Enhancing Cancer Immunotherapy Via Activation of Innate Immunity

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Given recent technological advances and advances in our understanding of cancer, immunotherapy of cancer is being used with clear clinical benefit. The immunosuppression accompanying cancer itself, as well as with current cancer treatment with radiation or chemotherapy, impairs adaptive immune effectors to a greater extent than innate effector cells. In addition to being less suppressed, innate immune cells are capable of being enhanced via immune-stimulatory regimens. Most strategies being investigated to promote innate immune responses against cancer do not require complex, patient-specific, ex vivo cellular or molecular creation of therapeutic agents; thus they can, generally, be used as "off the shelf" therapeutics that could be administered by most cancer clinics. Successful applications of innate immunotherapy in the clinic have effectively targeted components of the innate immune response. Preclinical data demonstrate how initiation of innate immune responses can lead to subsequent adaptive long-term cancer immunity. We hypothesize that integration of innate immune activation strategies into combination therapies for cancer treatment will lead to more effective and long-term clinical benefit.
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Except for the example of "graft-versus-leukemia" (GVL) following allogeneic bone marrow transplant,[1] prior to ~1985 few preclinical advances in cancer immunotherapy were being translated clinically. This was due to limitations in our: (1) understanding of cancer; (2) animal models, which were not simulating clinical cancer treatment; and (3) technologic ability to create agents in sufficient quantity to impact cancer. In this regard, the ability to make recombinant human cytokines [interferons (IFNs), interleukin-2 (IL-2)] and monoclonal antibodies (mAbs) advanced this research greatly. Thus clinical immunotherapy is being more frequently used with clinical benefit.[2]

However, several barriers to efficacy remain. First, when cancer is diagnosed, the growing neoplasm has already escaped from the immune system, and thus has been selected for its ability to not be recognized or destroyed by endogenous immunity.[3] Thus, in a subset of patients, effective immunotherapy requires the induction of mechanisms far more potent than those that the ineffective endogenous immune response tried to muster. The second barrier is that cancer itself, and current cancer treatments, are highly immunosuppressive, particularly to the adaptive (T-cell) response.[4] Although current data with immune checkpoint inhibitors demonstrate potent restoration of T-cell anti-tumor immunity in subsets of advanced cancer patients, nevertheless, innate immune cells [especially natural killer (NK) cells and macrophages], are much less suppressed[5] and are thus attractive effectors as part of an immunotherapeutic strategy. The third barrier is that some of the most potent current cellular therapy approaches require local, patient-specific, high-tech, good-manufacturing practice (GMP)-lab

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support that is not available for patients treated at most cancer clinics. In order to potentially enable broader application of immunotherapy, there are advantages in strategies that combine reagents that could be stored in any hospital/clinic pharmacy, and be readily applied "off the shelf" for patients worldwide.

A number of immunotherapeutic approaches towards enhancing innate immunity have demonstrated clinical efficacy. In this review, we describe strategies in which innate immune cells have been successfully augmented as part of an immunotherapy regimen. In addition to stimulation of adaptive immunity, we hypothesize that many forms of clinically successful immunotherapy of cancer will likely involve components of innate immune stimulation.

COMPONENTS AND BIOLOGY OF INNATE IMMUNITY

Natural Killer Cell Biology

At the interface of a developing cancer and its interaction with the immune system, NK cells play a central role in cancer elimination.[6] In mouse models, the role of the NK cell in preventing metastatic dissemination has been clarified.[7] A role for NK cells in the prevention of spontaneous cancer is supported by their cell surface expression of Natural Killer Group 2, Member D (NKG2D) a receptor capable of recognizing signs of stressed/pre-malignant cells. NK cells, unlike the B and T cells of adaptive immunity, are capable of spontaneously destroying cancerous cells without prior sensitization. This unique capability is the result of the mechanisms by which NK cells target cancerous cells for destruction.

The cytolytic activity of NK cells, mediated in part by pre-synthesized granules, requires a balance between "activating" signals and the lack of "inhibitory" signals. The main inhibitory signals in humans, which function to prevent the destruction of "self" tissues, are the inhibitory killer cell immunoglobulin-like receptors (KIRs). The classical ligands for the NK cell's inhibitory KIR are certain major histocompatibility complex (MHC) class I surface molecules. These MHC class I molecules are polymorphic cell surface molecules found on all mature nucleated cells. In contrast to mature $CD4^+$ or $CD8^+$ T cells, which are activated upon presentation with MHC class II– or class I–bound antigen, NK cells are inhibited from killing when their inhibitory KIR specifically recognize their cognate specific MHC class I molecules. By circumventing this inhibitory mechanism, "naïve" NK cells can activate and lyse tumor cells that lack the MHC class I "off switch." These receptor interactions also explain the wide variability in NK cell activity in the population, as an individual's NK KIR repertoire and MHC I ligands, are encoded on separate chromosomes and independently inherited. Thus different degrees of activating or inhibitory interactions are determined by an individual's KIR repertoire as well as the spectrum of MHC class I molecules the NK cells encounter. These important relationships were first identified clinically in the setting of the allogeneic graft-versus-leukemia (GVL) effect for recipients of T-cell–depleted allogeneic bone marrow transplantation (BMT).

Neutrophils

Neutrophils are short-lived granulocytes well recognized for their role in the immediate response to a bacterial or fungal inoculation. Although neutrophil activity may potentially be incorporated into effective immunotherapies, their functions can at times promote tumors. In the tumor microenvironment, upregulation of neutrophil chemotactic factors augments the presence of these short-lived cells. The presence of neutrophils within the tumor microenvironment has been significantly associated with worse prognosis in a number of solid tumors.[8,9] Neutrophils have been implicated in tumor initiation, via the genotoxic effects of neutrophil generated reactive oxygen species. Neutrophils can also foster tumor progression. For example, some tumor cells secrete IL-8, recruiting neutrophils to the tumor site.[10,74] The pro-tumoral role of neutrophils includes: inflammatory cell recruitment, tumor cell proliferation, tumor angiogenesis, enhanced invasiveness, and neutrophil-aided extravasation leading to metastasis.[11] Neutrophil elastase—a major antibacterial effector mechanism of the cell—can lead to tumor cell proliferation if internalized by the tumor cell.[12] Since they have effector function and also have Fc receptors, neutrophils can mediate antibody dependent cell-mediated cytotoxicity (ADCC). Some have suggested that most of the anti-tumor effect of human neutrophils, demonstrated via ADCC, is primarily an in vitro finding and may not play a substantial role in vivo.[13] However, mouse work indicates that tumor associated neutrophils may differentially polarize towards an anti-tumor function, capable of tumor cytotoxicity.[14] Furthermore, clinical data from Cheung and colleagues have demonstrated in sequential trials that the addition of granulocyte-macrophage colony-stimulating factor (GM-CSF) to tumor-reactive mAbs seems to provide augmented anti-tumor efficacy.[15]

Macrophages

As observed for neutrophils, macrophage functions may potentially be incorporated into cancer immunotherapies, but their native activities are often