LETTER

Are most cancer cases a consequence of an immune deficiency caused by thymic involution?

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In a recent article in PNAS, Palmer et al. (1) challenge the accepted idea that cancer is the result of the multistep accumulation of DNA changes. According to the established paradigm, cancer incidence increases dramatically with age because the cell that gives rise to cancer needs time to acquire the multiple independent changes required for carcinogenesis. If cancer were caused by one single event, this event could occur at any time, and cancer incidence would be rather similar at different ages (2, 3).

Palmer et al. (1) propose that cancer is caused by a single event, and that the dramatic increase in cancer incidence with age is caused by an exponential decline in T cell production by the thymus. This proposal is based on a strong link between thymic involution and rising cancer incidence over the 18- to 70-y age range, and on the potential of T cells to eliminate cancer cells. Malignant cells would arise at any age, but these cells would be controlled as long as the thymus is functional. The thymus would be a major barrier against cancer.

Palmer et al.'s (1) proposal can be tested by comparing the incidence of spontaneous cancers in mice with and without a thymus. Although the absence of the thymus can increase or decrease the occurrence of specific cancer types in response to particular carcinogens, the incidence of spontaneous tumors in athymic mice is similar to that in thymus-bearing animals (4, 5).

In humans, thymus dysfunction does not seem to impose a high risk of cancer either. Approximately 75% of people with a 22q11.2 deletion syndrome have an immune deficiency due to thymic hypoplasia and impaired T cell production; some individuals with this condition are even athymic (complete DiGeorge syndrome). People with 22q11.2 deletion syndrome have an increased susceptibility to viral, fungal, and bacterial infections, but they are not characterized by having a high risk of malignancies (6, 7). According to the immunological model proposed by Palmer et al. (1), cancer incidence rates in young people with 22q11.2 deletion syndrome would be rather similar to those in aged people without the syndrome. This is not the case.

If the thymus were a critical barrier against cancer, the incidence of all cancer types would increase exponentially with age, because thymus functionality declines exponentially with age. However, cancer incidence decelerates or even decreases late in life for most cancer types. It also decreases during the first decade of life. In addition, the incidence of some cancer types does not increase exponentially with age, even in the middle decades of life; for example, testicular cancer incidence peaks during the third decade of life and then progressively declines (3, 8) (see also www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk). These data do not support the model by Palmer et al. (1).

The role of the immune system in the prevention of infection-associated cancers is widely recognized (9), as is the clinical potential of T cells to eliminate cancer cells. However, the idea that most cancer cases are a consequence of an immune deficiency caused by thymic involution is difficult to accept.

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