Oncogenes in Tumors of Gallbladder and Biliary Tract

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https://doi.org/10.15017/19208

出版情報：福岡医学雑誌. 95 (2), pp.31-35, 2004-02-25. 福岡医学会
バージョン: published
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Oncogenes in Tumors of Gallbladder and Biliary Tract

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Introduction

Progress in molecular biology has clarified the involvement of several genetic alterations of proto-oncogenes and tumor suppressor genes in carcinogenesis and cancer progression. Currently, some very sensitive methods suited for the analysis of mutational events in cancer are being successfully employed. Here we give an outline of the well-established mutations of K-ras, p53, and p16 in gallbladder and bile duct carcinomas, which occur in high incidence.

1. K-ras

The K-ras proto-oncogene is thought to exert control over some of the mechanisms of cell growth and differentiation. This gene is converted to an active oncogene by point mutations significantly concentrated in codons 12, 13, or 61. Such activating mutations have been detected in a variety of human neoplasms at different frequencies. The incidence of the mutations has variously been reported to be 17–59% of gallbladder carcinomas1)-4) and 23–100% of bile duct carcinomas5)-6). These variations within the same types of tumors may be caused by different sensitivities of the methods used, background of the patients, location of the tumors, or quality of the samples, etc. Recently, several new findings have been reported from the clinicopathological point of view.

1) Pancreaticobiliary maljunction is often found to be associated with gallbladder carcinomas and is thought to be a cause of carcinoma arising in the biliary tract. An anomalous junction of the pancreaticobiliary duct allows reflux of pancreatic juice into the biliary tract, which then stagnates in the common bile duct or in the gallbladder. The changes in bile may induce damage of the mucosa by chronic inflammation, resulting in regeneration which may lead to genetic alterations, various histologic changes, and ultimately carcinogenesis in the biliary tract epithelium. In fact, the incidence of K-ras mutations in biliary tract carcinomas with a background of pancreaticobiliary maljunction is significantly higher than in those without it, namely, 50–100 % and 6–36 %, respectively7)-9). In addition, a much higher incidence (36–63 %) is identified in the dysplastic precancerous lesions of cases with pancreaticobiliary maljunction7)-9). This suggests that alteration of the K-ras oncogene may be
very important in the early stages of carcinogenesis of biliary mucosa, especially in association with anomalous connections of the pancreatobiliary ducts. Because the highest incidence of K-ras mutation (75–100%) has been reported in cases of pancreatic ductal carcinoma\(^{10–14}\), the high incidence of K-ras mutation in the biliary tract carcinoma of patients with pancreatobiliary maljunction may reflect a pathogenetic process similar to pancreatic ductal carcinoma.

2) It has been reported that K-ras mutation is more frequently detected in carcinomatous and dysplastic lesions in gallbladder carcinoma cases with gall stones than in those without stones\(^4\). Some kinds of environmental changes such as physiological stimulation and repetitive inflammation caused by the presence of stones are possible triggers for the mutations, but more cases need to be analyzed before statistically valid conclusions can be drawn.

3) There was a large difference in the incidence of K-ras mutations between distal (47–75%) and middle or proximal (0–8%) bile duct carcinoma\(^{15}^{16}\). K-ras codon 12 mutations are much more common in distal bile duct carcinoma. Several reasons for this observation can be considered. There may be a difference in biological behavior between distal and proximal portions, which could reflect, for example, different survival rates for resected proximal and distal bile duct carcinomas. Cancer of the pancreas head may be included in the cases of distal bile duct carcinoma. The distal portion may be to some extent influenced by pancreatic juice because of its anatomical location.

4) Most reports indicate that K-ras mutations in biliary tract carcinomas are not statistically significantly correlated with tumor staging, histological type and age, sex, or survival of the patients\(^{1}–9^{15}^{16}\). However, for more reliable conclusions further investigations are required.

2. p53

Wild-type p53 plays an important role in the regulation of the cell cycle process, cell growth and apoptosis in the event of DNA damage. The protein therefore has tumor suppressor properties. Mutations of the p53 gene are the most common genetic alterations in human cancers. The syntheses of mutant proteins from the mutated genes, which disrupt critical growth-regulating mechanisms, are thought to play a crucial role in the carcinogenesis of many types of human neoplasia. Since the mutant p53 proteins have a longer intracellular half-life than the wild-type proteins, a large amount of stabilized mutant protein accumulates in the cells. Therefore, routine immunohistochemical staining is used for the detection of p53 gene mutations, because widespread nuclear staining usually correlates with p53 mutations, even though correlative studies with DNA sequencing to confirm mutation are desirable.

The reported incidence of p53 mutation is 31–92%\(^{17}–26\) in gallbladder carcinoma and 33–73%\(^{22}–29\) in bile duct carcinoma. It is considered that the main reason for the differences between these reports may be due to the use of different p53 antibodies and the differences in cut-off criteria in immunohistochemistry. High expression of p53 protein is more specific for the presence of mutations in the p53 gene\(^{29}\).

There are many reports on the relationship between p53 immunoreactivity and grades, clinical stages of the biliary tract carcinomas, or prognosis of the patients. In general, there is a tendency for higher grade carcinomas to express more p53 protein\(^{17}^{18}^{22}^{24}^{26}\), although
other have reported no correlation between them\textsuperscript{27,28}. These findings suggest that p53 abnormalities may appear early during the transition from low-grade to higher-grade tumors and may play a role in the development of more malignant tumor phenotypes. On the other hand, with the exception of limited data from a small number of reports, alteration of the p53 gene seems to be unrelated to tumor progression or metastatic spread\textsuperscript{27,28,30}. The correlation between p53 expression and prognosis of the patients is not significant\textsuperscript{23,26-28}, although some reports do suggest that p53 protein expression was related to shorter survival of the patients harboring p53-immunopositive tumors\textsuperscript{22,29}. Larger series of patients with complete follow-up data are required to draw statistically significant conclusions.

A statistically significant difference is found for the incidence of p53 protein expression between extrahepatic bile duct carcinomas from the distal portion and those from the lower mid-region\textsuperscript{22}. These investigators reported that 66% of tumors from the distal portion showed mainly a marked immunopositivity for p53, but, in contrast, only 30% from the proximal portion showed p53 immunopositivity, and even this was weak. Because this tendency is the same as that for K-ras mutations, the reasons for the discrepancy between the distal and proximal carcinomas may be the same as mentioned in K-ras section, namely that the pancreaticobiliary maljunction may override the effect of p53 gene mutations\textsuperscript{8}.

3. p16

p16, cyclin-dependent kinase 4 inhibitor, has been identified as a regulatory protein in the cell cycle. The tumor suppressor gene p16 is commonly inactivated in many neoplasms. Three distinct mechanisms of p16 inactivation have been reported in biliary neoplasms: deletion and point mutations of the p16 gene, and hypermethylation of 5' regulatory regions of p16. Although available data are limited, it has been reported that 60-80% of primary biliary tract cancers had point mutations in the p16 gene\textsuperscript{31,32}. Allelic loss at the p16 locus on chromosome 9p21 occurred with sufficient frequency in extrahepatic bile duct cancers\textsuperscript{33} and in gallbladder carcinoma including dysplastic or metaplastic regions\textsuperscript{29}. p16 promoter hypermethylation was present in 9 of 21 primary bile duct cancers\textsuperscript{33}. Therefore, the p16 gene, rather than the p53 and K-ras genes, may possibly be crucial for biliary tract carcinogenesis and progression of biliary tract carcinoma. However, the number of cases analyzed thus far is still small, and investigations comparing p16 mutations and the clinicopathological situation of the tumors have not yet been extensive enough to permit a definitive conclusion to be drawn.

References

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(References with numbers in bold are listed as important ones for readers.)