To dream the maybe possible dream: A breast cancer vaccine

The *Journal* generally does not publish articles on topics not yet clinically relevant. But since the topic of immunization is so often in the news, and since immunotherapeutic strategies against cancer continue to be tested in clinical trials, we decided to include in this issue an edited transcript of a Medicine Grand Rounds presentation at Cleveland Clinic by Dr. Vincent Tuohy (page 605) on a novel strategy to develop a vaccine against a particularly virulent form of breast cancer.

The immune system's response to cancer is complex. Melanoma and renal cell carcinoma seem particularly susceptible to suppression by the native or augmented immune response. But most cancers seem to grow—and many metastasize—seemingly unaffected by our immune system, and sometimes even in the presence of detectable antitumor cell-directed lymphocytes and antibodies. Many attempts at devising human antitumor vaccines and immunotherapies have failed. On the other hand, we have seen the successful development of effective monoclonal antibody therapies (eg, rituximab for B cell lymphoma), immunomodulatory treatments for patients with advanced disease, and vaccines against viruses that cause cancer, ie, human papillomavirus and hepatitis B.

To fully appreciate the nuances of Dr. Tuohy's proposed strategy, which has not yet been tested in clinical trials, and the complexities of tumor immunology, a very brief primer on the challenges is in order.

CHALLENGES TO DEVELOPING CANCER IMMUNOTHERAPY

Solid tumors can be triggered by multiple mechanisms, alone or in combination, including viruses, spontaneous mutations, overexpression of tumor promoters, and underexpression of tumor suppressors. Once growing, the solid tumor establishes its own rogue growth community, complete with a new infrastructure to supply nutrition and oxygen, potential means for expansion locally and distally, and a system to defend itself from the body's immune system. The last of these poses specific challenges to successful spontaneous immune surveillance and to immunotherapy designed to kill cancer cells.

Microbial pathogens trigger both a nonspecific (innate) and a specific immune response in the human body. Initially, the immune system is nonspecifically "revved up," triggered by shared "danger signals" associated with the perceived pathogen and its specific antigens. Then, specialized cells including dendritic cells locally and in proximate lymph nodes are primed to present the de novo antigens in a way that generates a specific and maturing immune response capable of getting rid of the pathogen. Tumors are also pathogenic and in some ways "foreign." However, they are also similar to normal tissue and interact quite differently with the immune response in ways that enhance their likelihood of growth and survival. Tumor cells often do not send a danger signal to the immune system akin to what is generated by a staphylococcal or

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mycobacterial invader.

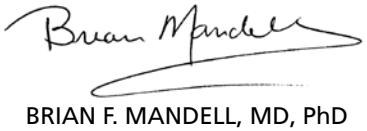
Tumor cells express specific antigens on their surface, such as viral proteins, cancer-associated mutated proteins, and overexpressed differentiated or undifferentiated antigens, including in some cases what Dr. Tuohy discusses as "retired proteins." But some of these antigens may also be expressed in normal tissues, especially in an environment of resolving inflammation. Some signal the immune system to down-regulate what could otherwise be a vigorous self-destructive response every time there was inflammation.

The dendritic cell activation of the potential antitumor T-cell response and the antitumor T-cell response itself seem to be systematically blunted by many tumors. Reversal of this blunting represents one strategy currently used with very modest clinical success in treating advanced melanoma. Some newly generated tumor-antigen–recognizing T cells may in fact exert suppressor (or regulator) and not cytotoxic activity. Some tumors exhibit systemic immunosuppressive activity; this can be manifested not only by unchecked tumor growth, but also by an increased susceptibility to certain infections.

PITFALLS OF MESSING WITH THE IMMUNE SYSTEM

Messing with the immune system is not without pitfalls. Not all toxicities will be predicted by preclinical animal studies, and human immunity is not a mirror image of rodents' or even other primates' immune systems. Augmentation of an antitumor response, in part from the interplay of the complexities noted above, may lead to destruction of normal tissue elsewhere, or even to disruption of tolerance with the expression of autoimmunity. The toxicities will be different than the somewhat predictable toxicities from traditional antiproliferative chemotherapies—witness the striking systemic toxicity from interleukin 2-based therapies.

Whether Dr. Tuohy's approach to developing a tumor vaccine will ultimately reach our formularies remains to be seen. The work is in an extremely preliminary phase. But the concept of immunotherapy for cancer remains an active area of research that is worth keeping an eye on.



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