For the 500,000 new cases of colorectal cancer in the world each year, identification of patients with a worse prognosis and those who are more likely to respond to treatment is a challenge. There is an increasing body of evidence correlating genetic mutations with outcome in tumours derived from human colorectal cancer cohorts. K-ras, but not p53 or APC, mutations appear to be associated with poorer overall survival in colorectal cancer patients.

Although an expensive challenge, the cancer field is rightly continuing to pursue the identification and evaluation of common human mutations in cancer, as evident by the Cancer Genome project. This activity will no doubt drive the development of specific therapeutic interventions to specific mutated targets. Despite the success to date in other cancers, this whole activity could be an expensive mistake if a combination of mutation complexity, aneuploidy, and epigenetic alterations in tumour cells ultimately determine prognosis and response to therapy, irrespective of targeted therapy to what are presumed to be key mutations.

"Although an expensive challenge, the cancer field is rightly continuing to pursue the identification and evaluation of common human mutations in cancer, as evident by the Cancer Genome project."

So what of mutations in colorectal cancer? The paper by the Dundee group in this issue of Gut contributes to an increasing body of evidence correlating mutation with outcome in tumours derived from human colorectal cancer cohorts (see page 1283). Before examining their findings, it is important to recognise that mutation analysis and genetic models have already identified the key pathways critical for initiation and progression of colorectal cancer. Deregulation of the Wnt signalling pathway, by either loss of function or gain of function mutations of adenosomatous polyposis coli (APC) and β-catenin, respectively, in both hereditary and sporadic colorectal adenoma, establish the principal initiation pathway. Although specific mutational hotspots occur that account for attenuated inherited phenotypes, most sporadic mutations of APC occur in a mutational cluster. The discriminating power and clinical utility of these mutations have proven to be less impressive, even though this pathway remains a critical therapeutic target. Genetic modifiers of the number, differentiation, and progression of...
colorectal adenoma can either derive from the host or from coexisting and selected mutations in the tumour. Dissecting these components has been problematic, mainly because a large number of variables exist (for example, variable penetrance, gain and loss of function mutations in each gene, and synergistic effects between modifiers that coexist in both tumour and stromal cell populations). Although these limitations are being circumvented using larger patient numbers with high throughput technologies, there will have to be a practical outcome that will essentially distort down this information to a fewer number of key mutations, and potentially to where we have started from, a classification based on morphology and identification of a subpopulation of localised cells that essentially determine overall outcome (for example, those at the micro-invasive front of the tumour).

“K-ras mutations, but not p53 or APC mutations, were associated with poorer overall survival, even when correcting for Dukes’ stage, age, and sex”

The Dundee group prospectively characterised mutations in three genes implicated in colorectal cancer (APC, p53, Kirsten-ras (K-ras)) and extended a previous study. They observed that the mutation frequencies were variable between genes (APC = 56%, p53 = 61%, K-ras = 27%), and when controlled for expected frequencies, p53 and K-ras genes rarely coexisted (observed 2% versus expected 16%), even though the reduction in expected frequency of combined p53 and K-ras appears to have been lost when mutations of APC coexisted in addition. Conlin and colleagues have also now correlated these mutations with survival in colorectal cancer. In a relatively small cohort of 107 patients, the significant additional findings were that K-ras mutations, but not p53 and APC mutations, were associated with poorer overall survival, even when correcting for Dukes’ stage, age, and sex. The surprise is that the magnitude of this effect for a single gene appears large in this cohort relative to the influence of Dukes’ stage alone, but on closer analysis, the frequency of mutations of K-ras was highest overall in more advanced disease. A similar examination of K-ras mutations in a larger cohort also showed association of the glycine codon 12 to valine mutation with high risk disease. Moreover, similar studies examining p53, chromosomal loss, and microsatellite instability also correlate with survival, with a subgroup recognised that neither falls within a chromosomal nor microsatellite unstable groups.

How should we view this information? Clearly, some of the data concern small cohorts, and the magnitude of the effects may be lost in larger studies. Moreover, the complexity of this analysis is complicated because mutations in some genes do not always generate the same phenotypic outcomes. For example, for p53, recent data implicate specific mutations of p53 with colorectal cancer outcome, although there does not appear to be an overall correlation, as Conlin et al have suggested. Ultimately, mutations and chromosomal abnormalities that are both easier to detect and at high frequencies will be selected first, simply because of the eventual contribution to statistical outcome.

“Ultimately, mutations and chromosomal abnormalities that are both easier to detect and at high frequencies will be selected first, simply because of the eventual contribution to statistical outcome”

So, are we making too many assumptions about the complexity of the task ahead? Probably not when it comes to deriving useful information, because studies such as Conlin et al highlight this fact in terms of specific and common gene mutational frequency in colorectal cancer tissue derived from patients. In addition, the few data there are, are also being immediately assembled with Dukes’ stage information, site, and ploidy into an increasing number of subgroups, despite the relatively small cohorts examined. The complexity is very high and no one should underestimate the difficulty. Not surprisingly, there is a need for newer approaches, perhaps to assemble mutations into various pathways, which are best exemplified by the six hallmarks proposed by Hanahan and Weinberg, and to then analyse what intermediate surrogate markers may be used to subdivide and target mutation testing. This may not mean an initial screen for all the potential mutually exclusive mutations along one pathway, but a “readout” of its overall activity based on histological, proteomic, or expression profiling. The goal of the latter must be to ultimately apply specific interventions, and to test the usefulness of the mutation in the overall context of prevention, diagnosis, prognosis, and therapy. In this case, mutations, and epigenetic and expression alterations are then judged by clinical utility.

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