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Loss of heterozygosity combined with promoter hypermethylation, the main mechanism of human MutL Homolog (*hMLH1*) gene inactivation in non-small cell lung cancer in a Chinese population

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ABSTRACT

Aims and background. The mechanism of human MutL Homolog (*hMLH1*) gene transcriptional inactivation in non-small cell lung cancer (NSCLC) is still unclear. The aim of this study is to further investigate the main mechanism of *hMLH1* gene inactivation in NSCLC samples of Chinese patients.

Methods and study design. This study was performed in surgically resected primary tumor and matched normal tissues from 116 NSCLC cases. The *hMLH1* gene alterations examined included loss of heterozygosity (LOH) by D3S1612 locus PCR-electrophoresis-silver staining and promoter methylation by *Hpa*II/ *Msp*I-based PCR analysis. Loss of *hMLH1* mRNA expression was analyzed by reverse transcription-polymerase chain reaction (RT-PCR) and loss of hMLH1 protein expression was studied by immunohistochemistry and Western blot.

Results. The frequencies of LOH and promoter hypermethylation of the *hMLH1* gene were 68.1% (79/116) and 72.4% (84/116), respectively. Among the 79 *hMLH1* LOH (+) cases, 68 (86.1%) showed hypermethylation, which was significantly higher than in the LOH (-) group. The frequencies of loss of *hMLH1* mRNA expression and protein expression in NSCLC were 79.3% (92/116) and 76.7% (89/116), respectively. The frequency of 2-hit inactivation of *hMLH1*, 75.3% (67/89), by LOH combined with promoter hypermethylation was related to the loss of protein expression.

Conclusions. Biallelic inactivation of the *hMLH1* gene by LOH combined with promoter hypermethylation is likely to cause inactivation of hMLH1 protein and to play an important role in the development of NSCLC in the Chinese population.

Key words: *hMLH1*, NSCLC, lung cancer, loss of heterozygosity, methylation.

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