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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.

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