Molecular Therapy
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Editorial

Advancing together and moving forward: Combination gene and cellular immunotherapies

Over the past decade, we have witnessed the successful translation of cancer therapies that have aimed to rewire the immune system to target a wide array of tumor types. These immunotherapies are composed of distinct modalities that include the release of immunological breaks by immune checkpoint blockade to boost endogenous anti-tumor responses, bispecific antibodies that redirect specificity of endogenous T cells to target tumor cells, adoptive transfer of engineered cell therapies that redirect cytolytic activity of T cells and other immune effector cells to target tumors, and therapeutic oncolytic viruses that are selective in infection, replication, and lysis of tumor cells (Figure 1). To date, each of these modalities have been approved by the U.S. Food and Drug Administration (FDA), starting with the approval of the anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody, ipilimumab, in 2011 for treating patients with melanoma. Since then, eight additional immune oncological (IO) agents that target programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have been approved by the FDA, including the newest agent that targets lymphocyte activation gene 3 (LAG-3), which was approved earlier this year. Additional immune checkpoints are being discovered, and hundreds of clinical trials are ongoing that are evaluating single and combination immune checkpoint-blocking drugs for treating patients with cancer and other disease indications. The first bispecific, called blinatumomab, which targets cluster of differentiation 19 (CD19) for treating patients with B-cell leukemia, was approved by the FDA in 2015. Since then, two additional bispecifics have been FDA-approved for treating patients with non-small cell lung cancer and patients with hemophilia, with numerous bispecifics in late-stage clinical development for treating patients with other tumor types.

Beyond targeting immune checkpoint pathways, chimeric antigen receptor (CAR)-based T cell therapies have been successful since 2017, including the first FDA-approved CAR T cell that targets CD19, called axicabtagene ciloleucel, for treating patients with relapsed refractory B cell lymphoma. This was followed by four additional FDA approvals of CD19-CAR T cells that target other B cell malignancies, including the approval of two B cell maturation antigen-redirected CAR T cells within the last 2 years for treating patients with multiple myeloma. Oncolytic viruses, which have been investigated for many decades, received the first and only FDA approval in 2015 for a genetically modified herpes simplex virus, talimogene laherparepvec, for treating patients with melanoma, with a variety of viral strains being evaluated as potential cancer treatments.

A new chapter in translational immunotherapy is evolving based on the combined knowledge of tumor immunology and better understanding of an IO agent's safety and efficacy. Through a collection of original research articles and reviews, this special issue of *Molecular Therapy – Oncolytics* presents many of the challenges and promises of cellular- and viral-based combination immunotherapies.

CROSSING A RIVER TO CLIMB A MOUNTAIN

Adoptive CAR T cell therapy can conquer the stream of challenges that comes with treating hematological malignancies by combining advances in genetic engineering and T cell manufacturing. The next step, after successfully crossing the river of liquid tumors, is to overcome the uphill battle of treating solid tumors. While advances in cellular engineering can be deployed to treat solid tumors, they clearly need to be optimized to be effective in the solid tumor microenvironment. The major challenges facing CAR T cell immunotherapies that target solid tumors are the lack of uniform and tumor-restricted antigen targets, and the ineffective trafficking, survival, and function of adoptively transferred cells in the immunosuppressive solid tumor microenvironment.[1,2]

COMBINATION CAR T CELL THERAPIES

In this issue, Kankeu Fonkoua et al.[3] published a review on the key features of the immunosuppressive solid tumor microenvironment and their perspectives on overcoming the physiological and immunological barriers currently being addressed in preclinical and clinical investigations. In this review, the authors highlighted the potential benefits of armored CAR T cells to improve trafficking and functionality of CAR T cells in the harsh solid tumor microenvironment. The regional delivery of CAR T cells is being investigated to overcome the first barrier in solid tumor CAR T cell therapy, namely, effective tumor infiltration.[4] Kimura e tal.[5] narrated local and regional delivery approaches as an alternative to systemic administration of CAR T cell therapies by using interventional oncology to promote effector T cell survival and function while decreasing the potential for unwanted toxicities. The authors outlined the approaches for aiding CAR T cell delivery, priming, and stimulation of the tumor microenvironment to promote effector cell survival and function and interventional monitoring of treatment response through selective, multiplex tumor or catheter-based venous sampling. Other novel approaches were presented, including augmenting CAR T cell function by preventing fratricide, overcoming immune exhaustion, and combining systemic infusions with non-ablative chemotherapy.[6,7]

BEYOND THE ENGINEERED T CELL

Engaging the wide spectra of the immune system has been studied in the context of tumor vaccines. These therapies target the innate immunity that aims to present tumor antigens to cytotoxic T cells to stimulate anti-tumor responses. In this issue, Chai et al.[8] developed a novel dual-targeting DNA-based vaccine, specifically for fibrinogen like 1 and carbonic anhydrase IX antigens for renal cell cancers, by

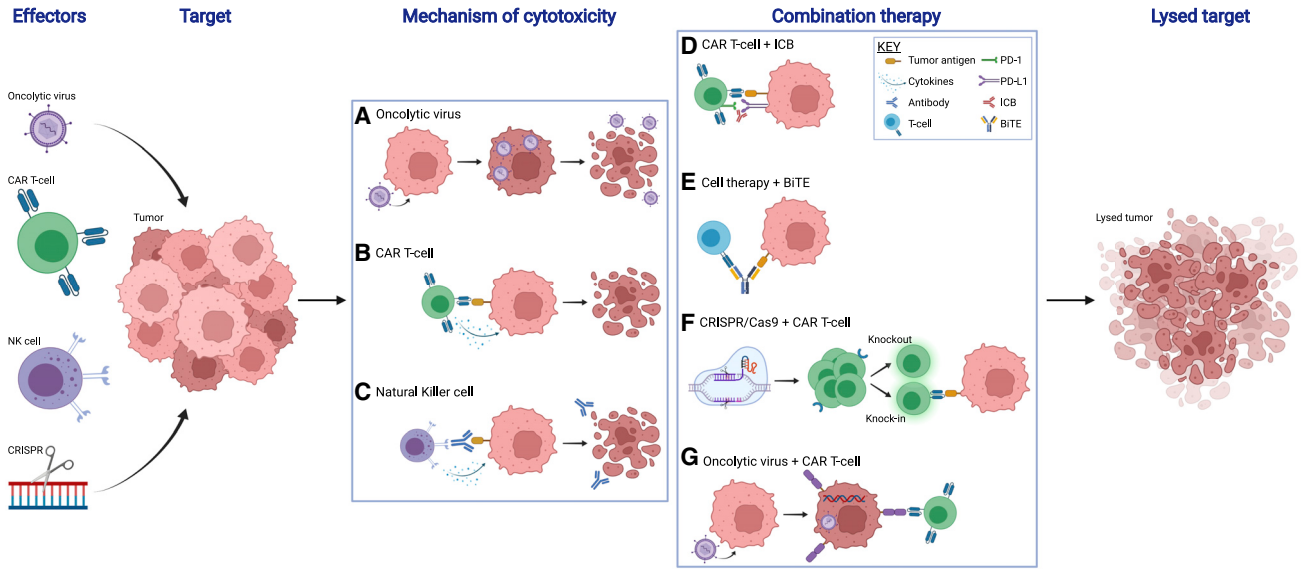

Figure 1. Combination gene and cellular immunotherapies: mechanisms of cytotoxicity and combination therapies

Novel combination therapies are being investigated by use of gene and cellular therapies, such as oncolytic virus, CAR T cell, NK cell, CRISPR, and BiTE technologies. (A) An oncolytic virus selectively infects and replicates within the cancer cell. As the infected cancer cell is destroyed by oncolysis, new infectious virus particles are released to aid destruction of the remaining tumor. (B) The CAR T cell binds to the tumor cell surface antigen, leading to its activation and causing the release of perforins, granzymes, and cytokines inducing tumor cell death. (C) Monoclonal antibody binds to tumor cell-surface antigen, allowing binding to the Fc receptor present on the NK cell. This initiates activation of the NK cell and release of perforins, granzymes and cytokines to induce tumor cell death. (D) CAR T cells with immune checkpoint blockade (ICB)—either in the form of anti-PD-1 and/or anti-PD-L1 antibodies or PD-1 dominant negative receptor or PD-1 knockout—block inhibitory signals, allowing CAR T cells to function effectively. (E) The bispecific T cell engager (BiTE), with two single-chain variable fragments (scFvs), allows for different specificities. One scFv is specific to the T cell (via CD3 binding), while the other is specific to tumor cell surface antigen. The BiTE engages both the tumor cell and the T cell simultaneously, activating the T cell and causing the release of cytolytic granules, inducing tumor cell death. CARs are engineered to secrete BiTEs targeting a second antigen. (F) The clustered regularly interspaced short palindromic repeat (CRISPR) and their associated protein (Cas-9) gene editing mechanism can knockout PD-1, transforming growth factor-β for improved therapeutic response. CRISPR/Cas9 can also knock-in/introduce CAR at a specific locus, such as TRAC, lowering the risk of random integration to recognize and bind to tumor-cell surface antigen, leading to T cell activation. (G) An oncolytic virus is used to immunologically warm up the tumor and/or deliver target genes for enhanced responses by CAR T cells.

targeting dendritic cell subsets to generate multi-functional $CD8^+$ T cell responses against metastasis. Yeo et al.[9] reviewed the challenges facing immunotherapy for treating patients with pancreatic cancer that is notoriously resistant to most therapeutic interventions, including cell-based therapies. The authors reviewed the list of ongoing CAR T cell trials targeting pancreatic cancer and the various strategies, including the use of alternative cell therapies beyond CAR T cells for effectively treating this disease. Of critical importance, the use of relevant preclinical model systems for pancreatic cancer was highlighted, which is increasingly appreciated in the immunotherapy field's attempt to optimize, validate, and translate therapeutic approaches for clinical usefulness.

Alternatives to engineered T cell therapies include the use of engineered natural killer (NK) cells, non-conventional T cells (i.e., gamma-delta), invariant NK T cells, and macrophages. CAR NK cell therapies have demonstrated significant clinical response rates in hematologic malignancies and are now being applied to solid tumors in early stage clinical trials. Fabian and Hodge[10] reviewed the role of these off-the-shelf approaches to engineering NK cells for treating patients with cancer, highlighting the opportunity of NK-92 cell line as a source for CAR-engineered cellular immunotherapy platforms. While both primary- and cell line-based NK and other alternative cell therapies are now being tested in the clinic for various tumor types, the same considerations will likely need to be created to improve the trafficking to and survival in harsh tumor microenvironments for this next wave of immune effector cells. Poggi and Zocchi[11] reviewed the importance of immune checkpoint pathways, which have historically been centered around T cell-specific pathways, including PD-1/PD-L1 and CTLA-4, and offered new insights into NK cell populations in regulating anti-tumor immune responses and NK-specific immune checkpoints that can be targeted as combination immunotherapy strategies.

ONCOLYTIC VIRUS-BASED IMMUNOTHERAPIES

Recently, oncolytic viruses have become an exciting immunotherapy strategy, in large part owing to the promise of addressing the two major challenges with solid tumor immunotherapies—tumor antigen heterogeneity and the immunosuppressive tumor microenvironment. Because of the tumor specificity of oncolytic viruses, they can infect a broad array of tumor types at various disease stages. Furthermore, their potential for reversing immunosuppression is highlighted by a unique ability to spark endogenous anti-viral and anti-tumor immunity. Multiple viral strains have been redesigned as oncolytic viruses,

including but not limited to adenoviruses, vaccinia, measles, herpes simplex viruses, Newcastle disease viruses, poxviruses, polioviruses, and reoviruses. Adenoviruses comprise the large family of viruses reported in clinical trials, followed closely by herpes simplex viruses. To date, the only FDA-approved oncolytic virus uses herpes simplex virus carrying granulocyte-macrophage colony-stimulating factor as an immunostimulatory cytokine transgene for treating patients with melanoma. However, it is likely that other viruses and transgenes, as both single agent and combination approaches, will reach commercialization in the next few years.

Biegert et al.[12] reviewed the current landscape of oncolytic adenoviruses for the treatment of cancer, focusing on the benefits of both genetic modifications to arm viruses with various modalities, including immunostimulatory molecules and immune checkpoint blockade, as well as rational combinations with standard of care or immunotherapies that enhance anti-tumor immunity. One example of genetic modifications to oncolytic adenovirus therapy, presented in this issue by O'Connell et al.,[13] incorporates a self-ligand receptor SLAMF7-Fc fusion protein or its intracellular adaptor, EAT-2, into the virus to augment oncolytic virus activity in solid tumors. Herein, they demonstrated that these adenoviruses carrying either SLAMF7-Fc or EAT-2 promote anti-tumor immunity by activating dendritic cells and macrophages. The authors also presented machine learning approaches to facilitate the understanding of how these viruses promote immunity in the tumor microenvironment to drive the anti-tumor effects. Oncolytic adenoviruses have the potential for efficacy in patients with malignant ascites. In a recent clinical study by Zhang et al.,[14] human type 5 adenovirus (H101) was intraperitoneally administrated in 40 patients with malignant ascites. Treatment with H101 was well-tolerated and showed ascites response rates in 40% of patients. Immune monitoring in the ascites of treated patients showed increased dendritic cell and $CD8^+$ T cell infiltration and marked tumor cell depletion.

Several challenges exist with current applications of oncolytic viruses, including their lack of trafficking to tumors, poor persistence with antibody- and T cell-mediated viral clearance, and limited induction of anti-tumor immune immunity. To overcome such limitations, various groups have engineered viruses to express transgenes that improve their homing to tumors, decrease their recognition by the immune system, or boost their ability to overcome the immunosuppressive tumor microenvironment. One such approach includes delivery of oncolytic viruses by infecting adoptively transferred cells that can better penetrate tumors and introduce viruses directly at tumor sites. Yoon et al.[15] reviewed this delivery approach, specifically the use of mesenchymal stromal cells (MSCs), which can serve as tumor-homing biological factories that promote delivery of oncolytic viruses to improve anti-tumor efficacy. In preclinical studies, Zhang et al.[16] used MSCs to deliver oncolytic adenoviruses, which showed greater anti-tumor responses compared with MSCs alone. However, incorporating an immunostimulatory molecule, called decorin, into adenoviruses delivered by MSCs unexpectedly decreased therapeutic responses, suggesting that further consideration is warranted for this type of delivery approach and for the choice of transgenes engineered into the oncolytic virus.

Other oncolytic viruses are being developed as cancer immunotherapies, which may allow for greater transgene space, potent cytolytic activity, and safety. Among oncolytic virus platforms, measles virus is gaining traction. In a study by Veinalde et al.,[17] oncolytic measles viruses were developed expressing PD-1 and PD-L1 checkpoint-blocking antibodies to further improve therapeutic efficacy in immune-excluded or immunosuppressed tumors. These recombinant viruses produced potent anti-tumor responses, improved inflammatory cytokine production in tumors, and potentiated memory T cell responses.

Increasingly, oncolytic viruses of various strains are incorporating novel transgenes, and combinatorial approaches are moving rapidly into clinical testing, which have the potential to offer new immunotherapy options to effectively target solid tumors. Examples of such strategies are abundant in this special issue, including the use of membrane-tethered IL-2, interferon-1-tolerant oncolytic virus, OX-40, sensitizer-mediated oncolytic therapy, and oncolytic viruses to reverse immune resistant tumors; these approaches are combined with checkpoint blockade inhibition in a strategic manner.[18–24]

CHALLENGES SPECIFIC TO COMBINATION THERAPIES

While it is challenging to monitor the safety and efficacy of single agent therapies, it is even more challenging to monitor each agent's contribution to toxicity and efficacy in combination approaches. Biomarkers, preferably non-invasive biomarkers, are sorely needed that can be used to monitor tumor infiltration of immune cells and therapeutic responses. The combination immunotherapy field is still in its infancy—methods are in development on how and when to administer each agent in combination therapy without overlapping toxicity and while improving efficacy. The importance of these investigations is underscored by the toxicities observed while combining anti-PD1 and anti-CTLA4 agents without significant therapeutic advantage. Early stage clinical trials with single agents are typically developed in cohorts of increasing doses. There is the open question as to how best to strategize combinations, their dosage, and frequency; this requires further investigations, and incorporating approaches such as predictive mathematical modeling could help to narrow down potential variables before clinical investigation. However, the rapid increase in combination immunotherapy approaches is promising, as evident in this special issue.

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