Influence of the Oldest Tumor Host on Tumor Biology

William B. Ershler

Abstract
For reasons now being clarified, processes of aging result in increased susceptibility to cancer, but this increased understanding has yet to result in tangible advances in prevention or treatment of cancer in older patients. Likewise, clinical oncologists have identified special needs and considerations with regard to the management of older patients, new protocols are being developed that address quality of life and preservation of function as key outcome variables, and pre-treatment assessment has become an active research domain. Yet, the aging/cancer interface has not been suitably addressed with translational research. New agents, such as resveratrol (discussed below) that are currently the focus of interventional aging research may become the prototype for such translational research, particularly as they impact cancer development. Additionally, 'targeted' cancer therapies available or under development will need to be specifically tested in older subjects for whom the targeted pathways may be obscured by factors that occur as a consequence of aging.

Background
The rate of cancer occurrence begins to rise steeply at approximately 60 years of age and by 75 years, approximately one in five will have at least one malignancy (1). The recognition that this small percentage of our overall population sustains a disproportionately large portion of the overall cancer burden raises a number of important questions and should also serve as a warning of clinical challenges on the horizon (2-8). The question of why there is more cancer in the elderly has been probed from different angles and it has been argued that it relates more to the requisite amount of time it takes to develop a clinically recognized malignancy than to any age-related physiological change (9, 10). However, age-related physiological changes have been implicated and these include an age-associated accumulation of DNA and protein damage from oxidative stress, ionizing radiation, environmental exposures, etc., and an age-associated decrease in capacity to repair DNA (11-13). Recently, evidence that the microenvironment within certain tissues is more conducive for tumor development has been advanced (14-16). The importance of age-associated decline in immune function (17), long conjectured to be a major contributor to the rise in cancer with age has yet to be fully-established, despite a small number of tantalizing reports (18, 19).

Clinical and Translational Leads
An appreciation for the interface of aging and cancer has been embraced by a number of laboratories where the commonality of genetic and epigenetic pathways leading
either to cellular senescence or neoplasia have been explored (20, 21). Similarly, clinical oncologists have come to recognize the importance of aging and geriatric issues in the management of cancer (3, 22-26) and have developed research protocols designed to determine optimal treatment in terms of the maintenance of quality of life and physical function. It is more difficult, however, to identify clear-cut translational research in which features of aging are targeted to diminish cancer incidence or proliferation.

Advances in geriatric medicine have led to various instruments to assess overall well being in elderly individuals. These assessments have proven useful in identifying those most at risk for functional decline, institutionalization and mortality (27-30). In recent years, oncologists have attempted to translate these fundamental elements of geriatric assessment in pretreatment considerations for older cancer patients (5, 25), but no single instrument has emerged that more successfully predicts the relevant outcomes of treatment-associated functional decline or increased toxicity than the established and widely-used performance scores assessed by busy clinicians in a minute or less. This does not diminish the importance of this objective, but rather, heightens the need for continued investigation.

Gerontologists are quite familiar with the anti-aging effects of caloric restriction (31-33), which remains the only well-established intervention that reliably and reproducibly prolongs maximal lifespan and reduces the rate of development of age-associated disease, including cancer (34, 35). The caloric restriction effect has been demonstrated in a wide range of species and ongoing studies in non-human primates (36-38) and in humans are currently underway (39). Although the current research in humans has demonstrated short-term beneficial effects, the likelihood of compliance over the long haul is unlikely, even for the most motivated. Recognition of this has led to the search for caloric restriction mimetics (40, 41) and several are under active investigation. To the extent that these agents influence metabolic pathways, proliferation, apoptosis, etc. in a manner similar to caloric restriction, diminished rates of cancer could be expected.

**SIR2** in yeast, or its ortholog in mammalian species **SIRT1** are genes which encode an NAD-dependent deacetylase and these may mediate many of the effects of caloric restriction (42, 43). Resveratrol (3,5,4-trihydroxystilbene), a modulator of **SIR2** extends the lifespan of diverse species including yeast, *c elegans* and *drosophila*. In mice on a high caloric diet, resveratrol supplementation was shown to oppose the effects of the increased caloric intake. When compared to controls, treated mice had increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-1) levels, increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1alpha) activity, increased mitochondrial number and improved motor function (44). Early clinical trials are underway with the ultimate goal of determining whether resveratrol, or related molecules, will favorably modulate metabolic pathways in a manner analogous to caloric restriction and thereby reduce the development of age-associated diseases, including cancer.
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Challenges and Future Directions

Translational research at the aging/cancer interface lags behind the advances made both at the bench in understanding aging processes and in the clinic where increased attention has been drawn to the management of older patients with cancer. To bridge the gap between the bench and bedside, investigators might consider the following unresolved questions:

1. What features of the host account for the observed biological differences in cancer incidence, growth, and spread in older patients compared to young?
2. How does age, comorbid diseases or associated organ function impairment influence cancer growth and spread?
3. What components of comprehensive geriatric assessment offer the most predictive value with regard to response rate or risk of toxicity? Are there age-sensitive biochemical markers that might add predictive value in this regard?
4. Do less intense (dose-reduced) treatment regimens provide any therapeutic value for typical older patients with comorbidity and functional impairment?
5. Given the explosion in targeted therapies, is there any reason to believe that an older host will be less or more likely to respond, and are older patients, particularly those who are frail or are burdened with comorbidities able to receive these agents at full dose?

There have been remarkable advances in both cancer/aging biology and geriatric oncology over the past decade. Yet, translational studies have been slow to get off the mark. With the breakthroughs in understanding of both aging and cancer pathways, the time is approaching to develop interventional strategies aimed at promoting normal healthy aging. Such strategies may pay off in terms of improved cancer management or, even better, cancer prevention.

References


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