Screening for colorectal cancer: does it all start with aberrant crypt foci?

Colorectal cancer (CRC) is important for at least 3 reasons. First, it is a major human cancer in the Western world in terms of the toll it extracts: its incidence and associated mortality are high, it imposes a huge financial burden on society, and it causes untold human suffering.[1] Second, it is almost paradigmatic of a multifaceted research effort that has yielded a deeper understanding of carcinogenesis. Third, it represents a case in which screening endoscopy has made cancer prevention possible. As often is the case, these 3 conceptual threads are intertwined, with their interactions propelling progress.

Over the last 4 decades, research on CRC has clarified many aspects of its pathogenesis. Morphologic studies demonstrated crucial crypt abnormalities, the adenoma-carcinoma sequence, and the flat adenoma. Molecular work, starting with the demonstration of *Apc* mutations in CRC, established the concept of multistep carcinogenesis and revealed deranged signaling cascades that propagate its growth and metastasis. The interplay among environment, cells, and heredity became apparent, although, most recently, the role of the colon stem cell in carcinogenesis is gaining increased appreciation.[2] In parallel, the growth of endoscopic imaging and the seminal studies that show that endoscopic interventions in the form of screening colonoscopy do make a difference have made secondary CRC prevention the standard of care.

These 3 lines of work, morphology, molecular analysis, and endoscopy, converge now on aberrant crypt foci (ACF), which seem to occupy a hitherto little-appreciated yet crucial spot in the evolution of CRC (reviewed in Bird and Good,[3] Cheng and Lai,[4] and Alrawi et al[5]). ACF were first reported by Bird[6] in 1987 in the colons of carcinogen-treated mice; not only did he describe the methodology for their detection, he also suggested that they are preneoplastic lesions. Four years later, Roncucci et al[7] and Pretlow et al[8] identified ACF in human beings, whereas, in 1998, Takayama et al[9] reported their colonoscopic identification and their response to sulindac.

Four aspects of ACF are critical to understanding the true role of ACF in CRC biology and medicine: (a) their precise definition, (b) their cellular and molecular pathogenesis, (c) their natural history, and (d) their putative usefulness, both as markers of colon cancer risk and as predictors of response to medical interventions. The article by Schoen et al[10] in this issue of *Gastrointestinal Endoscopy* is a welcome contribution to such an understanding of ACF.

ACF are lesions microscopically identified in colonic mucosa that appears normal on visual inspection. These lesions are composed of crypts that are microscopically elevated above the normal colonic mucosa, have thickened epithelia, altered luminal openings (often oval or slit-like), and are clearly circumscribed from adjacent normal crypts.

ACF are precursor lesions to CRC. The difficulty arises from the realization that, just as all ACF do not look alike, they also may have different genetic makeup, and, what is clinically important, they may have different clinical relevance, in that some may go on to malignancy and some may not.

Staining with methylene blue allows their visualization; deeper staining, compared with surrounding crypts, is one of their morphologic features. ACF with a single crypt have also been described (although, strictly speaking, they are not a focus of crypts). On histopathologic examination, ACF can be nondysplastic (ACF with hyperplasia fall under this grouping), dysplastic, or of the mixed type. Whether ACF may transition from one pathologic type to another is not yet firmly established, but, ominously enough, some ACF may harbor carcinoma in situ.[11] ACF are more frequently detected in distal animal and human colons, coinciding with the geographic distribution of CRC.

All available evidence indicates that ACF are precursor lesions to CRC. The difficulty arises from the realization that just as all ACF do not look alike, ACF also may have different genetic makeups, and, what is clinically important, they may have different clinical relevance, in that some may go on to malignancy and some may not. In an effort to ''understand ACF,'' a significant body of work (summarized in Alrawi et al[5]) showed changes within ACF in proteomic markers (eg, calreticulin, carbonic anhydrase, carcinoembryonic

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antigen, β-catenin, and nitric oxide synthase), genetic mutations (eg, *K-ras, Apc,* and *p53*), epigenetic alterations (eg, CpG island methylation), genomic instabilities, microsatellite instability, and loss of heterozygosity. At this time, it appears that, based on such features, there may be at least 3 distinct types of ACF: those associated with familial adenomatous polyposis, those associated with inflammatory bowel disease, and those of the sporadic variety.[12] Another rather complicating point is the suggestion that ACF may shuttle between histologic types. In terms of genomic instability (taken to mean whether ACF can evolve into neoplasms), results of one study suggest that about three fourths represent a stable set, whereas less than a fourth have features seen in adenomas and carcinomas.[13]

Magnifying chromoendoscopy has made the in vivo recognition of ACF fairly easy. The endoscopes are available from all major manufacturers, and the endoscopic technique for their recognition has been sufficiently simplified. This technique consists of spraying the dye (methylene blue or indigo carmine) onto the mucosa and inspecting the mucosa after switching the instrument to magnification mode by using a finger-operated knob. Although the basic elements are present, further refinements are possible and even desirable. The procedure per se and the endoscopic definition of ACF need to be standardized, and the segment of the colon that can yield the best information should be defined.

From a clinical point, the critical question is what an ACF will do once it forms. Current knowledge suggests 4 possibilities: it can evolve into cancer through a polyp stage; it can produce a cancer directly, without an intermediate polyp; it can remain stationary; or, as the article by Schoen et al[10] suggests, it can regress. There is no absolute certainty about any of these possibilities. Another intriguing aspect of ACF is that they may respond to treatment with agents that prevent CRC. Takayama et al[14] showed, in a chemoprevention trial of sulindac, that the number of ACF was reduced markedly after two months of treatment. This property of ACF, reminiscent of what was observed in colon polyps of patients with familial adenomatous polyposis, is likely one of their most useful clinical features. Presently, the natural history of ACF remains unclear; Schoen et al[10] attempt to expand our relevant knowledge.

In their pilot study, by using high-magnification chromoendoscopy, Schoen et al[10] examined for ACF the rectal mucosa from the anal verge to the middle rectal fold. The position of each ACF was recorded in terms of centimeter location and clock position to facilitate their recognition at reexamination one year later. Biopsy specimens of ACF were obtained from the segment that extended between the middle fold and the 20-cm mark, and left the distal area of observation unperturbed. One year later, 43% of the specific ACF observed at baseline were not identified, whereas 56% of the subjects showed new ACF. The immediate conclusion was that ACF are an unusually active component of the colonic mucosa, appearing and disappearing at rather rapid rates. As Schoen et al[10] also acknowledge, this conclusion may not be all that ''conclusive.'' The effect of aspirin, which these subjects were allowed to take during the intervening year, is not excluded with certainty; it is reasonable to consider that, at the very least, ACF are responsive to nonsteroidal anti-inflammatory drugs. The fact that this is a pilot study always elicits the reservations engendered by the proverbial learning curve. However, the team that performed the study is quite capable, and it is obvious that they took pains to minimize technique variation. That they devoted unequal times to the area of interest between the beginning and the end of the study may account for some of the changes that they report, but it would be difficult to explain all of them.

There is inherent difficulty in this nascent endoscopic field. Only about half of endoscopically identified ACF were confirmed by histology, and 5% of apparently normal mucosa biopsy specimens were identified by histology as ACF. This may reflect the difficulty of actually performing a biopsy of such a small lesion, but, more importantly, it may have to do with our endoscopic definition of ACF.

Regardless of such concerns, the ACF field is making huge progress. There are still issues that have to be resolved, which center mainly on methodology and a comprehensive understanding of the natural history of ACF. The role of ACF in colon carcinogenesis is not a question of simple academic interest but of practical clinical importance. Because ACF precede the development of polyps, it is only reasonable to ask whether the surveillance colonoscopy of the future should concern itself with the recognition of ACF rather than polyps. Although, at present, this is an unanswerable question, it may be useful to ponder it. To focus on ACF rather than on polyps (which can be removed when recognized) would require knowledge on what ACF mean clinically and the availability of the means to treat them. If ACF can indeed proceed directly to lethal malignancy, bypassing the polyp stage, then this would make the need to recognize and treat them even more compelling.

Our current situation is reminiscent of what gastroenterology went through when conventional endoscopy became practical and polyps came under direct vision in the human colon. As technology progresses, identification of ACF through magnifying chromoendoscopy, and their characterization by using genomic, proteomic, and perhaps other methods not yet reduced to practice, may generate a new approach to screen for CRC, stratify risk, decide on preventive intervention, and observe the patients.

To remember the physician and poet William Carlos Williams, ''that which is possible is inevitable.''[15]

DISCLOSURE

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Abbreviations: ACF, aberrant crypt foci; CRC, colorectal cancer.

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