EuReCa International PhD Program

PhD thesis project

2021 Call for application

Deciphering the role of transcription-replication conflict and R-loop in causing genome instability in breast cancer

General information

Call	2021
Reference	2021-02-CHEN
Keyword(s)	Replication stress; Transcription-replication conflicts; R-loops; Genome instability; Breast cancer

Director(s) and team

Thesis director(s)	Chunlong Chen
Research team	Replication Program and Genome Instability
Research department	UMR3244 - Dynamics of Genetic Information

Description of the PhD thesis project

DNA replication is an essential fundamental biology process. Replication program must adapt to changes in chromatin organization associated with cell differentiation and development, whose deregulation can challenge genome stability and leads to mutations, cancer and many other human diseases.

However, despite intensive studies, the mechanisms that coordinate where and when replication initiates in the human genome remain poorly known.

Our team focuses on using cutting-edge single cell and high-throughput genomic approaches to study the spatio-temporal replication program of the human genome and its impact on genome stability. Breast Cancer (BC) is the most frequently diagnosed cancer in women, in which Estrogen (E2) plays a critical role in the carcinogenesis of estrogen-receptor (ER)-positive BC (75% of all BC cases), while the underlying molecular mechanisms are still unclear. Transcriptional changes induced by E2 in ER+ BC cells, promote R-loop formation, strongly correlated with the genome instability observed in replicating cells. It highly suggests that the observed genome instability might result from transcription-replication conflicts (TRCs).

We and others have recently shown that, during replication stress, there is an increased head-on (HO) orientation replication, causing TRCs and R-loops.

The aim of the current PhD project is to study the link between transcription, DNA replication, R-loop modification and genome instability in both cell line model as well as breast cancer patient samples, in order to understand how E2 induces TRCs, R-loops and DNA damage, and their role in breast cancer development.

The results from human samples of ER+ breast cancer patients and PDX models will contribute to identify new predictive biomarkers in cancer prevention and treatment.

International, interdisciplinary & intersectoral aspects of the project

This is an interdisciplinary project addressing important fundamental biology question and with high clinical potential. The proposal will take advantages of merging molecular and cell biology techniques, high throughput sequencing/imaging approaches and bioinformatics/biostatistics analyses, providing novel data in understanding the TRCs and R-loop relationship in the E2-induced genome instability in breast cancer.

During the PhD project, the student will collaborate with the other team members (both experimental and computational biologists), colleges at Curie hospital, and the world-wide experts in the corresponding fields, as well as with the industry collaborators (such as Bionano Company).

Recent publications

1. Wang W*, Klein K*, Proesmans K*, Yang H*, Marchal C*, Zhu X*, Borrman T*, Hastie A*, Weng Z*, Bechhoefer J#, **CHEN C.L**.# (#co-last authors), Gilbert D.M.# and Rhind N#. (2020) Genome-Wide Mapping of Human DNA Replication by Optical Replication Mapping Supports a Stochastic Model of Eukaryotic Replication Timing. bioRxiv. https://doi.org/10.1101/2020.08.24.263459. Mol. Cell. Under revision.

2. Gnan S., Liu Y., Spagnuolo M., CHEN C.L. (2020) Impact of transcription-mediated replication stress on genome instability and human disease. Genome Instability & Disease (GIAD). 1:207-234. Invited review, doi: http://doi.org/10.1007/s42764-020-00021-y. (invited review)

3. Promonet A.*, Padioleau I.*, Liu Y.* (*co-first authors), Sanz L., Biernacka A., Schmitz1 A.L., Skrzypczak M., Skrzypczak M., Sarrazin A., Mettling C., Rowicka M., Ginalski K., Chedin F., **CHEN C.L**.# (#co-last authors), Lin Y.L.# and Pasero P.# (2020) Topoisomerase 1 prevents replication stress at R-loop-enriched transcription termination sites. Nat. Commun. 11:3940. (featured as Editors' Highlights) https://doi.org/10.1038/s41467-020-17858-2.

4. Brison O.*, EL-Hilali S.*, Azar D., Koundrioukoff S., Schmidt M, Naehse-Kumpf V., Jaszczyszyn Y., Lachages A.M., Dutrillaux B., Thermes C., Debatisse M. and **CHEN C.L.** (2019) Transcription-Mediated Organization of the Replication Initiation Program Across Large Genes Sets Common Fragile Sites Genome-Wide. bioRxiv, doi: https://doi.org/10.1101/714717, Nat. Commun. 10:5693. https://doi.org/10.1038/s41467-019-13674-5 (featured as Editors' Highlights).

5. Petryk N., Kahli M., d'Aubenton-Carafa Y., Jaszczsyzyn Y., Shen Y., Sylvain M., Thermes C., **CHEN C.L.**# (#co-last authors) and Hyrien O.# (2016) Replication landscape of the human genome. Nat. Commun. 7:10208 (cited by Faculty of 1000). Time Cited: 125.

Expected profile of the candidate

We are looking for a motivated PhD candidate, holding, or in the process of completing, a master degree in molecular and cell biology or related areas, with a strong biology background and solid experimental skills, desiring to do interdisciplinary research. Programming skills and expertise in genomics are a plus, but are not compulsory.