Preface: Aging and Oncogenesis

Given the dramatic increase in lifespan and the estimated rise in the number of persons surviving into old age, it is extremely timely to address the relationship between aging and cancer.[1] Indeed, older age is the greatest risk factor for developing cancer (even greater than smoking). Thus, advanced age might actually be considered a potent carcinogen. In humans, there is an exponential rise in cancer incidence during the 6th, 7th, and 8th decades of life, although this value decreases after age 90. Furthermore, more than half of new cancers occur in individuals older than age 65. Interestingly, HIV/AIDS, which shows many aspects of accelerated aging, is also associated with increased incidence of multiple types of cancer, appearing at younger ages, and with more aggressive or advanced stage disease.[2]

Several theories have been proposed for the increased cancer incidence with age, and each is, arguably, partially responsible. For example, the cumulative mutational load over a lifetime allows sufficient opportunity for the necessary mutations and/or epigenetic changes to develop. These mutations may be the result of prolonged exposure to various carcinogenic events, or to long-term infection with several persistent viruses that are associated with certain forms of cancer (e.g., HPV, EBV). The cellular process of senescence is also intimately connected to cancer. Indeed, senescence and cancer may be considered opposite sides of the same coin. Cellular senescence describes the innately programmed limitation in cell division that is characteristic of all human somatic cells, and which functions as a potent anti-carcinogenic mechanism. The process, which is controlled by the p53 and Rb tumor suppressor proteins, can be bypassed by a series of mutational events that allow a cell to continue dividing and to develop features necessary for oncogenesis, including critically short telomeres, which lead to genomic instability, the cornerstone of carcinogenesis.

The phenomenon of cellular senescence is, therefore, an example of *antagonistic pleiotropy,* in that it favors early life survival by curtailing cancer during the reproductive period, but then promotes many of the pathologies of aging, including cancer, due to the progressive accumulation of dysfunctional senescent cells.[3] Other physiological changes with age have also been implicated in making older age a strong risk factor for cancer. One example is the decline in DNA repair capacity, and another is the failure of appropriate apoptosis. The importance of the latter is illustrated by the enhanced apoptosis in mice that are calorically restricted, which is a strategy that increases maximum lifespan and delays cancer incidence.[4] Moreover, genetically engineered mice in which senescent cells are deleted by induced apoptosis show reduced incidence of multiple age-related pathologies.[5]

This special issue addresses several contributing factors involved in the increased cancer incidence during older age, as well as aging-specific considerations that relate to cancer immunotherapy and cancer vaccines. The plethora of changes that occur within the immune system during aging are addressed in the article by Fulop, Larbi, Witkowski, Kolb, Hirokawa, and Pawelec ("Immunosenescence and Cancer"). These authors summarize the role of age-associated changes within the immune system in the natural evolution of cancer. At the beginning of cancer development, tumor-associated antigens may induce immunity, so that the process of immunosurveillance may actually eliminate the tumor, particularly during youth when the immune response is still normal. However, over time, this interaction can result in the emergence of tumor variants that may evade the ongoing immune response. For various reasons, due either to the age-related alterations in the immune response or to the inherent tumor molecular characteristics, tumors can begin to actually orchestrate the immune response by producing various inhibitory factors that suppress immunity. Together with various age-related changes whereby certain suppressor cells become dominant, the host immune system is further compromised in its ability to eliminate the tumor.

In addition to the aging immune system, the metabolic syndrome constitutes a second important risk factor linking older age and cancer, as discussed in the article by Extermann ("Metabolic Syndrome, Cancer, and Aging"). Indeed, the metabolic syndrome

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is associated with an increased risk of cancer across multiple tumor types and worsens the prognosis of those cancers, increasing both their relapse and death rates. In this review, Extermann also discusses several important possible underlying mechanisms for this association, which can affect the actual tumor, the host, or both. For example, insulin has been shown to exert a direct mitogenic effect on tumors, and excess insulin can also stimulate angiogenesis. Since most tumors are glucose-avid (as demonstrated by the diagnostic effectiveness of PET scanning), sustained hyperglycemia may favor tumor growth as well. Advanced glycation endproducts (AGEs), which have been hypothesized to affect many age-related pathologies, are also implicated, along with their receptors (RAGEs), in various cancer signaling pathways. The article poses the intriguing possibility of targeting dysregulated metabolic syndrome pathways as an approach to simultaneously improve cancer prognosis. The author concludes by noting that, because many older cancer patients have multiple comorbidities, studies on one disease can help uncover unique, unsuspected shared mechanisms that can provide novel insights on both mechanisms and therapeutic approaches.

Sirtuins, named for the yeast "silent mating-type information regulation" gene, are a family of proteins that have been shown to regulate important biological pathways in bacteria, archaea, and eukaryotes. Sirtuins have been implicated in a wide range of cellular processes, including aging, but also in inflammation, stress resistance, mitochondrial biogenesis, and alertness during low calorie situation. Roth, Wang, and Chen ("Sirtuins in Hematological Aging and Malignancy") discuss the role of several of the sirtuins in aging of hematopoietic stem cells as well as in multiple hematological diseases, such as CML, AML, and lymphoma. They also review the involvement of several sirtuins in the regulation of p53 and NF-κB and mTOR signalling pathways. The article concludes with possible future "rejuvenation" prospects of blood stem cells from the bone marrow by manipulation of sirtuins *in vitro* followed by transplantation back into the patient.

As noted above, cellular senescence is viewed as a tumor suppressor mechanism during youth, but over a lifetime, as senescent cells accumulate, they may actually contribute to cancer. The article by Alspach, Fu, and Stewart ("Senescence and the Pro-tumorogenic Stroma") expands on this notion, discussing the role of senescent fibroblasts in creating a microenvironment that enhances tumor growth. The authors summarize the contributions of senescent cells during multiple stages of tumorigenesis. In particular, they discuss the senescence-associated secretory phenotype (SASP) that is one of the signature features of senescent fibroblasts. SASP, which is subject to complex regulation, is enriched in proteins involved in inflammation, alteration of the extracellular matrix, and cell division. Moreover, senescent cells also secrete certain chemokines that may actually select for cancer stem cells. A second population of so-called "cancer-associated fibroblasts" is also described; these cells promote every step of the transformation process by stimulating tumor growth, angiogenesis, invasion, and metastasis.

The article by Balasubramanian and Longo ("Aging, Nutrient Signaling, Hematopoietic Senescence, and Cancer") provides additional factors that contribute to the age-associated cancer connection. They review recent studies suggesting that oncogenic pathways, such as the insulin-like growth factor-1 (IGF-I), Ras, and Akt/PKB, can contribute to both aging and cancer, not only by favoring cell growth and preventing apoptosis, but also by promoting DNA damage and genomic instability. They suggest that strategies which delay aging itself may protect against cancer and other age-related diseases. The authors summarize recent studies showing that fasting or short-term starvation (STS) reduces circulating IGF-I levels by 70% in mice, and protects normal, but not cancer, cells from toxic chemotherapy drugs.

The theme of cancer therapy is expanded further in the article by Tomihara, Curiel, and Zhang ("Optimization of Immunotherapy in Elderly Cancer Patients"). Given the critical role of host immunity in preventing and combating cancer, these authors discuss the theoretical basis for developing immune-based cancer therapies for the elderly cancer patient. They review the key roles of most immune components and how the function of each cell type can be exploited in cancer immunotherapy. This article

also includes detailed information on the role of co-stimulatory molecules and Toll-like receptors in enhancing the anti-tumor immune response. Finally, the authors provide information on the impact of immunosuppressive cells on anti-tumor immunity in the elderly.

The final article, by Gravekamp and Chandra ("Aging and Cancer Vaccines"), addresses the challenges and complexities of developing cancer vaccines that are suitable for older individuals. Given the documented decreased responsiveness to influenza vaccination in this age group, it is clear that for successful cancer vaccination, the specific defects associated with immunosenescence must be taken into account. This article reviews some of the studies in mice using a metastatic breast cancer model, highlighting a novel approach in which *Listeria*-infected cells selectively migrate to the tumor microenvironment, and actually infect and subsequently kill the tumor cells. The authors also discuss how *Listeria* and other nonpathogenic bacteria can deliver tumor-killing agents selectively to the tumor cells. Finally, they underscore the need to incorporate both the innate and adaptive immune system in the development and testing of cancer vaccines.

The medical reality of increasing cancer incidence with older age is rapidly becoming a critical health issue, not to mention the economic burden due to the so-called Longevity Revolution. In almost every country, the proportion of people over age 60 is growing faster than any other age group. Whereas the overall aging of the population can be viewed as a public health success story, one of the challenges is to increase human health span in parallel with the increased life expectancy. I thank the authors who contributed the excellent articles presented in the special issue of this journal, devoted to the critical topic of aging and cancer. I am grateful to the Editor-in-Chief, Benjamin Bonavida, for his help and guidance in preparing this volume.

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