Summary

Chronic lymphocytic leukemia (CLL) usually follows an indolent course. Yet, progression into a diffuse large B cell lymphoma (DLBCL) known as Richter's syndrome (RS) occurs in 2-10 % of patients and results in a very poor prognosis. Mutations frequently involved in RS transformation affect *TP53*, *CDKN2A*, or *c-MYC*, however, a huge proportion of patients do not have acquired additional mutations and the molecular mechanisms involved still remain unknown. Due to the high dependence of CLL B cells on B cell receptor (BCR) mediated survival signals, the influence of a constitutively active AKT (AKT-CA), a pivotal signal molecule of the BCR, was investigated on a murine CLL background (Eµ-TCL-1) resulting in the TCA and TCγ1A mouse line. Here, we not only define a connection between high-risk mutations and elevated pAKT levels in CLL patients, but more importantly show that AKT-CA expressing CLL cells progress to RS in mice. Moreover, a small population of CLL cells expressing AKT-CA was sufficient to induce RS suggesting that the subpopulation clonally expands and outcompetes the other CLL cells. In 12.5 % of RS patients elevated AKT activation was identified, supporting the observation in mice that survival signals in CLL cells can drive disease progression to RS. The new RS mouse model will help to decipher the molecular mechanisms responsible for transforming events. Preliminary results show that pAKT likely acts via GSK-3β inhibition and subsequent c-Myc and/or Mcl-1 stabilization resulting in increased survival and proliferation. AKT activity is also linked to genomic instability, which in turn leads to further mutations resulting in transforming events within a cell. To identify new treatments for RS patients with elevated pAKT levels, models such as the TCA and TCγ1A mouse lines are essential to test therapies prior to clinical trials. Moreover, this work supports the use of pAKT staining as a prognostic tool to identify this subgroup of RS patients and to find the most effective and tailored treatment including the use of AKT inhibitors. Taken together, this study unraveled the critical impact of aberrant AKT activation in RS transformation and provides the first mouse model for Richter's syndrome.