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Immunotherapy: The Next Frontier in Cancer Treatment

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INTRODUCTION

Over the past decade, immunotherapy has redefined the landscape for cancer treatment, providing unprecedented survival benefits across a broad swath of tumors. The ability to harness and modulate the immune system has transformed outcomes for patients, from immune checkpoint inhibitors (ICIs) to advanced cellular therapies, such as chimeric antigen receptor (CAR) T cells and CAR macrophages (CAR-MΦ). However, these advancements have come with new challenges, such as variability in efficacy, toxicities, and lack of efficacy against the immunosuppressive tumor microenvironment (TME), especially in solid tumors[1].

In this editorial, we explore the major advances in immunotherapy, the potential of combination therapies with CAR-MΦ, and the need for these combination approaches to overcome evolving challenges.

Immune Checkpoint Inhibitors:

In cancers such as melanoma, NSCLC, and RCC, ICIs have become the cornerstone of immunotherapy. ICIs block inhibitory receptors such as PD-1, PD-L1, and CTLA-4, and thereby enable the immune system to overcome the suppression and unleash the immune T cells for effective anti-tumor response. In many patients, these therapies have provided durable responses and some patients have survived more than five years. We have landmark trials that show significant improvements in overall survival (OS) and progression-free survival (PFS) vs. chemotherapy in metastatic and refractory cancers[2].

Nevertheless, despite all these advances, not all patients respond to ICIs. Resistance is due to tumor antigen heterogeneity, immune evasion mechanisms, and the immunosuppressive TME. In addition, immune-mediated adverse events (images), including gastrointestinal, dermatologic, and endocrine toxicities, continue to be significant barriers. Biomarker discovery including PD-L1 expression and tumor mutational burden will become increasingly important as the field evolves for identifying patients most likely to benefit from ICIs for personalized therapy with minimal risk and cost[3].

Cellular Therapies: CAR-T Cells and the Emerging Role of CAR-Macrophages

However, ICIs are transformative; cellular therapies are now the new frontier in immunotherapy. Remarkable success with CAR-T cells, which involve engineering T cells to express tumor-specific receptors, has been shown in hematologic malignancies,

particularly leukemia and lymphoma. Despite these barriers, however, the efficacy of these approaches in solid tumors is still limited[4].

New CAR-MΦ therapies emerging as a novel solution to meet these challenges. Chimeric antigen receptors engineered into macrophages are capable of targeting tumor cells while modifying the hostile TME. After CAR-MΦ binds to tumor cells through phagocytosis, they actively engulf tumor cells while secreting pro-inflammatory cytokines to reprogram the TME to be immunostimulatory. In addition to stimulating other immune cells like T cells and natural killer (NK) cells, these engineered macrophages also amplify anti-tumor responses[5].

Promising safety and efficacy have been demonstrated by early clinical trials, including those in HER2-expressing solid tumors. CAR-MΦ therapies can persist within the tumor, can overcome physical barriers, and can synergize with other immunotherapies. Safety issues, however, remain, most notably the possibility of cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)[6]. Macrophages' intrinsic role in inflammation regulation, however, may provide a more controlled cytokine response than CAR T cells. These risks are being mitigated by tailored engineering strategies, such as IL-10 expression, to ensure safe clinical application[7].

Combination Therapies: The future of immunotherapy will be in combination with strategies to overcome its limitations and improve efficacy. In preclinical models, CAR-MΦ has synergistic activity with immune checkpoint inhibitors like anti-PD-L1 and anti-CTLA-4. Checkpoint blockade reinvigorates exhausted T cells, and CAR-MΦ remodels the TME, making it hospitable to sustained immune attack[8].

Efforts to overcome the physical and biochemical barriers within the TME are equally required. Since engineering CAR cells to secrete pro-inflammatory cytokines or enzymes that digest the extracellular matrix enhances immune cell infiltration and persistence in tumors, we hypothesized that CAR cells could be engineered to secrete diphtheria toxin, which elicits an immune response within the tumor site. Moreover, immunotherapies alone, when combined with conventional therapies like chemotherapy and radiotherapy, may increase antigen presentation, increase T cell infiltration, and increase overall immune response[9].

CONCLUSION

Immunotherapy has fundamentally changed how cancer is treated and has given many patients who were once untreatable hope. However, immunosuppressive TME and durable response in solid tumors remain challenges. CAR-MΦ therapy is a promising innovation with unique advantages because they are capable of phagocytosing tumor cells, presenting antigens, and reprogramming the TME.

A rational combination approach with ICIs, cellular therapies, and conventional treatments would be the future. Additionally, safety concerns need to be addressed through rigorous clinical trials and long-term follow-up to optimize treatment strategies. As we stand on the brink of this new frontier, the challenge for the scientific community is clear: Immunotherapy needs to be refined to expand its reach, to ensure it becomes a mainstay of cancer care, and to offer cures where none existed before.

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