undergoing stem cell transplantation, laughter therapy was one of several complementary stress-reduction techniques tested (the others were massage therapy and parental massage and relaxation/imagery). The authors found no differences between any of the interventions, compared with standard care, on measures of health-related quality of life. They concluded that “the current trial does not provide support for the benefits of massage and humor therapy in reducing distress in the pediatric [stem cell transplant] setting, and suggests some caution in the widespread application of these therapies.”

**Know Your Audience**

Even the biggest boosters of laughter therapy warn that it must be used judiciously. “I don’t think humor is always appropriate,” said Goodman. “There are occasions when the timing is just not right. We need to be sensitive to our audience, whether it’s someone who is facing a health crisis or a group of people who are under stress because, for example, they’ve just lost their jobs.”

Humor is highly subjective, said Lown. “One person’s funny story may be another person’s pain. It’s tricky to use humor if you’re not sure how it’s going to be interpreted by someone else. You have to know your patients, who they are, where they come from, and what their context is.”

“The more you know a person, the better your intuition will be,” added Goodman. “Look for nonverbal cues, for what makes them laugh or brings a smile to their face.” He suggested that clinicians interested in lightening their visits assemble a collection of amusing but inoffensive sayings and quotes. He offered one of his favorites, from Robert Frost: “The brain is a wonderful organ. It starts when you wake up in the morning and does not stop until you get to work.” When all else fails, Goodman uses the AT&T test: “Is it appropriate, timely, and tasteful? If you can answer yes to all three, chances are that humor will work for you rather than backfire against you.”

Clinicians should also become adept at identifying people who may not be receptive to laughter. “If [some people are] angry or extremely depressed, they’re not ready for the workshop,” Nelson pointed out.

Still, giving patients a place to laugh together and find support has real benefits, even if they cannot be precisely quantified. “It’s like taking a dose of medication,” Glenn said of the Strength through Laughter gatherings, “just laughing and smiling and not thinking about your sickness while you’re there.”

“I wish there were more data about this,” added Lown. “Unfortunately, sometimes the important things just can’t be measured. But it doesn’t mean they’re not important.”

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**At Loose Ends: Telomere Theories of Aging and Cancer Begin To Converge**

**By Ken Garber**

Age is the single greatest risk factor for cancer. About 60% of cancer diagnoses occur in the 13% of the population aged 65 years or older. Why does aging lead to increased incidence of cancer?

One view holds that it’s not aging but time that produces cancer. Only over time, typically decades, can cells accumulate the DNA mutations and other alterations that cause the common epithelial cancers of the lung, breast, prostate, and colon. From this perspective, cancer coincides with aging but is not caused by it. But over the last 15 years our concept of aging has evolved, from an accumulation of damage that “just happens” to a consensus that aging is a regulated process that’s at least partially genetic. And cancer is now commonly viewed as mechanistically linked to this aging process.

But no universally accepted view of how aging causes cancer exists. One theory posits that a progressive loss of telomeres—the caps of noncoding DNA that protect the ends of chromosomes—helps propel aging and that genomic instability caused by such telomere dysfunction drives malignancy. According to another theory, an age-dependent deterioration of mitochondria, organelles that produce energy for the cell, causes both aging and cancer by generating reactive oxygen species (ROS) that damage DNA and proteins. Recent mouse studies from the laboratory of Ron DePinho, M.D., formerly at the Dana–Farber Cancer Institute in Boston and now president of the University of Texas M. D. Anderson Cancer Center in Houston, raise the possibility that the two processes are linked in aging—and perhaps in cancer. “We provided a ‘unified field theory’ for aging,” said DePinho, “by providing a direct molecular link.” Broad acceptance of DePinho’s theory hinges on definitive validation in humans, including the success of interventions designed to forestall aging and prevent cancer.

**Linking Short Telomeres to Cancer**

The field has room for a new theory, because no consensus exists on what causes aging and what links it to cancer. And much about telomeres remains mysterious. Telomeres have been observed since the 1930s, but only in recent decades have researchers worked out telomere biology in any detail. In 1978, Elizabeth Blackburn, Ph.D., then at Yale University in New
“They thought we were going to cure aging,” recalled Jerry Shay, Ph.D., of the University of Texas Southwestern in Dallas, one of the authors. In fact, few biogerontologists take telomere loss seriously as the main cause of aging at the organismal level. To begin with, many small mammals, including mice, have long telomeres and plenty of telomerase, and live only a few years, whereas humans have short telomeres and scant telomerase and can live more than a century. More important, most human cells never approach the Hayflick limit. “Normally humans don’t undergo enough cell divisions to get toward the point at which our telomeres are getting either critically short or anywhere near short,” said Peter Hornsby, Ph.D., who researches aging at the University of Texas Health Science Center at San Antonio. And cells that do divide, Hornsby said, typically have sufficient telomerase. However, human population studies have shown an association between short telomere length in blood cells and many diseases of aging. “Telomere biology is going to explain maybe 10% or 15% of aging and cancer,” said Shay. “It’s important, but there are many ways to develop [a phenotype for aging].”

As in aging, the role of telomeres and telomerase in cancer is complex and still being worked out. Telomerase is detectable in about 90% of human tumors, so until the year 2000 the enzyme was thought to be necessary for tumor development. That year, DePinho’s group reported that telomerase- and p53-deficient transgenic mice, instead of abolishing cancer (mice normally develop lymphomas and carcinomas), surprisingly developed human-like epithelial cancers. These tumors displayed breakage–fusion–bridge cycles, in which the shortened telomeres of chromosomes fuse; are then pulled apart during cell division when chromosomes move to opposite poles of the cell, with the fused chromosomes forming bridges; and finally break. Then the chromosomes rearrange to create the translocations that characterize many human tumors. “That creates amplifications of oncogenes and deletions of tumor-suppressor genes,” said DePinho.

By engineering mice without telomerase, DePinho created a model of what may happen in premalignant human cells that lose telomerase function and then go through “telomere crisis.” Unable to replicate, most senesce or die, but a few find a way to keep dividing and emerge as malignant tumor cells. “It took Ron’s lab to figure out how to make a mouse model reflect what’s really going on in human cancer,” said Shay.

Linking Telomeres to Mitochondria

The recent telomere–mitochondria connection emerged from work by DePinho’s group on aging. Mice engineered to lack telomerase surprisingly have sick hearts and livers—quiescent organs not likely to wear down their telomeres. To understand how loss of telomerase damaged these organs, DePinho examined patterns of gene expression. These patterns pointed strongly to the repression of pathways related to mitochondria, including PGC-1α and PGC-1 β, master regulators of mitochondrial biogenesis and function. DePinho’s group worked out the following sequence of events: Telomere dysfunction activated p53, which—in addition to a major role in DNA repair—binds to the PGCs, repressing their activity and impairing mitochondria. Impaired mitochondria pour out ROS, which can damage DNA, especially the guanine-rich sequences in telomeres, in a self-reinforcing cycle. “You create a lot of ROS, which will create a feed-forward loop,” explained DePinho. “That increases damage, increases p53, further represses PGC, further messes up mitochondria and oxidative defense.” This model of aging...
for the first time linked telomeres to mitochondria: DePinho’s “unified field theory.”

But why were telomeres failing in these nondividing cells? “Telomere dysfunction is not simply the shortening of telomeres,” explained DePinho. Mutations that disrupt telomere function, or defects in the “shelterin” complex of proteins that binds them, could also be responsible, he said.

Researchers studying the biology of aging have cautiously welcomed the paper, published last year in Nature. By connecting telomeres to mitochondria and oxidative stress, DePinho is “linking two things that are very . . . central to the aging community,” said Toren Finkel, M.D., Ph.D., who studies aging at the National Heart, Lung, and Blood Institute. Such unifying hypotheses are badly needed in the fractured aging field, Finkel added, but proof that telomere dysfunction leads to a cascade of mitochondrial pro-aging effects in humans is still lacking. Finkel points out that mitochondrial deterioration over time can be explained without telomeres. “To what degree in the [human] heart, the brain, and the liver this is caused by telomeres eroding or just the sort of ravages of time I think is still an open question,” he said.

The work in aging enabled even newer research linking telomeres and mitochondria in cancer. In research published in February in the journal Cell, DePinho’s group took a mouse model of lymphoma and engineered these mice so that telomerase could be turned off and on at will. Consistent with the “telomerase off, tumors on” model he established in 2000, DePinho’s mice develop tumors, but feeble ones, because they lack the necessary telomerase for unchecked proliferation. Turning telomerase back on led to highly aggressive tumors. A second Cell paper from this group showed a similar tumor explosion, this one leading to bone metastases, in a mouse model of prostate cancer. These aggressive tumors, in DePinho’s view, are compelling evidence that telomerase does more than permit tumors to grow—it actually drives that process. Thanks to telomerase, such tumors “can acquire new events that can make them even more malignant,” he said.

But the most unexpected finding came when DePinho’s researchers turned telomerase off again: Tumor growth slowed, and then renewed, as tumors learned to lengthen their telomeres without telomerase, through a process known as alternative lengthening of telomeres. In these tumors, levels of PGC-1β were up, along with mitochondrial numbers. “The cell tries to make more of those mitochondria,” said DePinho. “And therefore they upregulate PGC. And you see massive upregulation of many, many antioxidant defense genes as well.” In effect, these tumor cells are reversing the mitochondrial hallmarks of aging seen in telomerase-knockout mice. They are becoming young again, even as they set out to kill their host. DePinho’s lab is now investigating whether mitochondrial loss and recovery takes place not only in tumor cells with alternative lengthening of telomeres but also in the more typical tumors that reactivate telomerase to grow and spread.

Validating the Telomere Hypothesis

Work is already under way to verify that telomere-related mitochondrial changes occur not only in mice but also in humans. For example, Rosa Ana Risques, Ph.D., in the pathology department at the University of Washington medical school in Seattle, has been studying bowel tissue from patients with ulcerative colitis (UC). About 10% of UC patients eventually progress to colorectal cancer. UC is a good model for understanding human colorectal cancer progression because most patients undergo annual colonoscopies, allowing researchers to track changes as cells progress through various stages of dysplasia to cancer. In a poster presented at the annual meeting of the American Association for Cancer Research in April, Risques’s group reported that a marker of mitochondrial function went down more often in UC patients who later progressed to cancer than in those who did not progress, and that the mitochondria recovered function once cancer appeared. PBC-1β levels also fell and then rose. “Our data align with DePinho’s data,” said Risques. “It matches, in theory . . . with these ‘turn off, turn on’ telomeres and mitochondria at the same time.” Risques is now checking whether these patients’ telomeres follow the predicted pattern.

Such validation is crucial. “Mouse studies are fantastic for us to learn cause and effect,” Risques said. “But then I think it’s necessary to move to human biopsies to see what is happening in the real tissue.”

Shay agreed. “You’ve got to separate mouse models where you knock out a gene from what really goes on in human beings,” he said. Researchers, including Risques and her Washington colleague Peter Rabinovitch, M.D., Ph.D., and especially Alan Meeker, Ph.D., at Johns Hopkins University in Baltimore, have over the past decade studied telomeres in human tissue for evidence backing the telomere hypothesis—that is, loss of telomeres leading to chromosome fusion and breakage, translocations and genomic instability, escape from telomere crisis, and finally telomerase reactivation and full-blown tumors. Almost uniformly, these studies have shown that changes in human tissues examined at different time points are consistent with this sequence of events.

“There must be a dozen papers that provide absolutely direct evidence that there is a fusion–bridge–breakage process at the time that telomeres are eroded in human cancers,” DePinho said. Loss of telomerase function may not cause cancer cells to initially transform, DePinho said, but it’s crucial for full malignancy.

But the case for telomeres driving human cancer is not closed. “The evidence is largely circumstantial, as it has been impossible to know what happens during actual tumor progression,” said Robert Weinberg, Ph.D., a cancer researcher at the Whitehead Institute in Cambridge, Mass., by e-mail. A demonstration in real time, he said, would help: “Extract cells from a human premalignant growth and demonstrate that such cells, upon culturing ex vivo, would go through the breakage–fusion–bridge cycles, crisis, and telomerase activation.” Weinberg acknowledged that such an experiment would be difficult. (Putting tumor cells in culture, Hornsby noted, leads to selection for cell subpopulations best
adapted to culture conditions and to loss of others, distorting results.)

DePinho argued that enough evidence already exists to validate the telomere hypothesis of cancer. “The genetic evidence, as well as the genomic evidence, showing that it is causal to the development of cancer is without question at this point.”

DePinho stressed that telomeres are not the whole story in cancer and aging. “Telomere dynamics are incredibly important,” he said. “However, they’re not the only reason [for cancer]. The accumulation of alterations, changes in the epigenome—a variety of things are going to undoubtedly conspire.” Complete acceptance of the telomere hypotheses of cancer and aging will probably not come until telomere-based interventions succeed. These interventions range from telomerase inhibitors now in clinical development for treating cancer (see J. Natl. Cancer Inst. 2010;102:520–1), to telomere-measuring diagnostic tests, to strategies for boosting telomerase to prevent cancer or even slow aging. Meanwhile, DePinho’s work plausibly explains how aging leads to cancer: Telomere dysfunction is the common element. “It may not be a driver of cancer neoplastic initiation,” he said. “[But] I would say it’s the main driver of the benign-to-malignant transition in cancer.”

DePinho is a consultant to Metamark Genetics in Cambridge, Mass. Shay is a consultant to Life Link in Madrid.

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Cutaneous T-Cell Lymphoma’s Confounding Nature

By Charlie Schmidt

W hen the rashes appeared suddenly last year around Thanksgiving, Jim Crane, 78, thought they were bug bites. But then they began to spread, mainly to his hands and feet. His doctors suspected psoriasis, or even a reaction to quinolones in the eye drops he was taking after cataract surgery.

Over the next several months, Crane endured several marginally effective treatments, and he didn’t get a more accurate diagnosis until late February: cutaneous T-cell lymphoma (CTCL) with blood involvement. Which specific subtype he suffers from isn’t clear: either an advanced stage of the most common type of CTCL—mycosis fungoides (MF)—or a rarer subtype known as Sézary syndrome. But with more appropriate care, Crane’s symptoms have improved, says his wife, Elaine. “His skin is a lot better and he’s lost a lot of that redness,” she said. “He’s basically clear, except for a few plaques, and that’s where we are now.”

Long timelines to diagnosis are common in CTCL, which can cause symptoms that resemble benign inflammatory conditions. But clinical awareness of these rare malignancies—which strike fewer than 2,000 people annually in the U.S., most of them aged 50 and older—is growing. And despite limited research funding, new treatments that improve on the 30%–40% response rates observed so far have begun to emerge, according to Francine Foss, M.D., a professor of medicine and dermatology at the Yale School of Medicine.

As a group, CTCL includes either cancers limited mostly to skin—such as MF, which accounts for approximately 60% of all CTCL cases—or cancers of the skin and the blood, such as Sézary syndrome, which constitute about 5% of new diagnoses. When disease is limited to the skin, the prognosis is generally good; patients can live more than 25 years with indolent MF that never progresses, according to Madeline Duvic, M.D., who chairs the department of dermatology at the University of Texas M. D. Anderson Cancer Center in Houston. Leukemic varieties such as Sézary syndrome have worse outcomes: Patients often die of infections within 3 years of diagnosis, for reasons that remain unclear.

New T-Cell Insights

Researchers once thought that Sézary syndrome could arise from MF, meaning that the cancer would progress from the skin into the circulation. But new research shows that’s almost never the case. Although MF might sometimes move into the blood, Sézary syndrome is a distinct illness involving a different T-cell population, according to Rachael Clark, M.D., an assistant professor at Harvard Medical School. Publishing in Blood in 2010, she and colleagues from Brigham and Women’s Hospital in Boston reported that MF is a malignancy of effector memory T cells that don’t leave the skin, whereas Sézary syndrome is a malignancy of central memory T cells that migrate between the skin, lymph nodes, and blood. And that finding has important treatment implications: Clark and her team followed up in Science Translational Medicine last January, reporting that alemtuzumab (Campath), a monoclonal antibody that targets CD52 surface proteins, was ineffective against MF but produced partial responses in every Sézary syndrome patient tested (18) and total remission in half.

In a companion focus article, Mark David, Ph.D. from Stanford University School of Medicine, called that finding a translational tour de force. Given subcutaneously, alemtuzumab clears all circulating B and T cells from circulation, but because effector memory T cells never make it into blood, they remain beyond the drug’s reach. Central memory T cells circulate routinely, however, making them vulnerable to the drug’s two-stage clinical effects: clearance of leukemic disease from blood, followed