Immunotherapy in Veterinary Oncology

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KEYWORDS

• Veterinary oncology • Tumor immunotherapy • Tumor immunology • DNA vaccine • Xenogeneic DNA vaccine • Monoclonal antibody

KEY POINTS

- The immune system is generally divided into 2 primary components: the innate immune response and the highly specific, but more slowly developing, adaptive or acquired immune response.
- Immune responses can be further separated by whether they are induced by exposure to a foreign antigen (an active response) or are transferred through serum or lymphocytes from an immunized individual (a passive response).
- The ideal cancer immunotherapy agent should be able to discriminate between cancer and normal cells (ie, specificity), be potent enough to kill small or large numbers of tumor cells (ie, sensitivity), and, lastly, be able to prevent recurrence of the tumor (ie, durability).
- Tumor immunology and immunotherapy is one of the most exciting and rapidly expanding fields.

The term, *immunity*, is derived from the Latin word, *immunitas*, which refers to the legal protection afforded to Roman senators holding office. Although the immune system is normally thought of as providing protection against infectious disease (and much of this issue of *Veterinary Clinics of North America* is devoted to such), the immune system's ability to recognize and eliminate cancer is the fundamental rationale for the immunotherapy of cancer. Multiple lines of evidence support a role for the immune system in managing cancer, including (1) spontaneous remissions in cancer patients without treatment, (2) the presence of tumor-specific cytotoxic T cells within tumor or draining lymph nodes, (3) the presence of monocytic, lymphocytic, and plasmacytic cellular infiltrates in tumors, (4) the increased incidence of some types of cancer in immunosuppressed patients, and (5) documentation of cancer remissions with the use of immunomodulators.[1,2] With the tools of molecular biology and a greater understanding of mechanisms to harness the immune system, effective tumor

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immunotherapy is becoming a reality. This new class of therapeutics offers a more targeted and, therefore, precise approach to the treatment of cancer. It is likely that immunotherapy will have a place alongside the classic cancer treatment triad components of surgery, radiation therapy, and chemotherapy within the next 5 to 10 years.

TUMOR IMMUNOLOGY

Cellular Components

The immune system is generally divided into 2 primary components: the innate immune response and the highly specific, but more slowly developing, adaptive or acquired immune response. Innate immunity is rapidly acting but typically not very specific and includes physicochemical barriers (eg, skin and mucosa); blood proteins, such as complement, phagocytic cells (macrophages, neutrophils, dendritic cells [DCs], and natural killer [NK] cells), and cytokines, which coordinate and regulate the cells involved in innate immunity. Adaptive immunity is thought of as the acquired arm of immunity, which allows for exquisite specificity, an ability to remember the previous existence of the pathogen (ie, memory) and differentiate self from nonself, and importantly the ability to respond more vigorously on repeat exposure to the pathogen. Adaptive immunity consists of T and B lymphocytes. The T cells are further divided into CD8 (cluster of differentiation) and major histocompatibility complex (MHC) class I cytotoxic helper T cells (CD4 and MHC class II), NK cells, and regulatory T cells. B lymphocytes produce antibodies (humoral system), which may activate complement, enhance phagocytosis of opsonized target cells, and induce antibody-dependent cellular cytotoxicity. B-cell responses to tumors are thought by many investigators to be less important than the development of T cell–mediated immunity, but there is little evidence to fully support this notion.[3] The innate and adaptive arms of immunity are not mutually exclusive; they are linked by (1) the innate response's ability to stimulate and influence the nature of the adaptive response and (2) the sharing of effector mechanisms between innate and adaptive immune responses.

Immune responses can be further separated by whether they are induced by exposure to a foreign antigen (an active response) or are transferred through serum or lymphocytes from an immunized individual (a passive response). Although both approaches have the ability to be extremely specific for an antigen of interest, one important difference is the inability of passive approaches to confer memory. The principal components of the active/adaptive immune system are lymphocytes, antigen-presenting cells, and effector cells. Furthermore, responses can be subdivided by whether they are specific for a certain antigen or a nonspecific response whereby immunity is attempted to be conferred by up-regulating the immune system without a specific target. These definitions are helpful because they allow methodologies to be more completely characterized, such as active-specific, passive-nonspecific, and so forth.

Immune Surveillance

The idea that the immune system may actively prevent the development of neoplasia is termed, *cancer immunosurveillance*. Sound scientific evidence supports some aspects of this hypothesis,[4–7] including (1) interferon (IFN)-γ protecting mice against the growth of tumors, (2) mice lacking IFN-γ receptor are more sensitive to chemically induced sarcomas than normal mice and more likely to spontaneously develop tumors, (3) mice lacking major components of the adaptive immune response (T and B cells) having a high rate of spontaneous tumors, and (4) mice lacking IFN-γ and B/T cells developing tumors, especially at a young age.