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The spindle assembly checkpoint, aneuploidy and gastrointestinal cancer

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Genomic instability is a common occurrence in solid tumors and it has long been conjectured that this process plays a causal role in cancer. Modern human molecular genetics has provided a means to test this hypothesis, fueled in part by the analysis of hereditary human cancer predisposition syndromes. Some of the first unequivocal support came from the discovery in 1993 that hereditary non-polyposis colon cancer is caused by germ line mutations of mismatch repair genes [1]. Work on the autosomal dominant hereditary breast and ovarian cancer predisposition syndromes, as well as on rare autosomal recessive syndromes such as Fanconi Anemia, revealed that inherited mutations in homologous recombination genes can predispose to breast and ovarian cancer, as well as other human cancers [2]. Notably, the study of a small number of families or even individual patients has often revealed novel connections between DNA repair, genomic instability and human cancer predisposition.

There are many different types of genomic instability, the pattern of DNA alteration being a reflection of the DNA repair/chromosome maintenance pathway affected. Cancers arising in particular tissue types sometimes reveal apparently restricted genomic instability patterns, for reasons that remain poorly understood. One such example is colon cancer, which falls into approximately two distinct genomic instability types. These are: “microsatellite instability” (MSI), indicating a defect in mismatch repair, and “chromosomal instability” (CIN), indicating frequent alterations in chromosome copy number (aneuploidy) but with apparently normal individual chromosome structure [3]. Although alterations in chromosome copy number dramatically impair organism development and might well be expected to accelerate cancer, determining the specific contribution of aneuploidy *per se* to cancer etiology has been challenging [4]. Nonetheless, human molecular genetics has provided some tantalizing clues in this area. To understand these clues, we need to briefly review the cellular mechanisms that normally enforce euploidy.

Mitosis entails the physical alignment of replicated chromosomes (sister chromatids) through attachments of their kinetochores – specialized protein/DNA containing structures located at the centromere of each chromosome. The kinetochore acts as both a physical bridge and a signaling platform [5]. Paired sister chromatids are held together by cohesion between their kinetochores and in tension by kinetochore attachments to the mitotic spindle, a microtubule apparatus that will pull the sister chromatids apart later in mitosis. Certain kinetochore-associated proteins sense when an individual kinetochore remains unattached to microtubules (a “lagging chromosome”), generating a signal that arrests the mitotic program until the lagging chromosome is correctly positioned. This sensing/signaling device, termed the spindle assembly checkpoint (SAC), is swiftly inactivated once all chromosomes are aligned. Importantly, dysfunction of SAC genes can allow cells to transition through mitosis prematurely, leading to missegregation of chromosomes and aneuploidy in the daughter cells. Mice lacking fully functional SAC genes develop aneuploidy and are cancer prone. SAC function is also sensitive to gene dosage effects, and simple reductions of individual SAC protein abundance can cause aneuploidy.

A clinical corollary of these observations occurs in a rare autosomal recessive human syndrome called Mosaic Variegated Aneuploidy (MVA). Individuals with MVA frequently suffer a variety of severe developmental defects in early childhood and are cancer prone. The cells of MVA patients, as the name suggests, reveal mosaicism with varying degrees of aneuploidy. Importantly, the genetic defect in MVA has been linked to germ line mutations in one of the human SAC genes, *BUB1B* (which encodes the protein BUBR1) [6]. MVA has therefore provided evidence that aneuploidy might have a causal role in certain childhood cancers. The importance of *BUB1B* in cancer was also suggested by the finding that some CIN colon cancers – in which aneuploidy is the predominant instability pattern – contain mutations of SAC genes including *BUB1B* [7]. Further, the product of a major hereditary CIN colon cancer gene, familial Adenomatous Polyposis Coli (*APC*), localizes to the kinetochore and interacts with BUBR1 [8, 9]. These data, in combination, support the idea that SAC dysfunction can promote gastrointestinal cancer by an aneuploidy mechanism.

The case reported in this issue of NEJM by Frio *et al.* extends the clinical syndrome of MVA and provides a new connection between defective SAC function and adult gastrointestinal cancer [10]. The report describes a man who survived a carcinoma of the ampulla of Vater at the age of 34 and, in later life, developed gastrointestinal polyposis and malignancies of the stomach and colon. Cells from the patient exhibit an MVA phenotype and full sequencing of the *BUB1B* gene revealed normal exons but a homozygous intron mutation that produces a novel splice site. This mutation reduces the abundance of wild type BUBR1 protein in the patient's cells and causes an impairment of the SAC – enough to allow occasional aneuploid cell divisions to occur. This case emphasizes several important connections between SAC gene dysfunction and cancer. First, it underscores a phenotypic similarity (gastrointestinal polyposis and cancer predisposition), but not identity, between *BUB1B* dysfunction and *APC* mutation. Second, it suggests that SAC dysfunction is an independent contributor to some common adult malignancies. Third, it emphasizes the sensitivity of the SAC to changes in gene dose/protein level. Conceivably, transient epigenetic changes in the abundance of SAC proteins early in tumorigenesis might cause aneuploidy *via* a “hit and run” mechanism.

Although these observations support a role for aneuploidy in cancer, BUBR1, like APC itself, may have functions additional to its role in the SAC [4]. The difficulty of isolating cancer-associated aneuploidy in a “pure” form is compounded by recent whole genome sequencing of cancer cells, which suggests that the conventional descriptors of genomic instability underestimate the number, complexity and indeed bizarreness of DNA rearrangements in cancer. More relevant to the clinic is the possibility that the SAC status of a tumor may guide therapeutic choices. We can expect still more cancer treatment stratifications to emerge from the information-rich new technology of whole genome sequencing.

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