PhD Student
(m/f/d)
in
„DNA polymerase theta (Polθ) on mediating R-loop-induced genome instability“

Project Description

R-loops are three-stranded nucleic acid structures consisting of an RNA-DNA hybrid and a displaced single-stranded DNA[1]. They form naturally during transcription, where they regulate gene expression, chromatin structure, and DNA repair processes such as immunoglobulin class-switch recombination (CSR) and telomere maintenance[1–3]. However, when improperly regulated, R-loops can lead to replication-transcription conflicts, DNA damage, and genome instability, contributing to diseases such as cancer and neurodegenerative disorders[4,5]. Despite their physiological importance, the mechanisms by which R-loops induce genomic instability remain incompletely understood.

DNA Polymerase theta (Polθ, encoded by the *polq* gene) is a predominant mediator of Polθ-mediated end joining (TMEJ) in most eukaryotes[6]. TMEJ is an alternative DSB repair pathway that operates when homologous recombination (HR) or non-homologous end joining (NHEJ) are compromised[7–9]. Unlike HR, which ensures error-free repair, TMEJ is highly mutagenic, utilizing microhomologies to ligate broken DNA ends and frequently generating deletions or insertions[10]. While initially considered a backup pathway, recent studies suggest that TMEJ is a primary repair pathway in specific contexts, including replication stress, DNA damage in cancers cells, and CSR[8,11,12]. Intriguingly, many of these conditions are also associated with R-loop accumulation, raising the possibility that Polθ may play a direct role in repairing R-loop-induced damage.

Caenorhabditis elegans (C. elegans) provides an ideal model to study this relationship. The *C. elegans* germline exhibits high TMEJ activity, particularly in response to replication stress, and mutants with elevated R-loops show increased DSBs in germline[11,13,14]. This study will provide fundamental insights into how R-loops influence DNA repair pathway choice and contribute to genome instability. Our findings may also provide novel therapeutic strategies targeting R-loop-associated malignancies.

Publications relevant to this project

1. Allison, D. F. & Wang, G. G. R-loops: formation, function, and relevance to cell stress. *CST* **3**, 38–46 (2019).
2. Fernandes, R. V., Feretzaki, M. & Lingner, J. The makings of TERRA R-loops at chromosome ends. *Cell Cycle* **20**, 1745–1759 (2021).
3. Huang, F.-T., Yu, K., Hsieh, C.-L. & Lieber, M. R. Downstream boundary of chromosomal R-loops at murine switch regions: Implications for the mechanism of class switch recombination. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 5030–5035 (2006).

4. Li, F. *et al.* R-Loops in Genome Instability and Cancer. *Cancers* **15**, 4986 (2023).
5. Perego, M. G. L., Taiana, M., Bresolin, N., Comi, G. P. & Corti, S. R-Loops in Motor Neuron Diseases. *Mol Neurobiol* **56**, 2579–2589 (2019).
6. Ramsden, D. A., Carvajal-Garcia, J. & Gupta, G. P. Mechanism, cellular functions and cancer roles of polymerase-theta-mediated DNA end joining. *Nat Rev Mol Cell Biol* **23**, 125–140 (2022).
7. Zatreanu, D. *et al.* Polθ inhibitors elicit BRCA-gene synthetic lethality and target PARP inhibitor resistance. *Nat Commun* **12**, 3636 (2021).
8. Ceccaldi, R. *et al.* Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair. *Nature* **518**, 258–262 (2015).
9. Schimmel, J., Kool, H., Van Schendel, R. & Tijsterman, M. Mutational signatures of non-homologous and polymerase theta-mediated end-joining in embryonic stem cells. *The EMBO Journal* **36**, 3634–3649 (2017).
10. Schimmel, J., van Schendel, R., den Dunnen, J. T. & Tijsterman, M. Templated Insertions: A Smoking Gun for Polymerase Theta-Mediated End Joining. *Trends in Genetics* **35**, 632–644 (2019).
11. Roerink, S. F., van Schendel, R. & Tijsterman, M. Polymerase theta-mediated end joining of replication-associated DNA breaks in *C. elegans*. *Genome Res.* **24**, 954–962 (2014).
12. Yan, C. T. *et al.* IgH class switching and translocations use a robust non-classical end-joining pathway. *Nature* **449**, 478–482 (2007).
13. Wang, S., Meyer, D. H. & Schumacher, B. Inheritance of paternal DNA damage by histone-mediated repair restriction. *Nature* **613**, 365–374 (2023).
14. Hicks, T. *et al.* R-loop-induced irreparable DNA damage evades checkpoint detection in the *C. elegans* germline. *Nucleic Acids Research* **50**, 8041–8059 (2022).

Contact Details

Email: S.Wang@imb-mainz.de

Webpage: https://imb.de/wang