American Journal of Pathology, Vol. 147, No. 3, September 1995

Commentary

Microsatellite Instability

Shifting Concepts in Tumorigenesis

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Occasionally in science a key discovery initiates an avalanche of ideas and scientific data. In its aftermath, parts of the scientific landscape are reshaped. Such is the case in microsatellite instability and the role it appears to play in tumorigenesis.

Microsatellites are short repetitive sequences of DNA that are scattered throughout the genome; they are stably inherited, unique to each individual, and have a low inherent mutation rate.[1,2] Instability within these microsatellites was described initially by three different groups of investigators studying colorectal cancers.[3–5] Specifically, the length of microsatellite DNA was found to vary in the tumor tissue and in the matching constitutional tissue of some patients with colon cancer. This variation in the length of microsatellite repeats represents a mutational process of insertions or deletions within the tumor DNA. As microsatellites are scattered throughout the genome, such mutations must be widespread. Thus, a mutator phenotype appears to be associated with and may possibly cause some colon cancers.

Fortuitously, investigators working on bacterial and yeast DNA repair recognized the pattern of microsatellite instability (MIN). The human microsatellite mutations mentioned above are similar to those seen with the breakdown of the mismatch repair system of yeast and bacteria. The two fields quickly converged, and the human homologues of many of the mismatch repair genes described in bacteria and yeast, have now been uncovered. These genes include hMSH2, hMLH1, hPMS1 and hPMS2. In addition, germline defects in these mismatch repair genes have been described in hereditary nonpolyposis colorectal cancer (HNPCC) and the variant syndromes of HNPCC: Muir-Torre syndrome, and a subset of patients with Turcot's syndrome.[6–12]

Whether microsatellite instability is always caused by defects in the four known mismatch repair genes is an area of continued interest. Although nearly 90% of colon cancers from HNPCC patients show microsatellite instability, germline mutations within the known mismatch repair genes have been found in only approximately 50%.[13,14] In patients with colon cancer who did not fit the criteria for HNPCC ("sporadic" colon cancer), Liu and colleagues[15,16] have found relatively few germline mutations in the mismatch repair genes. The exception to this is a subgroup of patients who developed cancer at a very young age.[15,16] The evaluation of acquired mutations in MIN$^+$ sporadic colon cancers required the use of tumor cell lines, less than one-half of which demonstrated a mutation in one of the mismatch repair genes. Thus, it is likely that genes in addition to those described thus far play a role in the development of microsatellite instability.

In shaping our concepts of tumorigenesis it is important for us to understand which neoplastic and preneoplastic lesions demonstrate microsatellite instability and thus may result from a mutator phenotype. Microsatellite instability appears to occur predominantly in tissues of endodermal origin, including sporadic colon, endometrial, pancreatic, esophageal, and gastric tumors. The work of Keller and co-workers, reported in this issue of the Journal,

Accepted for publication June 1, 1995.

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evaluated microsatellite instability in neoplasms of the upper gastrointestinal tract and demonstrated it in 24% (11/46) of gastric tumors and 13% (2/15) of adenocarcinomas of the esophagus.[17] These findings are consistent with previous studies of these tumor types. The detection of microsatellite instability in small bowel tumors (1/5) is a new observation.

Work is underway to determine whether sporadic MIN^+ tumors are markers of unsuspected familial cancer syndromes, especially syndromes in which there may be decreased penetrance. Keller and colleagues[17] found a significant correlation between patients whose gastric tumors were MIN^+ and a family history of gastric or colonic cancer. Their conclusion that patients with MIN^+ gastric cancer more frequently have a positive family history of gastric or colonic cancer is weakened somewhat by the study design; data were collected retrospectively and a larger percentage of the MIN^+ patients (82%) had family histories available compared with the MIN^- patients (57%). In contrast, a previous study of MIN^+ gastric tumors and familial clustering found no association, although inadequate numbers of microsatellite loci were evaluated to provide conclusive results.[18] Work in sporadic colorectal cancer has demonstrated that the MIN^+ phenotype only occasionally detects an occult HNPCC family that displays incomplete penetrance, except in a subset of patients who develop colon cancer before the age of 35.[15,16,19] Thus, it appears that most sporadic MIN^+ tumors are probably not caused by undiagnosed hereditary cancer syndromes; however, additional studies of upper gastrointestinal cancers are needed.

The mutator phenotype may have pathological and prognostic significance. Sporadic colon cancers that demonstrate microsatellite instability share similar histopathological features; they are usually right-sided, mucinous, poorly differentiated, and diploid.[3,5,20] Surprisingly, colonic tumors demonstrating microsatellite instability at two or more loci appear to have a better prognosis.[5,19] A notable observation in the current study by Keller and colleagues,[17] was the longer survival time of two patients with gastric cancer who had microsatellite instability at two or more loci. Although these numbers are too small to permit conclusions, they are intriguing and additional studies of the prognostic value of microsatellite instability will be of interest.

A better understanding of the mutator phenotype and its clinical significance can be gained by studying the HNPCC patients who carry germline mutations in the mismatch repair genes. A recent report describes mismatch repair deficiency in phenotypically normal lymphocytes from some HNPCC patients.[21] The implications of these results are fascinating. Despite an ongoing barrage of genome-wide mutations, normal human development can apparently occur. Although most of these patients had colon cancer, it was surprising that more cancers were not present. The fact that the mismatch repair defect is present in lymphocytes implies a constitutional repair defect present in all tissues and yet cancers were not present in other organs in these patients.

From this data arises a new set of questions and speculations. Are certain organs more susceptible to defects in mismatch repair than others? Many of the organs that develop cancers in HNPCC patients are endodermal in origin and/or undergo rapid cellular turnover; but perhaps more importantly these are organs that are exposed to repeated DNA repair stress, including that of exogenous mutagens. The hypothesis that repair stress may play a role in the process of tumorigenesis in HNPCC families could also explain why different organs are affected within some HNPCC families; that one family member may have endometrial cancer and another colon cancer may depend upon which organ was stressed. In addition, some family members appear to remain cancer-free despite having evidence of an ongoing mutator phenotype. This latter group of patients is of particular interest. Are there mitigating genes that influence the outcome of the mutator phenotype (*bcl-2*, APC, p53)? Or is it possible that these patients have less environmental exposure or that they consume chemopreventive compounds?

Elucidation of the mechanisms of microsatellite instability will broaden our understanding of tumorigenesis in general. In the future it seems likely that other genes involved in mismatch repair will be discovered. Why some HNPCC patients have a defective mismatch repair system and yet remain disease-free is a question of real interest. Whether environmental factors or unidentified modifying genes play a role in the development of microsatellite instability remains to be determined. Moreover, aside from patients with HNPCC, it may be possible that not all microsatellite instability is caused by defects in mismatch repair genes. For example, is a repair stressor such as chronic inflammation capable of saturating or overloading an intact repair system? Lastly, will the instability in these small, repetitive sequences of DNA reveal silent infidelity in the genome, which is perhaps more pervasive than ever imagined?

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