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Role of a childhood cancer-linked BRIP1/FANCJ germline variant in genomic instability and cancer cell vulnerability

Lifestyle factors are major cause of cancer in adults. In contrast, lifestyle factors are negligible in childhood cancer, where inherited variants in cancer predisposition genes contribute to a considerable proportion. Whole-exome sequencing of the germlines of parent–child trios (Trio-WES) is a powerful approach to identify rare, potentially causative genetic variants in childhood cancer. In this project, we specifically focused on a Trio-WES analysis performed on an 11-year-old cancer patient and parents,. Our Trio-WES analysis identified an inherited, rare monoallelic germline variant (c.485G>A; p.R162Q) in BRCA1-interacting protein 1 (BRIP1), a DNA helicase also known as Fanconi anemia group J (FANCJ). Notably, stable BRIP1 R162Q expression specifically heightened cellular sensitivity to DNA replication stress . Consistent with this phenotype, BRIP1 R162Q expressing cells displayed elevated basal phospho-RPA32 (Ser8) foci, reduced replication fork speed, increased fork stalling, and impaired fork symmetry, indicative for DNA replication stress. In addition, BRIP1 R162Q expressing cells showed increased chromosomal aberrations, directly linking BRIP1 R162Q to genomic instability, a hallmark of cancer. Mechanistically, we found that BRIP1 R162Q dependent DNA replication stress arises from an overload of unresolved DNA secondary structures, in particular G-quadruplexes and R-loops. Finally, we demonstrate that BRIP1 R162Q expression sensitizes cells to inhibitors of DNA damage checkpoint kinase ATR and DNA-PK, as well as G4 stabilizing drugs. In summary, our results propose that the rare BRIP1 R162Q germline variant identified in childhood cancer drives genomic instability, and reveals a potential therapeutic vulnerability associated with elevated DNA secondary structures in cancer cells.

Biography

Prof. Dr. Thomas G. Hofmann is Director of the Institute of Toxicology and W3 Professor of Toxicology at the University Medical Center of Johannes Gutenberg University Mainz, Germany. He is an internationally recognised expert in molecular toxicology, cancer biology, and the cellular DNA damage response. Since 2018, he has led the Institute of Toxicology, where his research focuses on understanding how cells respond to DNA damage and genotoxic stress, with the aim of developing innovative therapeutic strategies for cancer and age-related diseases

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