell may lose genetic information and no longer function properly, leading to cell death. Indeed, drugs that prevent cells from repairing their DNA can be used to kill rapidly dividing cancer cells, which are often particularly vulnerable to DNA damage.

To cope with constant exposure to environmental insults, cells must be able to repair lesions. However, it is unclear how this repair is coordinated with DNA replication. Scientists had previously assumed that replication stalls when DNA polymerase encounters a lesion, and that the damaged DNA would then relocate to dedicated DNA repair centres at the periphery of the cell nucleus, where other types of DNA damage such as double-strand breaks are repaired. However, this theory had never been experimentally proven.

To investigate how and where DNA lesions are repaired during replication, Prof. Ulrich and her colleagues labelled Replication Protein A (RPA), a protein which binds to DNA that is actively undergoing repair, with a fluorescent marker. They then used microscopy to monitor the location of the fluorescent RPA signal in dividing yeast cells that had been treated with a drug that induces DNA lesions.

To their surprise, the fluorescent RPA signal did not co-localise with known DNA repair centres at the nuclear periphery, indicating that the lesions were not being repaired in the same place as double-strand breaks. Instead, the RPA signals formed distinct foci inside the nucleus. Moreover, rather than binding to actively replicating DNA, the fluorescent RPA bound to regions of DNA that had already completed replication 30 min ago. This shows that lesions are not repaired in stalled, replicating DNA, but are repaired sometime *after* replication. Prof. Ulrich and her team named these previously unknown repair regions in the nucleus 'postreplicative repair territories', or PORTs.

As Prof. Ulrich says, “Our findings are surprising because they show that cells appear to go to great lengths in order to keep DNA repair processes well away from ongoing genome replication. This makes us reconsider our ideas about how cells deal with DNA lesions during replication.” Prof. Ulrich and her colleagues now hope to understand how PORTs are formed and the precise proteins and processes involved in repairing lesions. Understanding which repair proteins are responsible for fixing lesions could eventually reveal new drug targets for killing cancer cells.

Further details

Helle Ulrich is the Executive Director of IMB and Professor of Biology at Johannes Gutenberg University Mainz. Further information about research in Ulrich lab can be found at https://www.imb.de/research/ulrich/research/. The paper mentioned in this work can be found at https://www.cell.com/molecular-cell/pdfExtended/S1097-2765(19)30700-2.

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.

About Johannes Gutenberg University Mainz

Johannes Gutenberg University Mainz (JGU) is a globally recognized research-driven university with around 31,500 students. Its main core research areas are in particle and hadron physics, the materials sciences, and translational medicine, while its most outstanding research achievements in the humanities have been attained in the fields of American Studies and Historical Cultural Studies. JGU's academic excellence is reflected in its success in the Excellence Initiative of the German federal and state governments: In 2012, the university's Precision Physics, Fundamental Interactions and Structure of Matter (PRISMA) Cluster of Excellence was approved and the funding of its Materials Science in Mainz (MAINZ) Graduate School of Excellence was extended. Moreover, excellent placings in national and international rankings, as well as numerous other honors and awards, demonstrate just how successful Mainz-based researchers and academics are. Further information at www.uni-mainz.de/eng.

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.

Press contact for further information

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