Molecular analysis of endoscopic biopsies from gastrointestinal cancers

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One of the goals of our laboratory has been to establish molecular diagnostic factors for various aspects of tumor behavior, including response to specific protocols, recurrence and overall prognosis that can be measured in biopsy tissues and then can be used to design optimal therapy for each patient. Using a highly sensitive technique polymerase chain reaction (PCR)-based technique that could accurately determine the expression of specific genes in biopsy-sized tumor tissue specimens, we measured the expression of thymidylate synthase (TS), the target enzyme of the fluoropyrimidines, in endoscopic biopsies of invasive gastric adenocarcinoma (GAG) tissue.

TS expression varied over 20-fold range among GAG tumors and those tumors with TS expression less than the median had a response rate of 54% to 5-fluorouracil (5-FU)/cDDP while those above median had a response rate of 17%. As a determinant of response to cDDP, we also measured ERCCI expression in those tumors and found that low ERCCI expression predicted for higher response to the chemotherapy. GAG that had both low TS and low ERCCI had a response rate of almost 90% while those with high TS and ERCCI had a response rate of 0%.

In studies on esophageal tumors, we found that esophageal squamous cell carcinoma (ESCC) had a 3-fold lower mean TS expression than adenocarcinoma (EAC), correlating with an overall response rate of 74% in the SCC to 5FU-based protocols compared to 34% for the AC. Similarly to the GAG, EAC with high TS did not respond to treatment. We also compared the status of tumor suppressor genes in ESCC and EAC, P16 expression was absent in 50% of ESCC but in only 5% of the EAC. In ESCC, 70% of the transcriptional losses of p16 were by homozygous deletion (HD) of the gene and the rest by methylation silencing, while no HD was observed in the EAC. Expression of the recently discovered tumor suppressor gene FHIT was also frequently deleted from ESCC but not from EAC. In EAC, multiple transcripts of FHIT were observed corresponding to different exon deletion events. AC of the cardia region had the highest frequency of FHIT abnormalities and the stomach had the lowest. These data suggest that FHIT abnormalities may have a role in the tumorigenesis of esophageal cancers.

In summary, PCR-based analyses of endoscopic biopsies of gastrointestinal tumors were used to
identify gene expressions associated with tumor response to chemotherapy and to characterize molecular differences between different tumor types.