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Prespective

Clinical Investigation over Innate Immunity in Cancer Immunotherapy

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ABOUT THE STUDY

The development of immunotherapeutic approaches is a result of the discovery of the significant role that cancer immunity plays in malignancies. A majority of the immunomodulatory strategies under development now involve the adaptive immune system. Checkpoint inhibitors and Chimeric Antigen Receptor (CAR) T-cell therapy have had significant success in the treatment of hematologic malignancies since they were given clinical approval. The majority of patients with solid tumors, however, have made little or no progress. Research published in the most recent edition of Cell found that Mn^{2+} was crucial in the innate immune detection of malignancies because Mn-deficient mice had trouble controlling tumor development and metastasis. Mechanistically, Mn^{2+} enhanced CD8+ T-cell differentiation and activation, NK cell activation, and memory CD8+ T cells in a Cyclic-AMP Synthase (cGAS)-Stimulator of Interferon Genes (STING)-dependent manner, revealing a crucial role of Mn in bridging innate and adaptive immunity for tumor surveillance. These effects were all mediated by STING. The primary players in the innate immune system are different myeloid cell types, such as DCs, monocytes, and macrophages, all of which perform as professional Antigen-Presenting Cells (APCs), and innate lymphoid cells, such as Natural Killer (NK) cells, which depend on germ line-encoded Pattern Recognition Receptors (PRRs) and other cell-surface receptors to quickly detect microbial proteins or membranous molecules on tumor cells to orchestrate downstream.

In addition to mounting their own effector responses, such as macrophage phagocytosis and NK cell cytotoxicity naturally occurring, these cells also start adaptive immune responses. The ability of APCs to engulf tumor cells *via* phagocytosis, a cellular process involving target cell recognition, cellular engulfment, and lysosomal digestion that is governed by receptor-ligand interactions between the target cell and the phagocyte, is crucial to this bridging of innate and adaptive immunity. The core assumption that immunotherapies intrinsically target T cells, activating the tumoricidal capacity of the adaptive immune system, has served as the framework for successful cancer immunotherapy *via* the blockage of immunological checkpoints and CAR T cells. T cells continue to play a crucial role although they cannot act on their own while performing effector tasks. This has led to the identification of non-T-cell immune populations, including innate immune cells, as prospective targets for immunotherapy. Therefore, immunotherapies that try to reverse the protumor phenotype or promote the anticancer phenotype of innate immune cells constitute a promising antitumor strategy that may work in concert with current immunotherapies that target adaptive immunity.

Emerging data suggests that innate immune checkpoints, which prevent the detection and removal of tumor cells through phagocytosis and the suppression of innate immune sensing, also play significant roles in tumor-mediated immune escape and may therefore, represent potential targets for cancer immunotherapy. Targeting phagocytosis checkpoints, such as the CD47-Signal Regulatory Protein (SIRP) axis, either alone or in combination with other cancer medicines, has shown promise in preclinical research and early clinical evidence. The use of innate immune response agonists is yet another strategy that is possible. Pathways that were first discovered to play a role in the detection of infections have also been discovered to play a role in the detection of tumor cells. Endosomal Toll-Like Receptors (TLRs) and cytosolic nucleic acid sensors including RIG-I-Like Receptors (RLRs) and STING are both involved in nucleic acid sensing. In order to trigger the innate immune response at the tumor site for therapeutic purposes, synthetic molecules that resemble those brought on by infection have been produced. This approach utilizes the endogenous antigen repertoire that is present within the tumor, unlike other methods that rely on the prior identification of cancer antigens (for instance, CAR T cells). TLRs, STING, and RLRs that are synthetically targeted have demonstrated the capacity to suppress tumors through a variety of mechanisms, including the induction of tumor cell death, phagocytosis, the production of type I IFNs, proinflammatory cytokines and T cell-tropic chemokines, NK cytotoxicity, DC maturation, and the promotion of tumor-specific CD8 T cells, resulting in long-term systemic immunity. After the clinical breakthroughs made possible by CAR T-cell

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therapies, significant work has been put towards determining the efficacy of CAR non-T cells and any potential benefits these cells might have over their T-cell counterparts. NK cells are far more advantageous for cancer treatment than T cells.

Infusions of off-the-shelf CAR NK cells produced from Umbilical Cord Blood (UCB) are being explored in clinical studies against various forms of leukemia due to the absence of graft-versus-host disease following the injection of allogeneic NK cells. For the creation of CAR NK cells, NK cell lines, primary NK cells from peripheral blood, UCB, or induced pluripotent stem cells have all been employed. Additionally, CAR NK cells are attracting a lot of interest, in large part because of their ability to avoid the potentially fatal side effects of CAR T cells while recapitulating the powerful antitumor effects of CAR T cells. Innate myeloid cells, or macrophages, are expert phagocytes that can regulate homeostasis in the adaptive immune system. The idea for the development of CAR macrophages is that they can be polarized into an anti-tumor phenotype and that they are actively drawn to solid tumors, where they can enhance the activation and recruitment of immune cells like T cells. Therefore, immune cell penetration and the immunosuppressive milieu, which are some of CAR T cells' limitations in solid tumors, may be overcome by CAR macrophages. These findings add another platform to the growing list of cell therapy approaches for the treatment of solid tumors and emphasize the importance of the innate immune system when thinking about immunotherapeutic techniques.

Further research is necessary to fill key conceptual gaps in our knowledge of the dynamic interaction between cancer and immune cells inside the tumor microenvironment following therapeutic intervention, despite significant scientific and clinical advancements. Further defining the context-dependent functions of innate immune pathways in various tumors and genetic subtypes will be crucial. The "double-edged sword" of innate immunity activation is that it not only contributes significantly to the maintenance of these tumor-promoting characteristics but also to the development of antitumor adaptive immune responses to various malignancies.