Meeting Report: Translational Research at the Aging and Cancer Interface

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Introduction

A close relationship between aging and cancer has been recognized for many years. Age is, after all, the largest single risk factor for developing cancer. This point is illustrated by considering three broad categories into which most human cancers fall: hereditary cancers (associated with predisposing germ-line mutations); pediatric cancers (including those in young adults); and age-associated cancers (which begin to increase exponentially in about the fifth decade of life.) The vast majority of human cancers belong to this last category. Nonetheless, aging and cancer research remain largely separate entities. Consequently, an AACR conference that explores cancer and aging as intertwined processes is fitting.

Despite awareness that cancer is primarily an age-related disease, molecular hypotheses to explain how aging and cancer interrelate have emerged only recently. This emergence is due, in part, to progress in cancer research: understanding genetic and epigenetic factors that drive cancer, and how host factors influence tumor progression. It is also due to remarkable progress in understanding the genetics, molecular and cell biology, and evolutionary biology of aging. Thus, as cancer research progresses and aging research matures, these fields are beginning to coalesce and provide new insights into both cancer and aging.

The conference opened with keynote talks by Harvey Cohen (Duke University Medical Center, Durham, NC) and Judith Campisi (Lawrence Berkeley National Laboratory, Berkeley, CA). Dr. Cohen described the wide range of phenotypes, comorbidities, and challenges that face modern geriatric oncologists. Given that most cancer patients are elderly, he discussed the practical problems of enrolling older subjects in anticancer clinical trials and the difficulties of designing meaningful trials that measure appropriate end points. Dr. Campisi described the evolutionary underpinnings for the development of age-related diseases, including cancer. She discussed the idea of an evolutionary trade-off (antagonistic pleiotropy) between tumor suppressor mechanisms such as apoptosis and cellular senescence and the eventual development of aging phenotypes, including late-life cancer.

Each conference session included interesting and excellent short talks selected from submitted abstracts; owing to space limits, the short presentations are not reviewed here. [Cancer Res 2007; 67(10):4560–3]

Genetic and Molecular Factors

What roles do the nuclear and mitochondrial genomes play in cancer and aging? This question was addressed by Joseph Nevins (Duke University Medical Center, Durham, NC), Christopher Benz (Buck Institute for Age Research, Novato, CA), and Tomas Prolla (University of Wisconsin, Madison, WI).

Mammalian aging and cancer are associated with increases in mitochondrial DNA (mtDNA) mutations and deletions. MtDNA is replicated by the nuclear-encoded DNA polymerase γ (Polγ). Dr. Prolla described transgenic mice with elevated mtDNA mutation frequencies owing to a mutant Polγ. Although these mice displayed several signs of accelerated aging, cells from these mice showed no evidence of excessive mitochondrial oxidative stress and no increase in cancer incidence. Whereas this transgenic model might be a poor phenocopy of normal aging and age-related cancer, it also raises the possibility that cells with extremely defective mitochondria are eliminated by apoptosis, which suppresses cancer but accelerates aging in certain tissues.

Dr. Benz discussed the importance of age as a demographic risk factor for human malignancies. A retrospective analysis of nearly 4,000 breast cancer samples analyzed for >15 biomarkers showed that clinical behavior and biology are significantly affected by age at diagnosis. Some prognostic biomarkers are codependent on another age-related marker, estrogen receptor. Dr. Benz described an ongoing prospective study that controls for estrogen receptor while searching for other age-related differences. Surprisingly, few, if any, genetic changes distinguished estrogen receptor–positive breast cancers arising in younger (<46 years) versus older (>69 years) subjects; however, older and younger breast cancer cases showed significant differences in transcript levels for tumor suppressor and growth promoting genes. These findings suggest that transcriptome changes, rather than genetic abnormalities, account for biological and outcome differences among breast cancers that arise at different ages.

Dr. Nevins described an emerging strategy that predicts individual outcome in cancer patients, heralding the arrival of personalized cancer therapy. Only 25% of patients with stage IA lung cancer are at risk for metastatic disease, typifying the need for tools that predict outcome. Gene expression signatures can identify stage IA patients who are at greatest risk for developing metastases. These signatures are being integrated into clinical
trials in which prospectively identified high-risk early-stage patients are offered aggressive chemotherapy. Cancer gene expression signatures and bioinformatics are also linking specific signatures to particular oncogenic pathways and drug sensitivity profiles, enabling patients to be individually matched to more precise drug therapies.

Epigenetics in Cancer and Aging

The mounting evidence that epigenetic control of gene expression is important for both cancer and aging phenotypes was explored in a session that featured Thea Tlsty (University of California San Francisco, San Francisco, CA), Estela Medrano (Baylor College of Medicine, Houston, TX), and Darryl Shibata (University of Southern California, Los Angeles, CA).

Dr. Tlsty discussed the importance of epigenetic silencing of p16 (INK4a) in premalignant phenotypes in human breast epithelial cells, in culture and in vivo. p16 is a tumor suppressor that positively regulates another tumor suppressor protein, pRb. Loss of p16 expression, owing to hypermethylation, enables cells to accumulate short telomerces and become genomically unstable. Interestingly, p16 silencing results in stabilization of p53, another tumor suppressor, suggesting compensatory cross-talk between the two pathways. It is now apparent that INK4a silencing is controlled in part by Polycomb (Pc) group repressors, which keep cells in a progenitor-like state. Consistent with this observation, p16 in stem cells is silenced by a member of the Pc group, Bmi-1.

Dr. Medrano discussed melanocytes, which produce and transfer melanin to keratinocytes, thereby protecting against UV damage. Malignant melanomas are twice as frequent in men than in women, and increase markedly after about age 55 years. Melanocytes, like other mammalian cells, undergo senescence in response to short telomerces or damage, and this response curtails malignant transformation. Most mammalian cells use both the p53 and p16/pRb pathways for senescence, but melanocytes seem to depend largely, if not entirely, on the pRb/p16 pathway. An important function of this pathway is to remodel chromatin. Indeed, melanocytes senesce on modulation of histone deacetylase 1, and this entails a pRb-mediated assembly of specific chromatin remodeling complexes.

Cellular aging can be measured by chronological age or replicative age (number of cell divisions). One way to measure replicative age is to monitor genetic and epigenetic replication errors. Dr. Shibata argued that many cells within an individual can be organized by genealogy into a single somatic cell tree that starts from the zygote and ends with present-day cells in the organism. Epigenetic changes can be monitored as changes in DNA methylation; thus, the genealogy of any cell can be reconstructed by its methylation history. Using crypt cells and sequencing of 5 to 10 alleles, Dr. Shibata showed that methylation changes randomly increase with age, and that hypermethylation exceeds hypomethylation. These findings raise the possibility that cancers in older people originate from mitotically older cells.

Oncogenic Damage/Cellular Responses

Cells respond to oncogenic damage by undergoing senescence or apoptosis, which suppress cancer but can drive aging. How this occurs was addressed by Pier Pandolfi (Memorial Sloan-Kettering Cancer Center, New York, NY), Arlan Richardson (University of Texas Health Science Center San Antonio, San Antonio, TX), and Elizabeth Blackburn (University of California San Francisco, San Francisco, CA).

The Pten tumor suppressor curtails mitogenic signals, thereby opposing certain oncogenes. Such oncogenes induce normal cells to undergo senescence, which prevents progression to malignancy. Dr. Pandolfi described a prostate-specific gene knockout for Pten and showed that these mice accumulate senescent cells and develop cancer only after a long latency period; moreover, these animals never developed metastases. However, the combined loss of Pten and p53, which prevents cellular senescence, resulted in rapid tumor growth and metastases. Interestingly, mammalian target of rapamycin seems to act as an enhancer of p53 translation. These findings underscore the importance of cellular senescence for suppressing cancer.

Oxidative damage can cause both cancer and aging. Mice deficient in antioxidant defense enzymes are indeed more sensitive to oxidative stress and develop tumors. Dr. Richardson focused on the antioxidant defense enzyme Gpx4, which can directly detoxify lipid hydroperoxides. Transgenic mice that overexpress Gpx4 live slightly longer than wild-type mice. This longevity might be due to a role for Gpx4 in protecting mitochondrial membranes, thereby reducing the apoptotic response to mitochondrially generated reactive oxygen species.

Cell division and telomere shortening lead to senescence, which cancer cells overcome by expressing telomerase. Telomerase inhibitors are being developed as cancer therapeutics. Dr. Blackburn showed that systemic delivery of an interfering RNA against the RNA subunit of telomerase suppressed cancer cell growth and metastases in mice. The interfering RNA suppressed cancer cell growth without telomere shortening or uncapping and induced a distinct gene expression profile, suggesting that telomerase might have functions apart from telomere length maintenance. She further showed that mutant telomerase RNA templates also inhibit cancer cell growth, showing the crucial role played by telomerase and telomere structure in cancer progression.

Stem Cells

Stem cells are double-edged swords that promote longevity by promoting tissue renewal, but are also dangerous sources for carcinogenesis. Norman Sharpless (University of North Carolina, Chapel Hill, NC), Monica Bessler (Washington University School of Medicine, St. Louis, MO), and Irina Conboy (University of California Berkeley, Berkeley, CA) discussed the roles of stem cells in aging and cancer.

Dr. Sharpless described the role of p16 in limiting stem cell proliferation during aging. In mice, p16 expression increases with age, particularly in the stem and progenitor cells of several tissues, including pancreatic islet cells. This increase compromises pancreatic tissue renewal because the age-related decline in islet regeneration was ameliorated in p16-deficient mice. These findings indicate that p16-repression, which is controlled in part by the Pc protein BMI-1, may be important for maintaining stem cell pools, in addition to its well-established function as a tumor suppressor. Dr. Bessler discussed dyskeratosis congenita, a complex hereditary disease featuring segmental premature aging and a predisposition to cancer. In essence, dyskeratosis congenita is a disease of telomerase insufficiency, resulting in excessively short telomeres, particularly in tissues with high cell turnover. In dominant forms of the disease, telomere length is affected in the germ line, resulting in the accelerated appearance of symptoms in offspring. Dyskeratosis congenita provides unique insights into the role of telomerase in humans. The enzyme is important for maintaining stem or progenitor cell pools in multiple tissues, thereby postponing aging.
phenotypes. It also prevents genomic instability due to telomere dysfunction, thereby protecting from cancer.

Dr. Conboy studied muscle stem cells and their ability to participate in repair and regeneration during aging in mice. Repair depends on Wnt and Notch signaling pathways and declines with age. Transplantation and parabiosis experiments show that this decline is due in large measure to deterioration of the local organ and systemic milieu. Strikingly, a young systemic environment can partly reverse the diminished muscle regeneration seen in old animals, suggesting that secreted factors are involved. These studies also suggest that the ability of endogenous stem cells to participate in tissue repair, as well as stem cell therapies and organogenesis, may be restricted by the aged stem cell niche and systemic milieu.

The Aged Tissue Microenvironment and Cancer

The development of cancer requires a tissue environment that permits the progression of initiated cancer cells. James DeGregori (University of Colorado Health Sciences Center, Aurora, CO), Peter Nelson (Fred Hutchinson Cancer Research Center, Seattle, WA), and Zhi-Min Yuan (Harvard School of Public Health, Boston, MA) discussed the roles of cell and tissue aging in cancer progression.

Dr. DeGregori described how an age-associated decline in cell fitness, whether due to accumulated mutations or reduced proliferative capacity, can fuel leukemogenesis. He showed that young bone marrow progenitor cells effectively compete with leukemia cells (carrying a Bcr-Abl oncogene) for expansion in mice. By contrast, old progenitors, or progenitors in which proliferation was genetically or pharmacologically suppressed, competed ineffectively. These findings suggest that reduced cellular fitness within aged tissues can select for adaptive oncogenic events, such as Bcr-Abl translocations, thereby promoting cancer progression.

Dr. Nelson discussed how age-associated changes in the stroma might promote prostate cancer progression. One source of age-related stromal changes may be senescent cells, which increase with age in several tissues, including prostate. Gene expression profiling showed that senescent prostate fibroblasts up-regulate many genes encoding secreted factors that can favor epithelial cell proliferation, survival, and carcinogenesis. He described specific senescent stromal effectors that are candidates for modulating prostate epithelial cell behavior and provided strategies for interventions that oppose the effects of the senescent stroma.

A similar role for senescent stromal cells in cancer progression was discussed by Dr. Yuan. Using three-dimensional heterotypic cultures of human mammary epithelial cells and fibroblasts, he showed that fibroblasts induced to senesce by oxidative stress produce factors that disrupt the ability of mammary epithelial cells to form normal ductal structures. Under the influence of senescent stromal cells, mammary epithelial cells form masses that resemble premalignant lesions and develop resistance to radiation and chemotherapeutic drugs.

Inflammation, Cancer, and Aging

Inflammation figures prominently in the pathogenesis of many age-related diseases, including cancer, and may also be a prominent component of the aging process. The role of inflammation in aging and cancer was discussed by William Ershler (National Institute on Aging, Baltimore, MD), Michael Karin (University of California San Diego, La Jolla, CA), and Evan Keller (University of Michigan, Ann Arbor, MI).

Dr. Ershler reviewed epidemiologic data showing increased expression of proinflammatory cytokines during aging and their association with reduced mobility, decreased strength, loss of lean body mass, and frailty. Interleukin-6 (IL-6) has the strongest association with these outcomes and begins to increase at menopause/andropause. IL-6 has catabolic effects on lean body and bone mass and influences iron absorption and utilization. The transcription regulator nuclear factor κB (NFκB) is upstream of IL-6. NFκB activity increases with advancing age and is also involved in the pathogenesis of certain cancers.

Dr. Karin presented two examples of how inflammation might promote cancer. In one model, he showed that cancer-derived factors promote inflammatory cytokine production by macrophages. These cytokines, including interleukins, promote tumor progression by stimulating invasion and cell survival. In another model, Dr. Karin described how knockout of IκB kinase 2 and the resulting decrease in NFκB activity increased expression of maspin, a suppressor of metastasis. When IκB kinase 2 is active and NFκB induced, the resultant inflammatory cytokine expression inhibits maspin expression, which ultimately promotes metastasis.

Likewise, Dr. Keller suggested that age-related proinflammatory factors may promote prostate cancer metastasis, particularly to the bone, in older hosts. He showed that NFκB activation facilitates bone metastasis by stimulating production of granulocyte macrophage colony-stimulating factor, a pro-osteoclastogenic factor, and by sensitizing osteoclast precursors to the receptor activator of NFκB ligand, which also stimulates osteoclastogenesis. Further, he showed that IL-6 promotes prostate cancer progression by activating the androgen receptor. Thus, inflammatory mediators that increase with age promote prostate cancer progression and metastasis.

Angiogenesis

Malignant tumors require a vascular network (angiogenesis) for progression, and the vasculature undergoes marked related changes with age. How does the aging vasculature influence cancer progression? This question was discussed by May Reed (University of Washington, Seattle, WA). She reviewed the evidence for age-related differences in new vessel formation in experimental tumor models. In several models, angiogenesis was reduced in older animals. However, in a murine TRAMP-C2 prostate cancer model, robust angiogenesis was observed in aged mice, suggesting that some oncogenic mutations enable the tumor to overcome age-related host deficiencies in angiogenesis.

Clinical Research

The elderly are underrepresented in clinical investigations of new drugs, yet are major consumers of anticancer therapies. Problems inherent in clinical trials that enroll elderly subjects were discussed by Stuart Lichtman (Memorial Sloan-Kettering Cancer Center, New York, NY), and new promising therapies were discussed by Jerry Shay (University of Texas Southwestern Medical Center, Dallas, TX) and John Byrd (Ohio State University, Columbus, OH).

Dr. Lichtman described the heterogeneity of the older population and challenges of balancing longevity with quality of life in applying anticancer therapies. He highlighted the practical issues encountered in enrolling older subjects in clinical trials and described problems created by age-related changes in drug
handling, particularly excretion, and polypharmacy. Other challenges in trial design include selection of appropriate end points and toxicity measures, especially for some of the nonhematologic toxicities of newer biological agents, and the use of geriatric assessment methodologies.

Most human cancers have telomerase activity, suggesting that telomerase inhibitors might be efficacious antitumor drugs. Shay described anti-telomerase approaches that are now entering clinical trials. One approach is immunotherapy using hTERT-loaded dendritic cells or a modified hTERT peptide vaccine. A second approach is direct enzyme inhibition using an oligonucleotide. Both have shown promise in preclinical and early clinical trials.

Dr. Byrd discussed targeted antibodies for hematologic malignancies such as chronic lymphocytic leukemia (CLL). An anti-B-cell antigen antibody (to CD20), Rituximab, is now a component of therapy for CLL and other non-Hodgkin’s lymphomas. This therapy is particularly useful in the elderly because of low toxicity. Antibodies to other B-cell targets are under development. Also under development are small modular pharmaceuticals, derived from antibodies and containing key binding sites but lacking other parts of the molecule. One example targets CD37, a B-cell lineage specific target, which binds B-cell CLL and has activity in vitro.

**Summary**

This conference identified multiple areas in which the biology of aging and the biology of cancer overlap. Answers to several questions hold great promise for providing mechanistic insights, as well as potential therapies. How do epigenetic mechanisms suppress stem cell proliferation or create premalignant cells? How do the biology of normal and cancer stem cells intersect? What causes age-related changes in tissue environments, and how do these environments set the stage for cancer development? And, finally, how can our knowledge of how aging influences cancer be translated into better anticancer therapies in the clinic?

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