Observing the invisible: successful tumor immunity in humans

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A recent review¹ in this journal cogently discussed the history and some of the current evidence that the immune system has a normal role in suppressing cancer. In part, this review was meant to counter skepticism of this concept held by many interested in basic tumor biology. However, the review has apparently not convinced all of the tumor biology community². Some of the uncertainty centers on the nature of human tumor antigens and their relationship to normal cellular proteins, and some results from the difficulty inherent in trying to observe human tumor immunity as a means of confirming observations made in animal models.

The core of the history reviewed is the 'tumor surveillance' hypothesis of Thomas and Burnet³. This hypothesis culminated in the prediction by Burnet that "if there were tumor immunity, it would be invisible"³. The implications of this quote have not been fully appreciated, leading to continued confusion. Correctly, scientists have realized that if tumor immunity exists, then in the most straightforward instance its 'invisibility' means that it could not be studied. In this view, the tumor surveillance hypothesis was dangerously close to being a pseudo-scientific hypothesis, in that it originally appeared to be nontestable.

Perhaps for these reasons, scientists have tried to address the hypothesis largely with animal models and attempts to correlate human tumor incidence with induced immunodeficiency states. Schreiber and colleagues¹ summarized early, overreaching conclusions made by others from studies in nude mice erroneously assumed to be immunoincompetent, and recent, elegant studies revisiting this problem in truly immunoincompetent animals, including RAG-2^{-/-} and STAT1^{-/-} mice. The latter experiments have convincingly shown that immunodeficient mice develop spontaneous and chemically induced tumors of nonviral origin, and have thus rekindled broad interest in the concept of cancer immunosurveillance. However, skepticism remains regarding their relevance to human tumor immunity².

A solution to the dilemma of how to study successful human tumor immunity is offered by a rare set of human diseases, the paraneoplastic neurologic degenerations (PNDs)^{4,5}. In PNDs, effective tumor immunity is linked to a set of neurologic symptoms that rapidly bring patients to clinical attention at a time when the tumor typically remains invisible.

PND patients develop degeneration in discrete regions of the nervous system. Clinical examination reveals systemic malignancies, most commonly breast or ovarian adenocarcinoma or small cell lung cancer. These patients are unaware of their cancers, and they harbor malignant tumors that show unusually limited spread and robust responses to treatment. In some instances only microscopic foci of tumor can be found, often with inflammatory infiltrates, and in rare instances spontaneous tumor regression has been documented^{6,7}.

Tumor suppression in PNDs is associated with an autoimmune response to defined

neuron-specific antigens. PND patients harbor high titer antibodies in their blood and spinal fluid directed to these neuronal antigens⁸. Western blot analysis, immunohistochemistry and cloning of PND antigens have revealed that tumors from PND patients ectopically express neuronal proteins⁹.

Because the neurologic symptoms in PNDs may lead to earlier tumor diagnosis, the smaller size of the tumor cannot be used as conclusive evidence of tumor immunity. However, the peripheral blood of all PND patients studied harbors killer T cells directed against these neuronal antigens, at the same time that these patients have clinical and pathologic evidence of suppression of tumor growth^{9,10}. Moreover, some cancer patients mount a PND immune response but do not develop neurologic disease. These patients have smaller tumors and longer survival than those without such immune responses^{11,12}.

These studies have offered the first direct evidence of naturally occurring, successful tumor immunity in humans, evident only because it is linked to a second phenomenon—autoimmune neurologic disease. Thus, the study of PND has provided a solution to the paradox put forth by Thomas and Burnet, and, together with evidence obtained using animal models, now makes an irrefutable case for the role of the immune system in controlling the development of cancer.

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