14P LINE-1 hypomethylation is a specific aberration in human hepatocellular carcinomas and correlates with shorter overall survival and CIMP-phenotypes

S.L. Anwar1, A. Vogel2, U. Lehmann3
1Gadjah Mada University/Dr. Sardjito General Hospital, Yogyakarta, Indonesia, 2Hannover Medical School, Hannover, Germany, 3Institute of Pathology, Hannover Medical School, Hannover, Germany

Background: Reactivation of interspersed repetitive sequences due to loss of methylation is associated with genome instability, one of the hallmarks in cancer. LINE-1 hypomethylation represents global methylation loss and has potential diagnostic and prognostic biomarkers in tumors. However, the correlation of LINE-1 hypomethylation with clinicopathological determinants and CpG island methylator phenotype (CIMP) in patients with liver tumors is not yet well defined.

Methods: We performed quantitative DNA methylation analysis in LINE-1, RASSF1A, and CCND2 genes using pyrosequencing in human hepatocellular carcinomas (HCC, n = 40), hepatocellular adenoma (HCA, n = 10), focal nodular hyperplasia (FNH, n = 5), and respective peritumoral liver tissues as well as healthy liver tissues (n = 5).

Results: We found loss of LINE-1 DNA methylation only in HCCs and significantly correlated with poor survival (log rank test, p = 0.007). Inverse correlation was found between LINE-1 with RASSF1A DNA methylation levels ($r^2 = 0.47$, p = 0.002). LINE-1 hypomethylation correlated with concurrent RASSF1A/CCND2 hypermethylation (Fisher’s exact test, p = 0.02). LINE-1 hypomethylation and RASSF1A/CCND2 hypermethylation were not found in benign hepatocellular tumors (HCA and FNH) representing specific aberrations only in malignant liver transformation.

Conclusions: LINE-1 hypomethylation might serve as a future predictive biomarker to identify HCC patients with unfavorable overall survival and CIMP-phenotypes.

Legal entity responsible for the study: Medizinische Hochschule Hannover, Germany.

Funding: DFG Deutsche Forschungsgemeinschaft.

Disclosure: All authors have declared no conflicts of interest.