DNA METHYLATION IN BLOOD LYMPHOCYTES AND RISK OF LUNG CANCER

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Background and Aims: Aberrant DNA methylation is a common event in cancer development, lung cancer included. Aim of our study is to determine whether alterations in global and gene-specific DNA methylation in peripheral blood lymphocytes (PBLs) can precede and thus predict lung cancer development.
Methods: The study subjects were selected from a Danish prospective study and were free-of-cancer at the enrollment (1993-1997). Blood samples and information on life-style (smoking habits, diet) were collected. 276 lung cancer cases were diagnosed (1994-2003) and a sub-cohort of 303 controls was selected and frequency matched on sex and age according to the case-cohort design. Methylation state of *LINE*-1 repetitive elements (global methylation) and of gene-specific promoters of *microRNA124a*, tumor suppressor (*p16, RASSF1A, DAPK*), DNA-repair (*MSH2, MGMT, hMLH1*) and cell-proliferation genes (*CDH1, CDH13, RARβ*) was measured in PBLs by PCR-Pyrosequencing.
Hazard Ratios (HR) for lung cancer were estimated with Cox models, adjusted for age, sex, and smoking status. We created gene-specific dichotomous variables (equal to 0 or 1 if methylation lays below or above the 75th percentile of each gene-specific distribution, respectively) and summed them (excluding *LINE*-1) to calculate methylation indexes for overall methylation (MI), tumor suppressor genes (TSGI), DNA-repair genes (DRGI), and cell-proliferation genes (CPGI).
Results: Gene-specific methylation indexes were significantly positively associated with lung cancer risk for MI, TSGI and DRGI [HR=1.25 (95%CI 1.14-1.36; p<0.001), HR=1.19 (95%CI 1.02-1.38; p=0.030) and HR =1.59 (95%CI 1.35-1.87; p<0.001)] but not for CPGI and microRNA124a [HR=1.09 (95%CI 0.92-1.29; p=0.301) and HR=1.10 (95%CI 0.84-1.44; p=0.502)]. LINE-1 index was inversely correlated with lung cancer risk [HR=0.13 (95%CI 0.07-0.22; p<0.001)].
Conclusions: Specific methylation tumorigenic patterns are found in PBLs (in particular DNA-repair and tumor suppressor gene hypermethylation together with LINE-1 hypomethylation) and precede lung cancer development. Such results suggest how DNA methylation changes could be predictive of lung cancer risk.