Abstract

Richter syndrome represents the transformation of chronic lymphatic leukemia (CLL) to an aggressive lymphoma, in the majority of cases in diffuse large B-cell lymphoma (DLBCL). Richter syndrome has a poor prognosis and the pathogenic mechanisms underlying transformation are poorly understood. The tumor suppressor gene TNFAIP3 (A20) is involved in the negative regulation of the NF-κB - pathway and has been shown to be inactivated in various lymphoid malignancies.

The A20 gene is encoded by a zinc finger protein containing a functional OTU domain at its N-terminal portion which hydrolyses polyubiquitin chains and seven zinc fingers at its C-terminal portion that show redundancy in inhibition of NF-κB activation. The aim of this study was to analyze whether TNFAIP3 is inactivated in Richter syndrome through genetic or epigenetic alterations.

Mutational analysis and promoter hypermethylation analysis of CpG islands showed that inactivation of A20 by mutation or epigenetic mechanisms seems to be of minor importance for the transformation to Richter syndrome. However, the gene copy number assay using real time PCR revealed 6/16 deletions (=37%) within the A20 locus. If confirmed by a complementary method these results indicate that deletions rather than mutations seems to be involved in the molecular pathogenesis of Richter syndrome and may represent a major contributor to lymphomagenesis in this lymphoma subtype.