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Methylation of p53-responsive microRNA genes in tumor tissue of lymphoma

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Motivation and Aim: The p53-mediated response to genotoxic cellular stress is largely carried out by activation of oncosuppressive and suppression of oncogenic microRNA [1, 2]. The aim of our study was to identify the frequency, specificity and clinical significance of *MIR-34B/C, MIR-34A, MIR-203* and *MIR-129-2* genes methylation in Diffuse Large B-cell Lymphoma (DLBCL).

Material and Methods: DNA was extracted from primary FFPE-samples and treated to convert unmethylated cytosine to uracil. Methylation status was analyzed by methyl-specific PCR and methyl-sensitive HRM in 73 tumor samples and 11 samples with reactive polyclonal B-cell proliferation. We evaluated the combined methylation of genes in pairs using the one-sided Fisher exact criterion (p-value) and multiple testing correction with Benjamin-Hochberg procedure (q-value).

Results: Methylation of *MIR-129-2, MIR-203, MIR-34A* and *MIR34B/C* in tumor samples occurred with a frequency of 67, 66, 27 and 62 % respectively. Methylation of the analyzed genes in the tissue of reactive lymph nodes was not detected. Combined methylation of *MIR-203, MIR-129-2* and *MIR-34B/C* genes (p = 0.013, q = 0.020), as well as pairs of *MIR-34B/C* and *MIR-34A* genes (p = 0.010, q = 0.029) has been shown. An assessment of the relationship between studied microRNA genes methylation and clinical and laboratory features of the disease showed that 18/20 (90 %) patients in the subgroup with the *MIR-34A* gene methylation had a high and intermediate/high risk according to International Prognostic Index against 26/53 (49.1 %, p = 0.002) in the subgroup of patients without this gene methylation. Methylation of *MIR-34A* was associated with reduced frequency of remission (p = 0.060) and decreased overall survival (p = 0.162). Methylation of *MIR-34B/C* (p = 0.026) and *MIR-203* (p = 0.011) was associated with Ki-67 expression level of more than 45 %.

Conclusions: Tumor-specific methylation of gene promoters can serve as a significant mechanism for reducing the miR-34B/C, miR-34A, miR-203 and miR-129 expression in DLBCL. Aberrant methylation of oncosuppressive microRNA genes associated with underlying p53 signalling pathways is a potentially useful molecular biomarker in the lymphoma diagnosis. *MIR-34A* gene methylation is helpful in prognosis and targeted therapy strategy development of DLBCL.

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