Determining if Telomeres Matter in Colon Cancer Initiation or Progression

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The nucleus of each human cell contains 46 linear chromosomes (92 ends) that are capped by thousands of repetitive TTAGGG DNA sequences (similar to the plastic tips on shoelaces). These ends, called “telomeres” have complex roles in aging and cancer and have proven to be intricately involved in such pivotal processes as the protection of genetic material, the completion of chromosome replication, the regulation of cellular aging due to progressively shortening telomeres throughout life, the initial protection against unlimited cellular growth, and, in combination with other alterations, the promotion of cancer progression. A collection of six proteins that either bind or associate with telomeres (the shelterin complex) begin to resolve a central question of how cells distinguish telomere ends from typical genomic DNA double-strand breaks (1). The consequences of telomere dysfunction are becoming more apparent by examining a growing list of human genetic diseases called telomeropathies. In certain inherited and familial cases of idiopathic pulmonary fibrosis, dyskeratosis congenita, and sporadic bone marrow failure ( aplastic anemia), inheritance of short telomeres due to mutations in genes involved in the ribonucleoprotein telomerase holoenzyme lead to premature aging phenotypes (2). Telomerase is the cellular reverse transcriptase that can add TTAGGG repeats onto the telomeres and is active during early human development (3) but is silent in most adult tissues except proliferating stem cells, unless it is upregulated as part of cancer progression (4).

In normal cells (in the absence of other alterations), progressive telomere shortening leads to replicative senescence (not cancer) that is associated with many of the hallmarks of aging. It is believed that cellular senescence may initially be a potent suppressor of cancer by arresting cell-cycle progression, either in response to short telomeres or to oncogenic or chemotherapy-induced DNA-damaging stimuli. In this issue of the Journal, Roger et al. (5) reports that extensive telomere erosion precedes initiation of colorectal cancer (CRC) in polyps obtained from familial adenomatous polyposis patients. They provide evidence that the combination of short telomeres together with adenomatous polyposis coli ( APC) gene alterations may lead to chromosomal instability potentially driving clonal evolution and CRC progression. Roger et al. (5) also observed that the progressive telomere shortening in combination with APC mutations led to large scale genomic rearrangements that were independent of polyp size.

Although, at first glance, telomere shortening contributing to both aging and cancer may appear to be contradictory, there may be a logical explanation. For example, there is a long history of studies showing that viral oncoproteins such as simian virus 40 large T-antigen and human papillomavirus 16 E6/E7 enable bypass of senescence, providing normal human cells with an extended lifespan and eventually leading to a phenomenon known as crisis (where the telomeres are so short that there is ongoing chromosomal end-fusion and bridge-fusion-breakage cycles) (Figure 1). One way to think about telomere shortening is that when a few telomeres are short this leads to a DNA damage signal resulting in cellular growth arrest (called M1 or mortality stage 1) (6). In the absence of other alterations, this would, at least for a period of time, prevent additional cell divisions. However, when certain driver oncogenic changes occur, cells ignore the DNA damage signal arising from a few upcapped telomeres and continue to divide. Eventually the vast majority of telomeres become so short that cells form end-end associations and then end-fusions (7) until they cannot continue to divide (telomere catastrophe). However, these cells in crisis are also being driven forward by oncogenic changes, which results in a tenuous equilibrium between cell growth and apoptosis. In very rare instances, a mechanism is engaged to permit cells to overcome telomere catastrophe. In 85% to 90% of carcinomas, telomerase is greatly upregulated or reactivated (8,9) to stabilize the chromosome ends, and then the cells escape crisis (or M2, for mortality stage 2). There is another much less common pathway involving DNA recombination at telomeres that can also lead to the escape from crisis (10).

Telomere crisis generally occurs in the transition period between benign lesions and carcinomas in most epithelial solid tumors (8). In the case of CRC, APC alterations are believed to occur early, perhaps before or during the early adenoma stage, and this may result in bypass of replicative senescence, leading to crisis when global genomic alterations occur and very rarely leading to cell immortalization (Figure 1) (11). It has been established that telomere length abnormalities occur early in the initiation of most, if not all, human epithelial cancers (12). In addition, colonocytes of ulcerative colitis patients with progressive chronic inflammatory disease show premature shortening of telomeres, which might in part explain the increased predisposition and earlier risk of CRC (13,14). These investigators (13,14) also observed that telomere shortening is associated with chromosomal instability and anaphase bridges (a result of end-to-end chromosomal fusions), providing a mechanistic connection between telomere shortening, chromosomal damage, and cancer.

It is important to remember that human CRC almost always emerges over years, if not decades (15). Thus, it is not surprising that premalignant cells may have some regulated telomerase activity (8,16). This has been noted for many tissues for which there is a high rate of cellular turnover, such as in the bone marrow, the skin, and the gastrointestinal tract (4,8). Thus, the low levels of telomerase activity in polyps in the Roger et al. study (5) may extend the proliferative lifespan of colonic stem cells but are insufficient to immortalize them. It is only in the context of crisis and critically short telomeres that telomerase becomes expressed at much higher levels, most likely

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to stabilize the complex genomic chaos caused by continuous bridge-fusion-breakage cycles. Thus, telomerase re-expression or upregulation may actually provide a mechanism to stabilize the genome and suggests that inhibiting telomerase in patients with premalignant lesions may actually prevent CRC progression.

With increased age not only does the emerging colon polyp contain shorter telomeres but so also do the cells of the microenvironment, such as fibroblasts around the colonic crypts, the endothelial cells of the vasculature, and the cells of the immune system. There are emerging reports demonstrating that short telomeres in stromal cells may contribute to cancer by a phenomenon known as the senescence-associated secretory pathway, which may fuel chronic inflammation (17). In premalignant epithelial cells, senescence-associated secretory pathways can induce an epithelial–mesenchyme transition and invasiveness, hallmarks of malignancy by autocrine or paracrine mechanisms. Thus in the prepolyp stage, stimuli that engage cellular senescence can be both beneficial, in initially preventing damaged cells from dividing, and deleterious, by having effects on the precancerous microenvironment. Thus short telomeres in cells of the colon microenvironment could result in bypass of senescence, extended cell divisions, initiating specific alterations such as in the *APC* gene (as well as in other oncogenes and tumor suppressor genes), leading to crisis and telomere end-end fusions. Although the Roger et al. (5) studies were done on familial adenomatous polyposis patients, it is likely that these same changes would occur in patients with sporadic CRC because almost all have mutations in the *APC* gene.

It has been suggested that modulation of telomere biology and/or inhibition of telomerase may be excellent targets for cancer prevention and treatment (18–21). For example, development of predictive biomarkers directed toward specific subsets of cancers has ushered in a new era of personalized therapeutics. Will the use of telomere length as an enrichment biomarker for clinical trials be valuable because short telomeres correlate with poor outcomes (20,21)? The challenge for the present is to understand telomere-associated senescence more fully to harness its benefits (e.g., tumor suppression) while preventing its drawbacks (e.g., genomic instability and cancer progression).

**References**

Lung Cancer, Histologic Stratification, and Resection Extent: Something for Surgeons to Think About

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You would think that thoracic surgeons have plenty to consider when planning for a lung cancer resection in 2013. We have been bombarded with “the small nodule” less than 2 mm, which we have learned can have various inhomogeneities in its computerized tomographic (CT) analysis (1); we have to decide whether the nodule merits a lobectomy (the standard of care) or a sublobar resection (2) (for those heretics in the minority who feel that we don’t need a randomized trial to answer the sublobar vs lobectomy debate); whether we should mark the nodule preoperatively so we don’t need a randomized trial to answer the sublobar vs lobectomy debate; and whether to perform the case as a video-assisted resection, a robotic resection, or (shudder) as an open procedure with rib resection/spreading. As if those deliberations were not enough, now we must start to worry about whether the (presumed lung cancer) solid or part-solid nodule presented to us on the CT scan has a critical quantifiable element of micro-papillary disease, which may be associated with tumor recurrence if we do a wedge resection or a segmentectomy (which, of course, will only be the standard of care for intentional lung cancer resections if this is confirmed by the results of CALGB 140503 “A Phase III Randomized Trial of Lobectomy Versus Sublobar Resection for Small (≤2 cm) Peripheral Non–Small Cell Lung Cancer” (3).

The article by Nitadori et al. (4) in this issue of the Journal is a continuation of the milestone publications by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society, which have revolutionized the pathologic classification of lung adenocarcinoma (5). As reviewed by Sub (6), the new classification eliminates the categories of bronchioloalveolar carcinoma and mixed subtype adenocarcinoma to achieve precise correlations between predominant histologic subtypes of lung adenocarcinoma and survival in surgically resected patients. The Nitadori et al. article (4) retrospectively analyzed 476 lobectomies and 258 limited resections (either by wedge resection or anatomic segmentectomy) at a single institution in patients with lung adenocarcinomas of 2 cm or less. An important validation of the prognostic importance of the new classification system was demonstrated in the patients who had lobectomies for these small tumors; however, this was not seen in the limited resection group. Why is this? Is it because of the heterogeneity of the procedures performed? Is it because of the absence of clear-cut large margins? There are some other intriguing aspects of the limited resection group in these patients that also should be mentioned. The authors specify that the limited resection group is a combination of compromised (77.1%) patients and patients...