Colorectal Cancer: Tackling the Genetic Aspects of the Disease

Diverse research efforts into the two genetic pathways that lead to the development of colorectal cancer have helped each other and aided in the pace of progress in the field. While the genes implicated in the mismatch-repair defective pathway for this disease have probably all been isolated, those that may be key players in the other pathway for the predominant form of colon cancer—accounting for about 85% of all cases—are proving more numerous.

Recently appointed head of pathology and laboratory of medicine at the University of Texas M. D. Anderson Cancer Center, Houston, Stan Hamilton, M.D., points out that in parallel with progress in gene research, good detection strategies for colorectal cancer have evolved. "Fecal occult blood testing, endoscopy, etc., are all quite good for catching cancers before they become metastatic. Reconstructive surgery has also made living with the aftereffects of rectal cancer much easier. There have also been good chemopreventive strategies with low toxicities developed that might be useful for people at high risk for the disease," he said.

These recent diagnostic and preventive advances may be put into practice more frequently as scientists get a better handle on the genetic aspects of the disease. As recently as 1996, Kenneth Kinzler, Ph.D., of Johns Hopkins University, Baltimore, said that "little is known about the roles that APC and other such genes play in cell growth and division, much less tumor formation." Now scientists know that colon carcinomas often contain mutations in such tumor-suppressor genes as APC (adenomatous polyposis coli) and p53, and that APC may play a predominant gatekeeper role in the non-mismatch repair form of the disease.

Initiation Role

A recent finding in humans is one example of genetics research that might help elucidate the role that APC plays in cancer initiation. Researchers at the University of Toronto found that germline mutations of APC might be involved in a form of colorectal cancer called attenuated adenomatous polyposis coli (AAPC), which is a variant of familial adenomatous polyposis (FAP).

The Toronto scientists hoped to find gene mutations that would code for specific phenotypes and mutations in one of three regions manifested in more severe upper-gastrointestinal problems. Although these initial studies were conducted in only a dozen or so FAP patients, further corroboration of this finding could help define the distinguishing characteristics for this particular pathway for colorectal cancer.

Hamilton said that "out of the handful of non-mismatch repair genes that have been identified so far, there are probably many more yet to be discovered. Some researchers have even hypothesized that genes play a role in all forms of colorectal cancer and that some genes confer susceptibility while others affect cancer development more directly."

He thinks however, that most investigators are comfortable with the notion that environment plays some part in determining who does and does not get colorectal cancer.

Hamilton notes that, "we're at a stage of discovery now where we're putting new technologies into place to ascertain frequencies of genetic mutations, and advances in colorectal gene findings could accelerate in coming years."

When queried, Hamilton and others such as Thomas Smyrk, M.D., of the University of Nebraska Medical Center, Omaha, believe that research into a hereditary form of the disease (hereditary non-polyposis colon cancer) has helped them understand the sporadic form of the disease.

It is now known that many HNPCC cancers are caused by increased genetic instability due to defective DNA mismatch repair. Defects in these proteins allow mutations to accumulate fairly rapidly in the DNA, thus influencing the rate of cancer development. HNPCC families make up less than 30% of mismatch repair defective cancers.

Given our understanding of the genetics of HNPCC, the problem of deciphering who is at greatest risk for HNPCC and thus how to tailor specific
therapies for this form of the disease still remains to be solved.

Recent Finnish research addresses this particular issue. HNPCC has some distinctive clinical features such as right-sidedness, but in this instance, the researchers focused on germ-line mutations of DNA mismatch-repair genes, a molecular as opposed to clinical feature of the disease. By screening 509 tumor specimens for DNA replication errors and looking at microsatellite-marker analyses of these tumors, the scientists were able to identify likely candidates for HNPCC due to mutations in the MLH1 or MSH2 mismatch-repair genes. (Microsatellites are tandem repeats of varying lengths in the DNA.)

Microsatellite instability is a marker for tumor genes which are more likely to have replication errors, and by comparing microsatellites in tumor DNA with control DNA from the same patient, the Finnish scientists were able to successfully screen an unselected set of patients with colorectal cancer to identify those who might be at greatest risk for HNPCC.

While this methodology holds great promise, the fact that only 10% to 15% of screened patients show evidence of these mutations means that reliance on family history will probably remain the first step in identifying those with HNPCC. Smyrk believes that, in the near future, "identifying whether a patient's tumor has a high level of microsatellite instability will give scientists a good marker for treatment of the disease."

These selected research findings do not fully represent the degree or variety of activity in the field of colorectal genetic research, but they give a flavor of the diversity of approaches that researchers are taking in trying to tackle this disease. Ilan Kirsch, M.D., Ph.D., of NCI's Division of Clinical Sciences, believes that there are probably unidentified genetic defects in patients who have yet to be identified.

"Since the two genetic colorectal cancer pathways are so distinct in cancer initiation, response to DNA damage, and degree of chromosomal instability, the use of targeted differential therapies is an interesting prospect for current researchers," said Kirsch.

For these reasons, most researchers are suggesting genetic testing for colorectal cancer only when there is a clear family history of the disease. But the day may not be that far off when the complete picture of how genes and the environment contribute to colorectal cancer is elucidated. How well baby boomers live out their retirement years hinges, to a great deal, on genetic research into these diseases.

— Mike Miller