
Correspondence

Aging, Immunity, and Cancer

To the Editor: Understanding and clarifying relationships among aging, immune senescence, and cancer are important for researchers interested in cancer prevention and control, especially as our population ages. The recent review by Burns and Leventhal¹ is a step in the right direction. However, there seem to be a number of conceptual issues related to immune surveillance and immunosenescence that need clarification, particularly with regard to the emergence and development of cancer. Further, behavioral variables that may confound the correlations between aging and cancer are not considered as alternative explanations. There are other alternative perspectives on the role of immune surveillance against neoplasia as well as other possible mechanisms underlying the associations between aging and cancer.

As correctly asserted by Burns and Leventhal, tumors arise from the clonal expansion of cells that have accumulated numerous somatic mutations in important regulatory genes. Subsequent to these mutations, the cells acquire behaviors that render them independent of stimulatory growth factors and insensitive to growth inhibitory signals.² Additionally, they may acquire other characteristics such as the capacity to evade apoptosis, to initiate and sustain the process of angiogenesis, to replicate without limit, and to invade tissue and metastasis.² Importantly, mutations may occur in any order, and mutated cells may or may not progress to a metastatic phenotype. All of these processes are internal to the cell nucleus, and it is currently unclear how or when components of the immune system might recognize these processes.

Although there is evidence that is consistent with the immune surveillance hypothesis, primarily in animal models, there are no unambiguous data suggesting that immune surveillance is

a meaningful mechanism in the protection of humans from spontaneous neoplastic disease. The theory of immune surveillance assumes tumors express specific tumor-associated antigens (TAAs), that the TAAs are recognizable by components of the immune system, and that the TAAs stimulate an immune response. Expression of TAAs is assumed to reflect processes of somatic mutation and therefore identify self-cells as altered. However, it is not clear that all tumors reliably express TAAs or at what point in the transformation process these antigens emerge. Additionally, tumors show significant heterogeneity with regard to expressed antigens, and each tumor will express unique antigens that are different from other identically induced tumors.³ Tumor cells do not necessarily illicit an immune response.⁴ Further, even if transformed cells express TAAs, the mechanisms by which the immune system (eg, NK cells) might recognize them are currently unknown. Finally, tumors may escape a fully functioning immune system through several mechanisms such as downregulation of MHC-1 expression, suppression of immune response by tumor-secreted products, and induction of suppressor T cells, among others.³ Based on these facts, it is premature to postulate that age-related immunosenescence leads to cancer.

The underlying model assumed by Burns and Leventhal is mediational; that is, the effects of aging on cancer incidence or progression are mediated through immunosenescence. This suggests that tumor survival and metastases result in older people from age-related failures of the immune system to recognize or adequately control tumor cells. For mediational models to be valid, there are several relationships that must hold true. First, aging should be reliably associated with declines in measures of immune function. It seems clear from the reviewed research that there is likely a decline in both enumerative and functional measures of immunity in older people. However,

many host-related factors other than aging (eg, important health-related behaviors such as smoking, excessive alcohol consumption, lack of physical activity and poor fitness levels, sleep disturbance, and diet) can influence measures of immunity in older individuals.⁵ Many medications commonly taken by older people may also interact with components of the immune system, and psychological factors such as stress, anxiety, and depression have been shown to reliably alter immune measures.⁶ While these relationships hold true for people of all ages, older people may be subject to differential exposure. Unless these factors are controlled, the relationship between aging and immune senescence in humans will not be clear.

There must also be clear associations between measures of immunity and cancer. Examining evidence from individuals with systemic immunodeficiency syndromes or who are pharmacologically immunosuppressed may prove illustrative. Systemic immunosuppression is not reliably related to tumor development and malignancy, especially the more common cancers of the breast, colon, and lung.⁷ While people with advanced HIV disease suffer from the emergence of malignancies, they rarely develop common cancers of the lung, breast, prostate, or colon. Rather, they develop Kaposi's sarcoma, a defining feature of clinical AIDS rarely diagnosed in non-AIDS populations. Cancer incidence in transplant patients who are pharmacologically immunosuppressed ranges from 4% to 18% with an average of only 6%.⁸ Further, these malignancies are predominantly leukemias and lymphomas, that is, cancers of the immune system itself. These likely result from ingestion of immunosuppressive agents that are themselves mutagenic. Finally, a common feature of these cancers is their association with specific viral infections such as human herpes virus.⁹ While it is likely that the immune system recognizes and combats tumors of viral origin, it is probable

that this results from recognition of virally infected cells rather than tumor cells per se. These data argue against a significant role for the immune system in the emergence of the more common cancers.

Since somatic mutation is the de facto final common pathway to tumor initiation and progression, it is possible that a sharper focus on other relevant biological processes involved in carcinogenesis, such as alterations in DNA damage and repair, may explain more of the variance in accumulation of somatic mutation and disease outcomes.¹⁰ For example, data suggest that there is an age-related decline in repair of damaged DNA and that this decline is related to an increase in the accumulation of somatic mutation.^{11,12} Additionally, the declining fidelity of DNA repair with age may underlie both cancer and immunosenescence.¹³ This seems a promising area of research that will potentially explain the mechanisms whereby aging is related to cancer.

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In Reply: Michael Forlenza's letter raises two issues: one targeting our proposal that immunosenescence is a possible pathway for the relationship of age and cancer, and the second that immune dysfunction is related to cancer. We will respond first to the two questions he raised regarding the first of these issues, ie, that immunosenescence is a pathway for cancer. First, he indicates that aging must be reliably associated with a decline in immune function for this hypothesis to hold. Second, assuming that immune function declines with age, as Mr Forlenza appears to accept, we cannot assume it is responsible for the age-related increase in cancers unless we can rule out alternative causes of immune decline that are associated with aging. As examples, he includes health behaviors (eg, smoking, excessive alcohol consumption, and lack of physical activity), psychological factors (eg, as stress, anxiety, and depression), and medication for treating other non-cancer, age-related conditions. All of these factors can reduce immune surveillance and may be responsible for

the increase in cancer with advancing age. At least two points can be made about these suggestions. While several of these factors (eg, smoking) are implicated in cancer causation, reviews of the literature suggest that many of these risky behaviors decline with advancing age (eg, smoking), and many health-improving behaviors increase with age; exercise is a critical exception to the latter. It is also widely reported that psychological distress declines with advancing age. For example, the percentage of major depressive disorders declines to less than 1% of the older population in community-based studies.¹ Thus, though we agree with Mr Forlenza on the importance of statistical controls for such factors, we suggest that the evidence is not overly supportive for these suggested alternatives.

The second — and more important — issue is whether these health risk and health promotion behaviors should be seen as “alternatives” to the hypothesis that immunosenescence is linked to aging and therefore to declines in surveillance for cancer, or whether these factors should be considered as links between age and immunosenescence. As we have suggested elsewhere, there are good reasons not to treat age as a “causal” variable; it is the variables and processes linked to age that have causal status.² Time (ie, age) is a marker of the *opportunity* for both harmful and helpful processes to influence health, cognition, affective status, physical performance, economic status, and social relationships. The hypothesis that age is a marker for immunosenescence and therefore declines in surveillance for cancer opens the door for examining the processes affecting immune decline on the one hand and those linking this decline to cancer on the other.

The second issue concerns the link of immune competence to cancer. In

the first of his three points, he states "...there is no unambiguous data suggesting that immune surveillance is a meaningful mechanism in the protection of humans from spontaneous neoplastic disease." He cites several findings supporting this ambiguity, such as the difficulty of immune recognition of heterogeneous antigens expressed by cancer cells, that some tumor cells do not express antigens and therefore fail to elicit an immune response, and indicates that the mechanisms by which NK cells recognize tumor associated antigens is unknown. His second similar point concerns the rarity of common cancers of the lung, breast, prostate, etc, in pharmacologically immunosuppressed persons and in persons immunosuppressed from advanced AIDS. The tumors seen in these cases are of the immune system itself and tumors of viral origin. Finally, he reviews what is likely the complex life history of a cancer from somatic mutations through the production of growth factors, the evasion of apoptosis and angiogenesis, to metastasis, and he suggests there is little evidence that the immune system can recognize or modulate the various regulatory failures that take place in this process. Mr Forlenza's point is that investigators should look elsewhere to account for the correlation of age with cancer.

Specifically, age-related alterations in DNA damage and repair may account for both cancer and declines in immune competence.

Although Mr Forlenza's hypothesis is indeed interesting, it does not preclude the role of immune surveillance in the control of some cancers. It appears that the vast majority of cancer-related mutations are environmentally induced, and some (but not all) by agents that the immune system is designed to detect. Perhaps additional scrutiny should be given to detectable antecedents in tumors other than Kaposi's sarcoma. Given that animal studies find that immune enhancement slows or destroys tumors while suppression encourages proliferation and death, there may be good reason to examine which types of cancer are associated with immunosenescence and which are not and to ask whether the latter type are cancers that evade immune detection throughout the life span while the former do not.

In summary, Mr Forlenza raises interesting questions that may clarify the nature of the relationship between age-related immune decline and cancers. Much work will be needed to determine whether these pathways will provide productive lines for

research. Though we find this second set of issues interesting, we feel it necessary to raise a cautionary note. Specifically, it is tempting to argue that the accrual of DNA damage and incomplete repair are the answers to the aging-cancer issue and occur independently of immune function. This is a reductionist view that downplays the role of the vast number of exogenous viral and chemical events that do indeed lead to DNA damage but also trigger immune mechanisms of defense. This includes the factors identified in the first issue. Some exogenous agents causing DNA damage may leave markers for immune attack, while others may not. If so, it will be the age-related increases in those selected tumors that will be causally linked to immunosenescence.

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