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Review

Cancer vaccines: Harnessing the potential of anti-tumor immunity

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ABSTRACT

Although the presence of cancer suggests failure of the immune system to protect against development of tumors, the possibility that immunity can be redirected and focused to generate an anti-tumor response offers great translational possibility. The key to this is identifying antigens likely to be present in any given tumor and functionally critical to tumor survival and growth. Such tumor-associated antigens (TAAs) are varied and optimally should be absent from normal tissue. Of particular interest are TAAs associated with the tumor stroma, as immunity directed against the stroma may restrict the ability of the tumor to grow and metastasize. Important to directing the immune system toward an effect anti-tumor response is the understanding of how TAAs are processed and how the tumor is able to evade immune elimination. The process of immunoediting happens in response to the selective pressure that the immune system places upon tumor cell populations and allows for emergence of tumor cells capable of escaping immune destruction.

Efforts to harness the immune system for clinical application has been aided by vaccines based on purified recombinant protein or nucleic acid TAAs. For example, a vaccine for canine melanoma has been developed and approved based on immunization with DNA components of tyrosinase, a glycoprotein essential to melanin synthesis. The performance of cancer vaccines has been aided in some cases when supplemented with immunostimulatory molecules such as interleukin 2 or a novel extracellular matrix vaccine adjuvant. Vaccines with the broadest menu of antigenic targets may be those most likely to succeed against cancer. For this reason, tissue vaccines produced from harvested tumor material may offer significant benefit. With several cancer vaccines on the veterinary and human markets, efforts to understand basic tumor immunology are soon to yield great dividends.

Introduction

The idea that the immune system plays a critical role in protecting the host from cancer originated with Paul Ehrlich early in the 20th century (Ehrlich, 1909) and anti-tumor immune responses remain a subject of considerable interest as the idea of using immunotherapy for the treatment of cancer has gained greater acceptance. Although complex, several key components of the immune response to tumors have been defined and studied, with the cytotoxic T lymphocyte response being identified as a critical link among these components. Interestingly, while cells associated with the immune system can inhibit tumor growth and progression, immune responses sometimes promote tumor cell growth and survival through induction of inflammation (Dougan and Dranoff, 2009; Chow et al., 2012).

Tumor antigens and immune responses

Most tumor cells express antigens that are not found on normal cells. These tumor-associated antigens (TAAs) come from several sources, including oncogenic viruses, expression of oncogenes or mutated oncosupressors, or expression of mutated genes. As an example, melanoma is characterized by the expression of several TAAs, including gp100, tyrosinase, MAGE-A1, and NY-ESO (Dunn et al., 2007; Pandolfi et al., 2008). Colorectal tumor cells often express carcinoembryonic antigen (CEA), a glycoprotein involved in cell adhesion. Though CEA is normally present during fetal development, it is absent from normal adult tissue; however, CEA expression correlates with progression of colorectal cancer, and has been used as a clinical marker of the disease (Boghossian et al., 2011; Mazurek et al., 2011).

Because tumor tissue is characterized by a variety of antigens not typically found in normal tissue, the immune system may mount a protective response. Innate immunity against the tumor is invoked very quickly, as macrophages which are innately programmed to attack and destroy tumor cells much in the same fashion that they eliminate invading pathogens, are drawn to the

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tumor. Likewise, granulocytes such as polymorphonuclear leukocytes serve not only as effector cells in anti-tumor immunity, but also as a source of cytokines which are involved in the activation and regulation of effector cells of the adaptive immune system (Mantovani et al., 2011).

With time, adaptive anti-tumor immune responses develop. Dendritic cells migrate to the tumor as part of the innate immune response and serve as a link between innate and adaptive immunity. After processing tumor antigens, dendritic cells stimulate specific immune responses by directly interacting with T and B lymphocytes and by releasing cytokines that further stimulate the immune response. As with immune responses to infectious pathogens, both cell-mediated and humoral adaptive immunity may be invoked. Cell-mediated immunity represents the primary means by which tumors are attacked by the immune system.

The initial response of the immune system to a tumor is to recruit lymphocytes in an attempt to clear the tumor. These tumor-infiltrating lymphocytes (TILs) include cytotoxic T lymphocytes (CTLs), helper T cells, and natural killer (NK) cells. A common process by which immune rejection of tumor tissue occurs begins with presentation of TAAs to major histocompatibility complex (MHC) class I molecules present on the surface of TILs. Because CTLs are particularly abundant among TILs, this process may result in a robust anti-tumor immune response when substantial amounts of TAAs are present (Bennett et al., 1992; Hishii et al., 1997). When CTLs are activated, the death activator Fas ligand is expressed on the CTL surface and apoptosis of tumor cells results via the Fas/FasL pathway (Giovannetti et al., 2008; Rippo et al., 2010). Alternatively, CTLs may induce apoptosis using a Fas-independent pathway, specifically the granzyme-mediated pathway which involves the release of serine esterases which induce fragmentation of DNA in target cells (Groscurth and Filgueira, 1998).

Upon recognizing tumor cells as abnormal through interaction with TAAs, CTLs are the first to attack the tumor and represent a primary anti-tumor defense. NK cells are derived from the common lymphocyte progenitor and are part of the innate immune system. Both CTLs and NK cells directly destroy tumor cells after recognizing changes in MHC class I surface molecules of tumor cells. Helper T cells interact MHC class II molecules on the surface of tumor cells and are then stimulated to release cytokines which enhance the activity of CTLs and macrophages. Further, surface molecules such as CD40 are upregulated in the helper T cell, which can then interact with B lymphocytes, thereby stimulating humoral immunity. In total, the cellular response to a tumor consists of multiple players on a team which, if vigorous and coordinated, can eliminate the tumor.

Coordination of the anti-tumor response requires communication between cells of the immune system. Cytokines represent the language that permits the immune cells to organize a successful attack (Dranoff, 2004). For example, interleukin (IL)-6, produced by T lymphocytes and macrophages, enhances the proliferation of both T and B lymphocytes. Granulocyte macrophage colony-stimulating factor (GM-CSF) is produced by T lymphocytes, NK cells, and macrophages and enhances tumor antigen presentation to lymphocytes. Likewise, gamma-interferon (IFN-γ) is produced by NK cells, T lymphocytes, macrophages, and B lymphocytes and enhances both tumor antigen presentation and cell-mediated cytotoxicity. The interplay of cytokines and effector cells is complex, as demonstrated by transforming growth factor (TGF)-β, which has a cytostatic effect on normal cells but a mitogenic effect on tumor cells (Meulmeester and ten Dijke, 2011). An exhaustive description of the role of cytokines in tumor immunity is beyond the scope of this review.

Proteins that are associated with tumorigenesis or malignant growth may stimulate not only cellular immunity, but also humoral immunity. For example, serum antibody to the TAAs, HER2, p53, and MUC1, have all been found in breast cancer patients with tumors expressing those antigens (Lu et al., 2008). HER2 is a tyrosine kinase which plays a critical role in cellular growth and is upregulated in many cancers, including breast carcinoma. Patients with HER2-overexpressing metastatic breast cancer and vaccinated with a recombinant protein consisting of extracellular domain and a portion of the intracellular domain of HER2, and administered the HER2 kinase inhibitor, lapatinib, demonstrated anti-HER2 serum antibody with downstream signaling inhibition of HER2-expressing tumor cells (Hamilton et al., 2012). This approach was evaluated as a treatment for patients previously treated with, and who subsequently developed resistance to, the anti-HER2 monoclonal antibody, trastuzumab. Patients developed anti-HER2 antibody responses and disease progression was delayed by 55 days. However, these studies demonstrated that, although humoral immunity may offer some initial benefit, inhibition of disease progression may require multimodal approaches to therapy.

An emerging body of evidence shows that dynamic epithelial–stromal interactions in solid tumors may select subsets of stromal cells with the ability to modulate tumor behavior, and the local microenvironment promotes emergence of tumor-associated stromal cells with functions different from the normal stroma (Briest et al., 2012). For example, fibroblasts derived from breast tumors stimulated morphogenesis and growth of breast pre-neoplastic epithelial cells, while fibroblasts derived from normal breast tissue inhibited this process (Shekhar et al., 2001). Such functional changes in tumor stroma may partly be derived from the changes in secretion of growth factors and in the extracellular matrix (Schor and Scor, 2001; Haslam and Woodward, 2003).

The predominant cell type within tumor stroma is the fibroblast. Further, cancer-associated fibroblasts produce a number of factors which promote proliferation and progression of cancer. Among these factors are osteonectin, vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs) (Räsänen and Vaheri, 2010). VEGF, for example, has been implicated in a number of aspects of cancer growth, including angiogenesis, remodeling of the extracellular matrix, generation of inflammatory cytokines, and hematopoietic stem cell development. However, because many of these moieties are widely produced by normal cells, the immune system wisely restricts itself from attacking these otherwise inviting targets.

Important to the innate immune response to tumors are a type of pattern recognition receptor referred to as toll-like receptors (TLRs) which are localized on the membranes of both immune and tumor cells, as well as fibroblasts and endothelial cells associated with the tumor stroma (Goutagny et al., 2012). The ligands recognized by TLRs are varied and include bacterial DNA and endotoxin, and viral RNA. For reasons not understood, some TLRs are often upregulated on some types of tumor cells. For example, TLR4 is upregulated in ovarian, colon, and head and neck tumors (Huang et al., 2005; Kelly et al., 2006; Szczepanski et al., 2009). Triggering of TLRs via administration of appropriate ligands has been observed to initiate anti-cancer responses and TLRs are being studied in clinical trials primarily for their adjuvant activity. It appears that TLR activation may result in enhancement of antigen uptake, processing, and presentation by dendritic cells, thus contributing to the activation of antigen-specific T cells (Iwasaki and Medzhitov, 2004).

More specifically, circulating (plasmacytoid) dendritic cells selectively express TLR7 and TLR9 and when activated produce interferons that subsequently activate tissue dendritic cells, T and B lymphocytes, and NK cells (Palma et al., 2012); thus, activated circulating dendritic cells potentially yield significant downstream anti-tumor activity. This feature has been exploited as a means of therapeutic cancer vaccination. For example, the sipuleucel-T vaccine for human prostate cancer is prepared from