LETTER TO THE EDITOR

Frequency of Genetic Alterations Observed in Cell Cycle Regulatory Proteins and Microsatellite Instability in Gallbladder Adenocarcinoma: A Translational Perspective

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Dear Sir

Genetic alterations are considered to play an important role in both biological behavior and progression of human malignancies. However, cancer of gallbladder (CAGB) is an obscure phenomenon and is highly malignant with underprivileged diagnosis and poor survival (Chan et al., 2003). Earlier, we reported a significant higher prevalence of CAGB amongst victims of Bhopal gas tragedy exposed to methyl isocyanate (Mishra et al., 2009). This necessitated us to undertake a separate and detailed retrospective characterization of archived CAGB tissue samples for validating potential biomarkers for translational modalities. Tissues from 92 cases of CAGB (31 men and 61 women, age range 16–85 yrs, mean age 45.83 ± 1.50 yrs) with 70 adenocarcinoma (13 well differentiated, 48 moderately differentiated and 09 poorly differentiated), 10 adenosquamous carcinoma and 12 gallbladder adenoma were examined for Kirsten rat sarcoma viral oncogene homolog protein (K-ras), p-53, cyclin-E and Rad-50 expression through immuno-histofluorescence using spectral bio-imaging approach (Mishra et al., 2009). Microsatellite instability (MSI) was determined from PCR amplifications of six-microsatellite marker loci (D16S539, D13S317, D7S820, F13A01, FES/FPS, vWA) using an in-house standardized protocol. Cases were classified as having high-frequency MSI (MSI-H) (/= 2 loci showing instability), low-frequency MSI (MSI-L) (only one locus showing instability), or as microsatellite stable.

Recent research has demonstrated that presence of K-ras mutation may influence diagnosis and clinical management of the patients with CAGB (Kamisawa et al., 2009). In support of our previous study, cases of adenocarcinomas occupied the major share of mutations and analysis of K-ras displayed alteration in its expression pattern among 55 of 70 adenocarcinoma (Figure 1a), with significant frequency being 78.6% (P<0.0001). Simultaneous analysis for p-53, Rad-50 and cyclin-E proteins showed analogous mutational frequency in 51 of 70 (73%), 28 of 70 (40%) and 23 of 70 (32.8%) respectively (P<0.0001).

Of all adenocarcinomas, the expression frequency of above four genes was higher in moderately differentiated adenocarcinoma in comparison to poorly and well differentiated ones. The positivity of mutations in adenosquamous cell carcinoma for above four genes were

Figure 1. K-ras Protein Expression. a) Over expression in adenocarcinoma. Photomicrograph representing hematoxylin and eosin image of K-ras overexpression (i), immunohistofluorescence detection of k-ras protein overexpression in the nuclei of well differentiated adenocarcinoma (ii) moderately differentiated adenocarcinoma (iii), poorly differentiated adenocarcinoma (iv) of gallbladder. (Green spots: positive nuclear staining; DAPI counter-stained tissue: grey color) (K-ras; original magnification 200 X). (b) Immunohistofluorescence detection of k-ras protein overexpression in adenosquamous carcinoma (i), and adenoma with dysplasia (ii) of gallbladder. (Green spots: positive nuclear staining in background of DAPI counter-stained tissue: grey color) (K-ras; original magnification 200 X).
in adenomas. These results imply that expression patterns of p-53, Rad-50, Cyclin-E and K-ras genes were altered along with mixed chimerism of STR loci. Results of our study establish Rad-50 and cyclin-E as potential biomarkers for early diagnosis of the disease hitherto unreported. Investigations are in progress to undertake similar studies on archived tumor tissues of varied origins and forms which might help in identifying and validating potential biomarkers for early prognosis of the carcinogenesis. These might also provide modalities to translate robust and reproducible strategies for defined clinical utility.

References


