Evolutionary history of transformation from chronic lymphocytic leukemia to Richter syndrome.

Parry EM, Leshchiner I, Guièze R, Johnson C, Tausch E, Parikh SA, Lemvigh C, Broséus J, Hergalant S, Messer C, Utro F, Levovitz C, Rhrissorrakrai K, Li L, Rosebrock D, Yin S, Deng S, Slowik K, Jacobs R, Huang T, Li S, Fell G, Redd R, Lin Z, Knisbacher BA, Livitz D, Schneider C, Ruthen N, Elagina L, Taylor-Weiner A, Persaud B, Martinez A, Fernandes SM, Purroy N, Anandappa AJ, Ma J, Hess J, Rassenti LZ, Kipps TJ, Jain N, Wierda W, Cymbalista F, Feugier P, Kay NE, Livak KJ, Danysh BP, Stewart C, Neuberg D, Davids MS, Brown JR, Parida L, Stilgenbauer S, Getz G, Wu CJ.

Nat Med. 2023 Jan;29(1):158-169

The molecular basis of CLL transformation to Richter syndrome (RS) is an area of intense research. In this important paper the authors provide results of comprehensive genomic and transcriptome interrogation both at the level of the bulk tumour population but also at single cell level.

Using matched CLL, RS DNA samples and where available germline, the authors identify mutations in *NOTCH1,* DNA damage response and the MAPK pathway, that are similar to pre-existing CLL, but they also observe alterations in epigenetics, interferon/inflammatory signalling, cell-cycle deregulation and immune evasion, the features that are specific to RS only.

The authors undertook genomic analysis of RS following targeted treatments as a separate cohort and observed that in this instance, transformation is an heterogenous process that is distinct from acquired resistance in CLL and is characterized by complex evolution marked by accumulation of multiple events.

Furthermore, by using combined genomic and transcriptomic analysis, the authors identified five molecular subtypes of RS. They observed that subtypes 1,3 and 5 were all enriched for *TP53* alterations and showed an elevated number of genomic copy number alterations.

In particular, RS1 was characterised by *MYC* amplification and whole genome duplication. In addition to *TP53* alterations, the RS3 subtype showed evidence of *NOTCH1* mutations as well as deletions in the long arm of the chromosomes 14, 19, 15 16 and 2, whereas RS5 had similar features but was lacking *NOTCH* mutations.

RS subtype 2 was characterised by trisomy 12 ant *NOTCH1* mutations as well as *KRAS* mutations; and RS4 featured mutations in *SF3B1* and *ERG2* on the background of a 13q deletion.

Genomic analysis also identified mutational processes that could potentially underlie transformation to RS, including AID and POLE signatures as well as the signature associated with mismatch repair.

Overall, the genomic analysis suggested that in the majority of patients RS was unrelated to the pre-existing CLL, but was genetically different from de novo DLBCL. Namely, DLBCL-like RS, which is unrelated to pre-existing CLL tumour, has a better prognosis.

Finally, a single cell analysis of RS clonal evolution, identified two principal patterns: one where mutations were acquired in a pre-existing CLL clone and intranodal cells resided on a genetic and transcriptional continuum from indolent to aggressive CLL towards RS, and the other where the RS clone was independent and could be detected early in CLL phase. This gave the authors an idea to explore the possibility of an early RS detection using cell-free DNA. Indeed, RS-associated genomic features could be detected in plasma.

This paper has a clear translational impact and identifies RS-specific molecular alterations that can be potentially targeted early in RS pathogenesis, before the emergence of the highly resistant RS clone.

Pathways that are selectively altered in Richter's syndrome are presented in light purple colour