Inactivating Mutations of T-Cell Factor 1 in Stomach, Liver, and Colon Cancers

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Background TCF-1 protein was originally identified as a transcriptional activator in Wnt signaling pathway. However, there is accumulating evidence that TCF-1 might also have tumor suppressor properties: (1) TCF proteins can associate with the corepressor proteins such as Groucho or CBP; (2) Mutation of TCF binding site in the promoter of cyclin D1 gene, which was recently identified as a Wnt target, enhanced its basal activity; (3) Tcf-1 knockout mice revealed multiple intestinal polyps.

Methods We performed PCR-based sequencing and LOH analyses of Tcf-1 gene in a total of 234 alimentary tract cancers to determine whether inactivating mutations of Tcf-1 could be involved in the carcinogenesis of alimentary tract cancers.

Results We detected seven somatic mutations of Tcf-1 gene (4 missense, 2 frameshift mutations, one 28-bp inframe deletion mutations); 4 of 99 gastric cancers, one of 54 colon cancers, one of 50 hepatocellular carcinomas and one of 31 hepatoblastomas. All of the mutations are located in Groucho binding domain or truncated large potion of Groucho binding region. Therefore, all the mutants interfered the binding ability of TCF-1 molecule with DNA and showed loss of transcriptional regressive effect in luciferase assay, which can loss of suppressor activity of TCF-1. The frequencies of LOH were 26% in gastric cancer, 33.3% in colon cancer, 23.5% in hepatocellular carcinoma and 20% in hepatoblastoma. Among the 7 cancers with somatic mutation in one allele, two cases showed loss of remaining allele of the Tcf-1 gene.

Conclusion These data strongly suggest that somatic mutation of Tcf-1 may cause the loss of tumor suppressive effect of Tcf-1 and contribute to the development of gastric, colon, and liver cancers.