Combination therapies: Enhancing the efficacy of adoptive cell therapy.

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Introduction

Adoptive cell therapy (ACT) has emerged as a promising immunotherapeutic approach for treating various cancers, particularly hematologic malignancies and solid tumors. However, despite its significant advancements, ACT faces challenges such as immune escape, tumor heterogeneity, and an immunosuppressive tumor microenvironment. Combination therapies have gained attention as an effective strategy to enhance ACT's efficacy, improve persistence, and reduce resistance. This article explores various combination therapies that enhance ACT's effectiveness, supported by recent research findings [1].

ACT involves the transfer of autologous or allogeneic immune cells, such as T cells, into cancer patients to recognize and eliminate tumor cells. The most common forms of ACT include chimeric antigen receptor (CAR) T-cell therapy, tumor-infiltrating lymphocytes (TILs), and T-cell receptor (TCR)-engineered T cells. Despite their success in hematologic cancers, these therapies face obstacles in solid tumors due to antigen loss, physical barriers, and immune suppression [2].

Immune checkpoint inhibitors (ICIs) such as programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) blockers have revolutionized cancer therapy. These inhibitors help reinvigorate T cells and prevent immune exhaustion. Studies have shown that combining PD-1/PD-L1 inhibitors with CAR T-cell therapy enhances persistence and tumor infiltration, overcoming immune suppression in solid tumors [3].

Cytokines, such as interleukin-2 (IL-2), IL-7, and IL-15, play a crucial role in T-cell expansion and survival. IL-2 is commonly used in ACT to boost T-cell proliferation, but its high toxicity limits its widespread application. IL-15, with a lower toxicity profile, has been explored to enhance CAR T-cell persistence and function, improving response rates in patients [4].

Targeted small-molecule inhibitors can modulate the tumor microenvironment (TME) and improve ACT efficacy. For instance, Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib, have been shown to enhance CAR T-cell expansion and persistence by reducing immune suppressive signals. Similarly, BRAF/MEK inhibitors can sensitize tumors to ACT by reducing tumor cell resistance [5].

Radiation therapy (RT) can increase tumor antigen presentation and recruit immune cells, making tumors more susceptible to ACT. Preclinical studies have demonstrated that localized RT can improve CAR T-cell infiltration and effectiveness by inducing immunogenic cell death and enhancing neoantigen expression [6].

Oncolytic viruses (OVs) selectively infect and kill tumor cells while stimulating an immune response. OVs can enhance ACT efficacy by modulating the TME, increasing antigen release, and promoting immune cell infiltration. Clinical trials combining OVs with CAR T-cell therapy have shown improved tumor regression and prolonged responses in solid tumors [7].

The metabolic state of T cells plays a crucial role in their persistence and function. Enhancing mitochondrial function and glucose metabolism can improve T-cell survival. Strategies such as the use of metformin or PGC-1α overexpression have been explored to enhance CAR T-cell function, leading to improved responses in preclinical studies [8].

Epigenetic reprogramming can enhance T-cell function and tumor recognition. Histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors have been investigated to improve the efficacy of ACT by increasing tumor antigen expression and T-cell persistence [9].

Bispecific T-cell engagers (BiTEs) can direct T cells to tumor cells by recognizing two different antigens simultaneously. Combining BiTEs with ACT can enhance tumor recognition and elimination, especially in tumors with antigen heterogeneity. Nanotechnology-based drug delivery systems have been explored to enhance ACT. Nanoparticles carrying immune-stimulating molecules, cytokines, or checkpoint inhibitors can improve T-cell activation and targeting [10].

Conclusion

Combination therapies represent a promising strategy for overcoming ACT's limitations and improving its clinical efficacy. Integrating immune checkpoint inhibitors, cytokine support, targeted therapies, radiotherapy, oncolytic viruses, metabolic reprogramming, and other innovative approaches can enhance ACT's durability and response rates. Continued research and clinical trials are essential to optimize these combinations and develop personalized treatment strategies.

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