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REVIEW

Connecting Chromosomes, Crisis, and Cancer

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Cancer is a disease of impaired genome stability. The molecular forces that maintain genome integrity and sense altered chromosome structure are invariably subverted in cancer cells. Here, we explore the contrasting contributions of telomeres in the initiation and suppression of cancer and review the evidence supporting a role for telomere dysfunction as a mechanism driving the radical chromosomal aberrations that typify cancer genomes. Recent work suggests that passage of cells through crisis in the setting of deactivated DNA damage checkpoints provides a mutational mechanism that can generate the diverse genetic alterations required for cancer initiation. A greater understanding of telomere-induced crisis and the cell's crisis management mechanisms should guide the rational development of new therapeutics for cancer and other disorders.

The genetic paradigm that now forms the foundation of our view of cancer pathogenesis has its deepest roots in the early cytogenetic analyses of cancer cells [reviewed in (*1*)]. Aberrant mitoses first noted by von Hansemann in 1890 (*2*) inspired Boveri's seminal concept of cancer as a genetic disease of somatic cells driven by chromosomal imbalances (*3*). This genetic hypothesis received experimental support from Muller's discovery that ionizing radiation, an agent already recognized as a potent carcinogen, also had mutagenic activity (*4*). Subsequently, Muller and McClintock began to explore the special role of chromosomal termini in the maintenance of chromosome structure (*5, 6*)—efforts that, years later, led to an integrated view of telomere dynamics in chromosomal stability and cancer [reviewed in (*7*)].

That genetic instability helps drive the development of cancer has emerged as a core concept in modern biology—continually reinforced by the increased incidence of neoplasia observed in human genetic disorders (and their animal models) of compromised genome stability [reviewed in (*8, 9*)]. In such disorders, genetic instability endows incipient cancer cells with the molecular alterations that deactivate growth arrest and apoptotic checkpoints and permits the engagement of pathways essential for immortal growth. Indeed, the identification of the molecular mechanisms governing genome integrity has been a central focus in the field of cancer. Disruption of these mechanisms in cancer cells is manifested as defects in mitotic checkpoints, impaired nonhomologous end-joining, imprecise DNA replication, and so forth (*8, 10*). The relative contribution of each of these mechanisms to the genome instability encountered in the majority of human cancers, particularly epithelial cancers, is not well understood. Here, we review the mounting experimental evidence that telomere dysfunction figures prominently in the evolution of cancer, providing a potential mechanism that enables cells to reach a critical threshold of cancer-promoting genetic changes during the formative stages of neoplastic transformation.

Telomeres, the structure at the ends of linear chromosomes, have long been recognized as critical for the maintenance of chromosomal integrity (*5, 6*). The replication of linear chromosomes presents a special challenge that stems from the inability of conventional DNA polymerases to complete synthesis of chromosomal ends (*11, 12*). Thus, as cells divide, this "end replication problem" results in the eventual reduction of telomeres to a short critical length that elicits the activation of cellular checkpoints not unlike those provoked by DNA damage [reviewed in (*13–15*)]. In human cell cultures, short telomeres result in activation of the Hayflick limit (Mortality Stage 1 or senescence), and the cells stop dividing [reviewed in (*16*)]. However, the Hayflick limit can be readily breached by inactivation of the p53 and Rb growth inhibitory pathways. Continued proliferation of cells beyond the Hayflick limit and further telomere erosion exacerbate telomere dysfunction and associated genomic instability, culminating in a period of massive cell death aptly termed "cellular crisis" (or Mortality Stage 2) (*16*).

The Hayflick limit presents a block to normal cell growth in culture, but because cancer cells invariably acquire Rb and p53 pathway defects, it has been difficult to document a direct role for shortened telomere–induced senescence in tumor suppression in vivo [reviewed in (*17*)]. We favor the hypothesis that crisis plays a more prominent role than senescence in tumorigenesis. Although crisis is a potent barrier to immortal growth in culture, the massive genetic instability associated with this state may well be the mechanism by which the rare cells surviving crisis acquire the constellation of genetic alterations needed for malignant transformation (*18–22*). These rare cells emerge from crisis by activating telomere maintenance mechanisms—most commonly by expression of the specialized ribonucleoprotein complex, telomerase (*18*). Telomerase consists of a catalytic telomerase reverse transcriptase (TERT) that synthesizes a sequence (TTAGGG in humans and mice) at the ends of chromosomes by using an RNA template encoded by the *telomerase RNA component* (*TERC*) gene (*23*). In human cells and tissues, the presence of telomerase activity correlates well with the level of *TERT* gene transcription, although additional levels of regulation such as RNA processing and posttranslation modification may also be important (*23*). In humans, *TERT* gene expression is limited

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mostly to embryonic tissues and activated lymphocytes. It is also detectable in a subset of adult hematopoietic and epithelial stem cell compartments, but at modest levels that are insufficient for telomere maintenance. In contrast, expression of the telomerase RNA component is more ubiquitous [reviewed in (*23*)]. Although telomere attrition takes place in primary human cultured cells, the extent to which critical telomere shortening occurs in normal human tissues, (for example, as a function of advancing age and/or in the context of organ renewal) is less well documented (*24*). Nevertheless, it is clear that substantial telomere attrition can occur in diseased human tissues that sustain chronically high rates of cellular turnover [reviewed in (*27*)]. Both in vitro and in vivo experiments document the importance of telomerase activity in maintaining the growth capacity of immortal cancer cells and thus their ability to navigate through crisis (*25–27*). For this reason, telomerase is viewed as a promising target for the development of anticancer drugs.

The Cellular and Organismal Response to Telomere Attrition.

Genetic evidence derived from *mTerc*-deficient mice (*28*) has pointed to highly complex roles for telomere-based crisis in carcinogenesis. In particular, the presence of deactivated DNA damage responses in mice engineered to experience telomere attrition and crisis appears to convert crisis from a suppressor to a promoter of tumorigenesis (*29*). The increase in cancer observed in these double mutant mice and in aged *mTerc* null mice is fueled, presumably, by the improved survival of cells during a period of genomic instability in which there are gains and losses of oncogenes and tumor suppressor genes.

The *mTerc* knockout mouse has also revealed that many of the forces operating in cultured human cells are at work in telomerase-deficient organs with high renewal activity. The organismal impact of telomere attrition, brought about by successive generational breeding of *mTerc* null mice (*28*) and by advancing age and organ renewal, has underscored the importance of telomere function in maintaining the long-term homeostasis of rapidly proliferating organ systems (*30–33*). Organ failure may be caused by compromised proliferative reserve and/or apoptotic elimination of resident tissue stem cells, although this hypothesis has not yet been experimentally validated.

Finally, these experimental observations in the mouse have provided a rational explanation for a group of chronic high-turnover diseases in humans that, paradoxically, are associated with both end-organ failure and cancer predisposition; examples include liver cirrhosis and hepatocellular carcinoma, Barrett's esophagus and esophageal cancer, and ulcerative colitis and colorectal cancer [reviewed in (*7*)] (*34*, *35*). Together, these genetic observations have reinforced the hypothesis that telomere dysfunction, while inhibiting the growth of normal cells, can in some instances promote the development of cancer.

At the molecular level, the cellular response to eroded telomeres has been shown to involve signaling pathways important in governing cell cycle progression, DNA repair, and cell survival. ATM (ataxia-telangiectasia mutated) and p53 play central roles in sensing and executing appropriate cellular responses to DNA damage (*36*, *37*). The ATM/p53 pathway was implicated in the response to telomere dysfunction in experiments with human cells that expressed a dominant-negative form of the TRF2 protein (*38*), an integral component of the telomere complex [reviewed in (*15*)]. Expression of mutant TRF2 disrupted telomere function, resulting in chromosomal end-to-end fusions and anaphase bridges and leading to induction of an ATM- or p53-dependent apoptotic response (*38*, *39*). Studies in the mouse have also documented p53 activation in the setting of critical telomere shortening (*40–42*) and have confirmed a central role for p53 in mediating the adverse cellular and tissue consequences of short dysfunctional telomeres (*40*). Whether and how ATM deficiency modulates the telomere dysfunction phenotype in vivo has not yet been determined; however, based on the TRF2 studies, an attenuated checkpoint response would be anticipated. Thus, in the setting of intact ATM/p53-dependent checkpoint responses, telomere-based crisis would be expected to trigger restraining mechanisms that impede the emergence of incipient cancer cells.

Beyond ATM/p53, an intriguing, albeit poorly understood, interplay also exists between telomeres and the DNA double-stranded break (DSB) repair machinery. Multiple DNA repair complexes, such as the Ku proteins and the MRE11 complex, function in normal telomere metabolism and capping [reviewed in (*15*)]. Although not rigorously proven, an eroded telomere is likely to be recognized as a DNA DSB. DSBs can be repaired by either homologous recombination, which repairs the damage by copying from a homologous sequence, or nonhomologous end joining (NHEJ), which ligates unrelated DNA ends (*43*). Of particular concern to cells undergoing telomere-induced crisis are the pathways that solve the problem of eroded telomeres and create the aberrant chromosomes typically found in cancer cells. For example, the homologous recombination pathway appears to be required for the alternative lengthening of telomeres (ALT) mechanism, which can regenerate telomeres in the absence of telomerase and potentially endow cancer cells with an escape from crisis (*44–49*). Which of the DSB repair pathways is responsible for the hallmark characteristics of cells experiencing telomere dysfunction, i.e., chromosome end-to-end fusions and nonreciprocal translocations, is not yet fully elucidated.

Telomere Dysfunction and Carcinogenesis

Most human tumors express telomerase (*50*), although a small minority are telomerase-negative and tend to exhibit ALT (*51*, *52*). These observations underscore the essential need for some form of telomere maintenance in the long-term survival of cancer cells. Expression of the *TERT* subunit in human fibroblasts results in stabilized telomere length and immortalization; hence, these primary cells bypass telomere-based senescence and crisis (*53*, *54*). More directly, enforced expression of *TERT*, together with RAS and viral oncoproteins that neutralize the p53 and Rb pathways and modulate PP2A phosphatase activity, has been shown to generate fully transformed human tumor cells in vitro, demonstrating that human cells require telomere maintenance to acquire an advanced malignant phenotype (*55*, *56*). Conversely, inhibition of telomerase in established human cancer cells can halt their growth and induce apoptosis as a result of telomere-induced crisis, thus disrupting their ability to form tumors in vivo (*25*, *26*).

Against this backdrop, it is perhaps not surprising that early neoplastic lesions typically possess undetectable or low telomerase activity, whereas the progression to advanced malignant lesions is associated with more robust levels of telomerase (*57–61*). Does this rather late onset of telomerase activation in advanced human tumors provide an opportunity for telomere erosion and some degree of cellular crisis during the early stages of tumor development? Several lines of evidence suggest that this is indeed the case. First, human cancer cells often have shorter telomeres than do cells in surrounding normal tissue, an observation consistent with an extended phase of proliferation in the context of insufficient telomerase activity during early-stage neoplasia (*19*, *20*, *62*). Second, and consistent with tumor-associated telomere attrition, human tumors often harbor telomeric associations and anaphase bridges, which can result from terminal fusions of chromosomes that lack functional telomeres (*22*, *42*, *63*) (Fig. 1A). Indeed, studies of *mTerc* mutant mice have shown that the number of intratumor anaphase bridges correlates well with the level of telomere dysfunction (*42*). Although chromosomal defects other than telomere dysfunction can lead to dicentric formation and anaphase bridges, it is intriguing that human colorectal cancers show a peak in the

anaphase bridge index (a numerical measure of the metaphases that contain anaphase bridges) in early high-grade dysplastic lesions and a decline in more advanced carcinoma stages (*42*). This pattern is consistent with the prolonged proliferative activity of benign adenomatous lesions and the subsequent onset of robust telomerase activity that can break the cycle of breakage-fusion-bridge in cancerous genomes (*57*, *58*, *60*). Finally, cytogenetic and array-comparative genomic hybridization analyses of epithelial tumors arising in mice with telomere dysfunction have revealed highly aberrant genomes particularly nonreciprocal translocations and regional amplifications and deletions of the type that are common in primary human cancers and less frequent in primary mouse cancers with intact telomere function (*29*, *64*, *65*). These observations indicate that telomere dysfunction and crisis represent a mechanism driving accumulation of cancer-associated chromosomal structural aberrations and strengthen the connections between cellular crisis, chromosomal instability, and cancer.

As noted above, one unanticipated outcome of the telomerase knockout mouse experiments was the finding that telomerase was not required for tumorigenesis. In fact, tumors appeared more frequently in aging mice with dysfunctional telomeres than in their counterparts with intact telomeres (*31*). How can this finding be reconciled with the evidence that telomere maintenance is critical for survival of human cancer cells transiting through crisis? The systematic analysis of how telomere dysfunction suppresses or enhances the cancer phenotype of several tumor suppressor mutant mouse strains has provided intriguing insights (Table 1). As summarized below, it appears that the status of DNA damage surveillance mechanisms, and perhaps cell type–specific factors, are major parameters controlling the neoplastic outcome of telomere-based crisis.

The successive interbreeding of mice doubly null for *mTerc* and *Ink4a/Arf* has allowed comparison of tumor type and frequency as well as tumor-free survival in relation to varying degrees of telomere reserve (*66*). Early-generation *mTerc Ink4a/Arf* null animals, which have intact telomere function, developed the typical spectrum of lymphomas and soft tissue sarcomas at the same frequency and showed similar survival trends as their telomerase-positive, *Ink4a/Arf* null counterparts. However, in the later generations, the onset of telomere dysfunction was associated with a marked suppression of tumorigenesis and increased survival, with the tumor spectrum largely unchanged. Consistent with these in vivo findings, late-generation *mTerc Ink4a/Arf* null mouse embryonic fibroblasts were also more resistant to transformation by dominantly acting oncogenes, and this resistance was quelled by somatic restoration of *mTerc* expression.

The finding that telomere dysfunction can suppress tumorigenesis has been replicated in other mouse tumor models. For example, *mTerc* null mice with short dysfunctional telomeres were found to be resistant to a standard 7, 12-dimethylbenz(a)anthracine–12-O-tetradecanoylphorbol 13-acetate (DMBA-TPA) skin carcinogenesis protocol, and p53 was implicated as a potential limiting factor in tumor growth in these animals (*41*). Additionally, the *mTerc* Min (multiple intestinal neoplasia) mouse model has been particularly informative in this regard (*42*). Min mice harboring a germline *apc* (*adenomatous polyposis coli*) tumor suppressor gene mutation develop dozens of benign adenomatous lesions in the intestinal tract upon loss of the wild-type *Apc* allele (*67*). In the face of mild telomere dysfunction, as evidenced by a moderate intratumoral anaphase bridge index, early-stage adenomas appeared more frequently—an increase thought to be stimulated by increased genomic instability and loss of the remaining wild-type *Apc* allele. However, higher levels of telomere dysfunction impaired the progression of these early-stage lesions into lethal macroadenomas, which correlated with activation of checkpoints and upregulation of p53. Thus, in the evolution of cancer in this mouse model, both faces of telomere dysfunction are manifest. In one, increasing genomic instability stimulates tumor initiation, and in another, intolerable levels of genomic instability halt tumor progression.

In light of these results, how can telomere dysfunction ever cause tumor progression? The particular genetic mutations that a cell

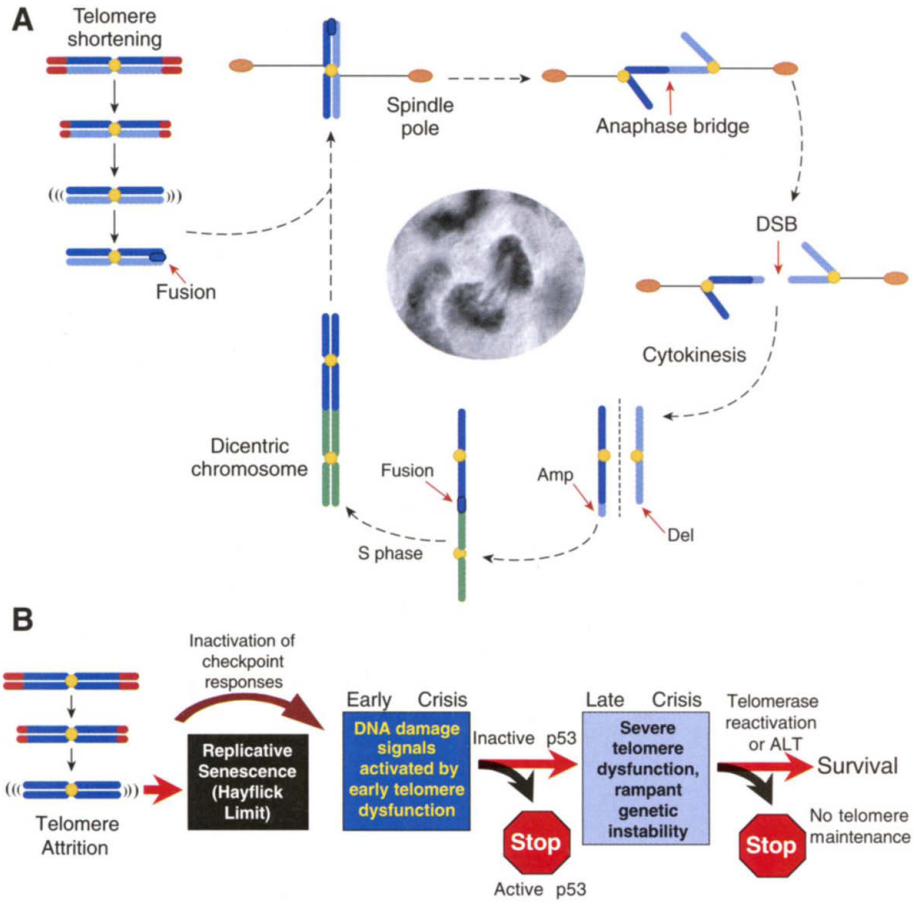

Fig. 1. (**A**) Telomere attrition and perpetuation of the BFB cycle. As cells divide in the absence of telomerase, telomeres (in red) erode, exposing the ends; DNA repair functions can then create chromosome fusions. Here, a fusion between two sister chromatids (in dark and light blue) forms a dicentric chromosome, which results in anaphase bridging during segregation in mitosis. The dicentric chromosome is broken when pulled to opposite spindle poles, creating changes in gene dosage [amplifications (Amp) and deletions (Del)] for the resulting daughter cells. The broken chromosome must then be repaired again and can become fused to another chromosome (in green), generating a second dicentric chromosome and perpetuating the BFB cycle. This cycle likely facilitates the accumulation of genetic changes that enable cells to emerge from crisis and proceed to malignancy. (**B**) A model for crisis induced by telomere attrition. Shortened telomeres elicit replicative senescence in vitro, blocking further proliferation, unless checkpoint responses are disrupted. Continued cell division will eventually cause telomere dysfunction and crisis. The early stages of crisis can be averted by loss of p53. Eventual emergence from late crisis requires not only p53 inactivation but also the acquisition of telomere maintenance mechanisms.

harbors may dictate its ability to replicate in the face of telomere dysfunction and breach the telomere-based senescence checkpoint (the Hayflick limit); that is, cells already harboring checkpoint deficiencies (e.g., mutations in p53 and Rb) are less susceptible to this initial block to continued proliferation. Additionally, it seems likely that the convergence of aberrant DNA repair function and lack of checkpoint responses would enhance genomic instability. Indeed, the preponderance of chromosomal rearrangements and other structural anomalies encountered in cells that have experienced crisis (*17*, *68*, *69*) is indicative that DNA repair activities have been at work. Inappropriate repair between broken telomeres, or a broken telomere and an internal site, from two different chromosomes can result in the formation of dicentric chromosomes and the creation of breakage-fusion-bridge (BFB) cycles (Fig. 1A) (*6*, *29*, *38*). In addition to a predisposition for chromosome nondisjunction, dicentric chromosomes are extremely unstable and can be pulled apart during cell division, causing a new break to form randomly between the two centromeres. Thus, chromosome breaks form anew, and a continuous BFB cycle can be perpetuated. Because DNA DSBs are sources of amplifications and deletions of DNA (*70*–*73*), these BFB events are likely associated with and responsible for genomewide regional changes in gene dosage. This is the recipe for a premalignant cell to acquire the molecular changes needed to evolve into a malignant cell.

The ability of telomere dysfunction to inhibit tumorigenesis in mice illustrated the power of checkpoints in restraining the growth of neoplastic cells. Given the importance of p53 in DNA damage and telomere-induced senescence checkpoints, and its high mutation frequency in human tumors (*74*), it was of interest to directly test whether p53 deficiency in mice could rescue the phenotypes associated with telomere dysfunction and cooperate in carcinogenesis. The generation of mice doubly null for p53 and telomerase revealed that p53 loss attenuates many of the phenotypes associated with telomere dysfunction, including growth arrest, germ cell apoptosis and testicular atrophy, and intestinal apoptosis (*40*). Telomere dysfunction cooperates with p53 nullizygosity to reduce tumor latency and, in the context of p53 heterozygosity and advancing age, shifts the spectrum of epithelial cancers to those typically encountered in aged humans (e.g., breast, colon, and skin) [reviewed in (*7*)] (*29*). Epithelial carcinomas are rarely observed in mice unless they are engineered to express dominantly acting oncogenes in epithelia (*7*). Tumors derived from these *mTerc p53* double mutant mice show a high level of genomic instability, similar to their human counterparts (*29*, *65*). This finding lends support to the hypothesis that, whereas telomere dysfunction may be an important checkpoint on growth when the surveillance mechanisms are intact, it can be a potent "carcinogen" in the absence of these critical checkpoints. Because most human tumors have disabled p53 function (*74*), it is tempting to speculate that telomere dysfunction may play an important role in driving the genomic instability seen in human epithelial tumors in the absence of this critical checkpoint.

Lastly, it is important to emphasize that p53 loss alone cannot neutralize the ravages of massive genomic instability, as evidenced by the failure of p53 loss to rescue organ failure in mice with severe telomere dysfunction (*40*). Thus, once tumors have survived initial crisis by p53 loss, tumors that emerge must still have some mechanism for telomere maintainence. The combination of telomere dysfunction and the consequent genetic instability, checkpoint inactivation, and eventual long-term telomere maintenance may be a critical sequence of events for tumor initiation and full malignant progression (Fig. 1B).

Telomerase-Based Therapy: Friend or Foe?

The observation that telomerase can extend cellular life-span in vitro (*53*) has opened up the exciting possibility that telomerase therapy may delay age-associated tissue degeneration (*75*) or reverse organ failure in chronic high-turnover diseases (*35*). Indeed, several studies have already explored transplantation of "telomerized" cells, such as vascular endothelial cells (*76*) and adrenal cells (*77*), to restore cellular function in the context of a whole organism.

Given the role of telomerase in cancer, however, will enforced expression of telomerase as a tissue-regenerative strategy be carcinogenic? Several recent experiments have sounded a note of caution regarding the use of somatic TERT therapy. In transgenic mice, *TERT* overexpression in basal keratinocytes renders those cells more susceptible to carcinogen-induced skin tumors (*78*). In addition, mice with *TERT* transgene expression in the mammary gland develop neoplastic lesions, again indicating that too much telomerase may be tumorigenic (*79*). Notably, in both of these experimental models, the mice presumably have intact, full-length telomeres and otherwise normal telomerase function; thus, telomeres are not limiting for growth. The molecular mechanisms driving tumorigenesis in these models need to be examined in greater detail.

Are these findings in mouse model systems relevant to human cells? A recent report indicates that hTERT overexpression can endow human mammary epithelial cells with resistance to growth inhibition by transforming growth factor–β (TGF-β), once these cultures have inactivated $p16^{Ink4a}$ (*80*). The extent to which these hTERT-associated perturbations are cell-culture related, dependent on $p16^{Ink4a}$ inactivation, or reversible will require further study. Additional experiments indicate that enforced TERT expression may inhibit apoptosis induced by multiple different stimuli, although again, whether this is

Table 1. The effect of telomere dysfunction on tumorigenesis in cancer-prone mice.

Mouse model	Cancer type	Effect of telomere dysfunction	Ref.
Aged mTerc$^{-/-}$	Lymphoma, teratocarcinoma, others	Increase in G4 to G6, as compared with wild type and G1 to G3*	(*31*)
mTerc$^{-/-}$; *Ink4a/Arf*$^{-/-}$	Lymphoma, fibrosarcoma	Suppression in G4 to G6, as compared with wild type, G1, G2	(*66*)
mTerc$^{-/-}$; Min (*Apc*$^{+/-}$)	Intestinal adenoma	Increase of microadenoma in G2, G3; strong suppression of macroadenoma in G4	(*42*)
MTerc$^{-/-}$; DMBA-TPA	Skin papillomas	Strong suppression in G5 mice compared with wild-type, G1	(*41*)
MTerc$^{-/-}$; *P53*$^{-/-}$	Lymphoma, sarcoma, adenocarcinoma	Reduced tumor latency in late generation; appearance of adenocarcinomas in 10% of mice	(*29*)
MTerc$^{-/-}$; *P53*$^{+/-}$	Epithelial carcinoma (breast, skin, colon); lymphoma, sarcoma	Reduced latency in late generation; majority sustain epithelial carcinomas	(*29*)

*G refers to successive *mTERC*$^{-/-}$ generations (where G1 represents the first *mTERC*$^{-/-}$ generation from an *mTERC*$^{+/-}$ intercross, G2 is the product of a G1 intercross, etc.) (*28*).

simply a reflection of the experimental conditions is not clear (*81*).

In our view, the evidence to date indicates that the potential of telomerase therapy in controlled conditions may outweigh the risks associated with carcinogenesis. Whereas cells that overexpress telomerase in culture are immortal, they do not become cancerous unless the p53 and Rb checkpoints and other signaling pathways are also commandeered (*55*, *56*). Indeed, several studies have demonstrated that enforced hTERT expression in primary human cultured cells enables extended growth beyond the Hayflick limit without altering the functional status of principal regulators of cellular mortality, growth control, and cell survival (*82–84*). Although a more comprehensive gene profiling study may be warranted, the normal cellular behavior of these hTERT-reconstituted cultures, coupled with its unremarkable molecular profile, supports the view that on its own, enforced high-level hTERT expression and telomerase activity could be innocuous.

In this context, it is worth emphasizing the staggering unmet needs of individuals who suffer from chronic organ failure and who succumb while waiting for a donor organ—for example, patients with end-stage liver cirrhosis. The possibility of telomerase-induced carcinogenesis may be of less concern in this particular clinical setting because the telomerase therapy would be transient [for example, delivered as a protein (*85*)], and in many cases the telomerase-treated liver would ultimately be removed once a donor organ was found. The beneficial effects of somatic telomerase therapy have been established in a mouse model of liver fibrosis (*35*) [reviewed in (*86*)].

The use of telomerase inhibitors as a therapy to thwart the growth of cancer cells is also being actively investigated [reviewed in (*87*)]. Among the inhibitors being evaluated are dominant-negative TERT subunits (*25*, *26*), peptide nucleic acids and oligonucleotides (*88*, *89*), and chemical inhibitors (*27*, *90*, *91*). In addition, TERT has been investigated as a potential homing target for immunotherapy of cancer cells (*92*). However, the majority of these methods would take time to be effective, because cancer cells will continue to divide until their telomeres shorten to the point of inducing crisis. This lag in cell killing may allow ALT or other adaptive responses to develop, rendering those cells resistant to telomerase inhibition. Additionally, whether telomerase inhibitors harm the population of normal cells that rely on telomerase will merit careful attention. Nonetheless, encouraging experiments have highlighted the potential for telomerase inhibitors to synergize with conventional chemotherapeutics in killing cancer cells (*91*, *93*).

In summary, the experiments reviewed here illustrate how crisis can be used both as a weapon by normal cells to ward off the instability that drives cancer and as a mechanism by premalignant cells to achieve the high threshold of changes required for malignant progression. Continued investigation into the ability of crisis to endow cancer cells with new growth properties, and the identification of the relevant accompanying genetic changes, will hopefully allow us to design smarter therapies to treat this disease.

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94. We thank J. Shay, K. Collins, N. Schreiber-Agus, L. Chin, and K. Wong for critical reading of the manuscript; and L. Chin for assistance with figures. R.A.D. is supported by grants from the NIH and is an American Cancer Society Professor and a Steven and Michele Kirsch Investigator. R.S.M. is supported by the Damon Runyon Cancer Research Foundation Fellowship DRG-1701-02.