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Multi-omics characterization of Richter syndrome unlocks classifiers and predictors of outcome into broader and heterogeneous lymphoma datasets

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Richter syndrome (RS) is the onset of a dismal diffuse large B-cell lymphoma (DLBCL) subtype that exemplifies aggressiveness and chemoresistance occurring in the context of indolent chronic lymphocytic leukemia (CLL). In this study we characterize a large series of human RS samples [1] by genome-wide DNA methylation and whole-transcriptome profiling from a multi-omics setup including additional copy number alterations, exome and proteome data. We comprehensively compare them to i) the paired CLL component, i.e. samples acquired before the aggressive transformation in the same patients, ii) a broad CLL reference group [2] and iii) *de novo* DLBCLs of different cell-of-origin (COO) and molecular classification.

Recent genomic studies combining DNA and RNA sequencing extended DLBCL subtyping beyond COO, identifying subgroups defined by their genomic alteration patterns and associated clinical courses, but a notable proportion remains unclassified [3]. Distinguishing between CLL-derived RS and *de novo* DLBCL in a diagnostic setting based on histology and immunochemistry alone is challenging. Most RS cases arise from the preceding CLL clone, while the remainder are in fact independent *de novo* DLBCLs, a dichotomy of importance for treatment decisions. Indeed, *de novo* DLBCLs are chemosensitive in most patients, whereas CLL-derived RS are chemoresistant, with a median overall survival of around 12 months.

Adjusting for the lack of appropriate human or animal models to study RS, our integrative approach provides insights into its epigenomic architecture, corroborates two evolutionary groups of RS [4] and unravels a CLL epigenetic imprint in clonally related samples. Thus removing the need for the initial CLL tumor DNA, a significant improvement since CLL stage is often undiagnosed and/or corresponding samples unavailable. We also define two novel classifiers: a methylation-based predictor to detect a stable CLL “memory” over disease evolution, and a gene-expression-based scoring method outlining a novel DLBCL subgroup from public datasets harboring this CLL-derived RS epigenetic imprint. Applying both classifiers to omics data from landmark studies uncovers a subset of “RS-type” DLBCL enriched in cases with a specific COO signature, unclassified or undetected by other genomic classifiers, and with the same unfavorable prognosis as RS. These findings directly translate prognostication of *de novo* DLBCLs, the most common human B-cell lymphoma, and associate them linearly with overall and progression-free survival, independently of known clinical factors and biological covariates.

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