



HAL
open science

Integrating the miRnome into multiple omics of Richter Transformation: Insights into the development of aggressive lymphomas

Romain Piucco, Ghislain Fievet, Pierre Feugier, Julien Broséus, Sébastien Hergalant

► **To cite this version:**

Romain Piucco, Ghislain Fievet, Pierre Feugier, Julien Broséus, Sébastien Hergalant. Integrating the miRnome into multiple omics of Richter Transformation: Insights into the development of aggressive lymphomas. JO-BIM2023, Jun 2023, Plouzané (Brest), France. , 2023. <hal-04160201>

HAL Id: hal-04160201

<https://hal.science/hal-04160201v1>

Submitted on 12 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY 4.0 - Attribution - International License

Integrating the miRnome into multiple omics of Richter Transformation: insights into the development of aggressive lymphomas

Romain PIUCCO, Ghislain FIÉVET, Pierre FEUGIER, Julien BROSEUS, and Sébastien HERGALANT

Nutrition, Genetics and Environmental Risk Exposure (NGERE) – Inserm U1256, Campus Biologie Santé, Nancy, France

Corresponding author: romain.piuccio@univ-lorraine.fr

Chronic Lymphocytic Leukemia (CLL) is the abnormal proliferation of small, mature B cells in lymphoid tissues, blood, and the bone marrow. CLL is a slow-progressive often asymptomatic disease manageable in most cases. However, it may transform into an aggressive lymphoma with a Diffuse Large B-Cell Lymphoma (DLBCL) histology in 90% cases, called Richter Transformation (RT). RT is resistant to chemotherapies and associates with a dismal prognosis: the median overall survival is < 12 months [1]. Most RT, but not all, derive from one of the preceding CLL clones (80% cases). Although multiple studies explored the genetic characteristics and the mechanisms involved in the transformation, none of the corresponding CLL histological and molecular features are currently usable to anticipate it. Moreover, discriminating between RT and *de novo* DLBCL is impossible without knowledge of the preceding CLL. This information is often missing, and to date, only a few classifiers of DNA methylation and gene expression data are available to infer the CLL origin of RT [2].

MiRNA (microRNA) are small epigenetic modifiers interfering with the translation process of many transcripts, including those involved in DNA accessibility and chromatin remodelling [3]. In CLL, deregulation of the miRnome, the omic layer quantifying every miRNA, and an overall disrupted epigenetic landscape have been observed, but few data are available at RT stage. The goals of this project are thus to explore RT miRnomes for further insights into the epigenetic mechanisms underlying the disease, improve existing classifiers discriminating RT from DLBCL, and predict outcome in CLL and in previously unclassified lymphomas. Here we will analyse more than 50 RT, CLL prone to RT and DLBCL miRnomes by small RNA-sequencing, perform differential and discriminating analyses, and integrate the data into a multi-omics setup covering other molecular layers available for these pathologies: coding and non-coding transcriptomes, overlapping proteomes and phosphoproteomes, DNA methylomes, exomes and copy-number variations [2,4,5]. To this aim, we are designing a specific miRNA-sequencing integrative pipeline encompassing a mixture of unsupervised methods (mixOmics) [6], deep-learning tools (custOmics) [7], and in-house approaches for paired and independent samples.

References

1. Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. *Blood*. 2011;117(12):3391-3401.
2. Broséus J, Hergalant S, Vogt J, et al. Molecular characterization of Richter syndrome identifies *de novo* diffuse large B-cell lymphomas with poor prognosis. *Nat Commun*. 2023;14(1):309. 2023.
3. Treiber T, Treiber N, Meister G, Regulation of MicroRNA Biogenesis and Its Crosstalk with Other Cellular Pathways. *Nat Rev Mol Cell Biol* 2019, 20 (1), 5–20.
4. Ferreira PG, Jares P, Rico D, et al. Transcriptome characterization by RNA sequencing identifies a major molecular and clinical subdivision in chronic lymphocytic leukemia. *Genome Res*. 2014;24(2):212-226.
5. Kulis M, Merkel A, Heath S, et al. Whole-genome fingerprint of the DNA methylome during human B cell differentiation. *Nat Genet*. 2015;47(7):746-756.
6. Rohart F, Gautier B, Singh A, Lê Cao KA. mixOmics: An R package for 'omics feature selection and multiple data integration. *PLoS Comput Biol*. 2017;13(11):e1005752.
7. Benkirane H, Pradat Y, Michiels S, Cournède PH. CustOmics: A versatile deep-learning based strategy for multi-omics integration. *PLoS Comput Biol*. 2023;19(3):e1010921