Shortcomings of the immunological model of carcinogenesis

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With great enthusiasm, I read the PNAS article by Palmer et al. entitled "Thymic involution and rising disease incidence with age" (1). The authors address the somatic mutation model, which introduces the gradual accumulation of mutations as the reason for increased rates of cancer in older ages, and proposes the immunological model, which introduces the decline of the immune system as the primary reason for the strong relationship between age and cancer. Based on their model, Palmer et al. also propose that therapies either reversing T cell exhaustion or restoring T cell production can be considered as promising treatments. Despite its strengths, the paper has at least two major shortcomings.

The first shortcoming of the Palmer et al. (1) paper is due to ignoring this key point that while the incidence of most (not all) cancers increases with age, cancer rates normally decline or plateau among the very elderly (2). It is worth noting that cancer is uncommon as a cause of disease or death after the age of 90 y (3). Adults with the longest longevity are less likely to develop cancer (3). Some studies show that familial factors can be linked to both low cancer incidence and longevity. A study that was aimed at investigating the hypothesis of whether longevity potential comes with the cost of increased cancer risk (longevity in one twin is associated with increased cancer risk in the cotwin), showed that longevity in one twin was associated with lower cancer incidence in the cotwin (4). Moreover, some cancers are more common in children (e.g., leukemia) (5). In addition, there are cancers that peak at young ages (although it can be observed at any age, about 50% of testicular cancers occur in men between the ages of 20 and 34 y) (6).

Another shortcoming of the Palmer et al. (1) paper comes from ignoring the preventability of many cancers. It is worth noting that a substantial body of scientific research supports the preventability of many cancers. For example, it has been estimated that more than 90% of lung cancer cases can be prevented in the United States by stopping smoking (7). About 19% of all cancers (confidence interval 12–29%) are estimated to be associated with the environment (8). Despite this, people have lived for many generations in areas with extreme environment (e.g., very high background radiation levels) without any recorded adverse health effects (9, 10). It is evident that an immunological model and T cell exhaustion/restoring cannot easily explain these findings. In summary, ignoring some key factors in the study conducted by Palmer et al. (1) has possibly affected the validity of their proposed model.

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