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COMMENTARY

Empowering immune responses against cancer by IL-21-driven T cell reprogramming

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INTRODUCTION

The global cancer burden necessitates innovative therapeutic strategies to improve patient survival and quality of life. The field of oncology has witnessed a significant advance with the emergence of checkpoint immunotherapies, which empower the immune system to identify and destroy tumor cells.[1] Durable clinical responses in a range of malignancies have been achieved through immunotherapies targeting immune checkpoints such as CTLA-4 and PD-1, exemplified by nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4). However, these advancements are constrained by challenges such as limited response rates, acquired resistance, and significant immune-related adverse events.[1] Furthermore, the immunosuppressive tumor microenvironment (TME) disrupts immune cell infiltration and function, further constraining the therapeutic potential of immune checkpoint blockade (ICB).[2] Overcoming these barriers is essential to broaden the scope and effectiveness of immunotherapy.

Recent insights into cytokine-mediated signaling within the TME have revealed its critical role in augmenting immune responses and optimizing ICB efficacy. Among these cytokines, interleukin-21 (IL-21) exerts anti-tumor effects by modulating key immune cell populations crucial for tumor control. It enhances the cytotoxicity, proliferation, and survival of $CD8^+$ T cells, enabling them to eliminate tumor cells and establish durable immune memory. Additionally, IL-21 enhances natural killer (NK) cell's cytotoxic activity and stimulates the production of key cytokines like IFN-γ, further bolstering anti-tumor immune responses.

Building on these foundations, Zhang et al. have established the crucial role of IL-21 signaling in enhancing the cytotoxic reprogramming of T cells during anti-CTLA-4 therapy.[3] Complementing this, Zhu et al. introduced an innovative IL-21 receptor-engineered T cell therapy that enhances the functionality and persistence of adoptively transferred T cells in solid tumors.[4] Although IL-21 has long been recognized for its therapeutic potential, its clinical application has faced inherent challenges, including limited stability, insufficient immune activation within the TME, and the need for combination strategies to achieve durable responses. Moreover, the risks of toxicity associated with systemic IL-21 administration demand the development of refined approaches. Zhang et al.'s study represents a significant advancement over previous IL-21 therapies by demonstrating how IL-21 selectively reprograms exhausted $PD\text{-}1^+CD8^+$ T cells, referred to as responding $PD\text{-}1^+CD8^+$ T cells (T_{Resp} cells), within the TME. Unlike general T cell activation strategies, their work highlights the transcriptional rewiring of these cells, restoring cytotoxic function and proliferation while minimizing off-target immune effects. This precise mechanism sets it apart from many previous approaches that relied primarily on systemic cytokine administration or non-specific immune activation. Together, the findings of Zhang et al. and Zhu et al. underscore the transformative potential of IL-21 signaling in reshaping the immune landscape. This commentary delves into Zhang et al.'s fascinating findings while integrating insights from Zhu et al., illustrating how IL-21 bridges mechanistic discoveries and translational innovations to shape future cancer immunotherapies.

IL-21 AS A CYTOTOXIC REPROGRAMMING AGENT

Enhancing T cell cytotoxicity remains a cornerstone of cancer immunotherapy. Zhang et al. demonstrated that IL-21 is pivotal in reprogramming exhausted T_{Resp} cells into highly functional cytotoxic effectors (Figure 1). Through transcriptional reprogramming, IL-21 restores essential T cell functions such as proliferation, granzyme secretion, and tumor lysis. This restoration of effector function significantly enhances the antitumor effects in CTLA-4 blockade therapy. Notably, the findings were validated in both monotherapy and dual-ICB strategies combining CTLA-4 and PD-1 inhibitors.

IL-21 produced by $CD4^+$ T follicular helper (TFH) cells activates $PD\text{-}1^+CD8^+$ T cells through IL-21 signaling, reprogramming them into cytotoxic T cells. These reprogrammed T cells target and shrink tumors by overcoming the immunosuppressive tumor microenvironment, highlighting the therapeutic potential of IL-21 in cancer immunotherapy (some components of this figure were created with BioRender.com).

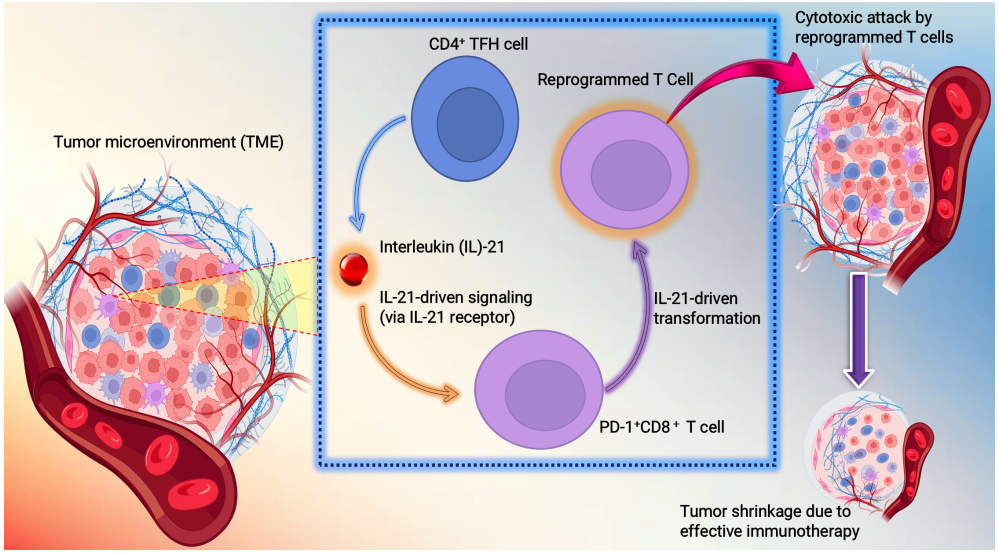

Figure 1. IL-21-driven reprogramming of T cells enhances tumor immunotherapy IL-21 produced by $CD4^+$ T follicular helper (TFH) cells activates $PD\text{-}1^+CD8^+$ T cells through IL-21 signaling, reprogramming them into cytotoxic T cells. These reprogrammed T cells target and shrink tumors by overcoming the immunosuppressive tumor microenvironment,highlighting the therapeutic potential of IL-21 in cancer immunotherapy (some components of this figure were created with BioRender.com).

Employing advanced single-cell RNA sequencing and SCENIC regulon analysis, Zhang et al. revealed that IL-21 drives distinct STAT1 and STAT3 transcriptional programs that govern key functional enhancements in T_{Resp} cells. These pathways enhanced cytotoxic function, proliferation, and enriched tumor-specific T cell clones to amplify the anti-tumor immune response. Notably, the distinct STAT1 and STAT3 activities observed in

monotherapy versus dual-ICB settings underscore the context-dependent roles of IL-21 signaling in modulating the TME. These findings convincingly demonstrate the role of IL-21 in restoring cytotoxic function and proliferation which are critical for enhancing ICB efficacy. Mechanistic experiments using IL-21 receptor-deficient mouse models confirmed that IL-21R expression on $CD8^+$ T cells is indispensable for the efficacy of CTLA-4 blockade therapy. The absence of IL-21R in these models significantly impaired T_{Resp} cell reprogramming, as evidenced by reduced granzyme expression, diminished tumor control, and decreased $CD8^+$ T cell proliferation. These findings directly link IL-21R signaling to the efficacy of CTLA-4 blockade, establishing a causal relationship between IL-21 signaling and tumor regression. Conversely, IL-21R signaling played a less pronounced role in anti-PD-1 monotherapy, highlighting the specificity of IL-21 in the context of CTLA-4 blockade. The influence of IL-21 extends beyond $CD8^+$ T cells. It modulates the broader immune landscape by stimulating IL-21 production from $CD4^+$ T follicular helper (TFH) cells, a process regulated by ICOS-CD28 signaling. These TFH cells support cytotoxic $CD8^+$ T cell responses and enhance immune cross-talk within the TME. Additionally, dual-ICB was found to activate distinct STAT2 and STAT5 signaling pathways which suggest potential synergies between IL-21 and IL-2 in enhancing immune responses. Collectively, these findings establish IL-21 as a critical mediator of cytotoxic T cell reprogramming and a vital enhancer of ICB.

IL-21 AS A SYNERGISTIC DRIVER IN IMMUNOTHERAPY

IL-21 signaling emerges as a powerful tool for integration into combination immunotherapy strategies, extending its influence beyond CTLA-4-based therapies. By modulating cytokine networks and the TME, IL-21 can synergize with checkpoint inhibitors targeting pathways such as TIGIT, PD-1/PD-L1, etc. This versatility opens avenues for enhancing immune activation and addressing resistance in refractory cancers. IL-21's capacity to prime dendritic cells and amplify cytokine signaling further supports its role in revitalizing the TME, making it an ideal candidate for combination therapies aimed at overcoming immunosuppressive barriers.

Adding to this potential, Zhu et al. demonstrated the transformative impact of IL-21 receptor-engineered T cells.[4] This innovative platform equips adoptive T cells with constitutive IL-21 signaling. It circumvents the challenges of systemic cytokine delivery while enhancing persistence, infiltration, and antitumor activity in preclinical hepatocellular carcinoma models. Remarkably, engineered T cells exhibited naive-like phenotypes with reduced exhaustion and enabled sustained cytotoxic responses against solid tumors. By bridging checkpoint blockade and adoptive cell therapies, IL-21 offers a dual-pronged strategy to optimize immune activation and overcome therapeutic resistance. These insights position IL-21 as an important component in developing future cancer immunotherapeutic strategies.

EXPANDING THE HORIZON OF IL-21 IN CANCER IMMUNOTHERAPY

IL-21 signaling stands out as a promising avenue for advancing next-generation cancer immunotherapy. While the findings discussed here have laid a robust foundation, further exploration is imperative to unlock its full therapeutic potential. Synergizing IL-21 with emerging checkpoint inhibitors such as LAG-3, TIM-3, and TIGIT, or dual-target combinations like LAG-3/PD-1 and TIGIT/PD-1, presents a compelling opportunity to expand its clinical applicability. These novel strategies could harness the capacity of IL-21 to modulate immune activation and overcome resistance, particularly in refractory or "cold" tumors. Cold tumors, characterized by low immune infiltration and an immunosuppressive TME, remain a major challenge in immunotherapy.[5] Enhancing immune cell infiltration and activation through IL-21 signaling could help convert these tumors into "hot" tumors with robust immune engagement to improve treatment outcomes.

IL-21 has been evaluated in early-phase clinical trials for cancers such as melanoma and renal cell carcinoma, demonstrating immune activation. However, these trials also revealed variable efficacy and raised safety concerns. These challenges, including patient heterogeneity, potential autoimmune side effects, and prolonged cytokine exposure risks, underscore the need for refined approaches. Strategies like precision delivery systems and biomarker-guided patient selection hold promise for addressing these limitations and enabling broader clinical use of IL-21-based therapies.

Beyond checkpoint blockade, elucidating IL-21's broader immunomodulatory effects on regulatory T cells, NK cells, and dendritic cells could unveil additional pathways for enhancing antitumor responses. Leveraging advanced drug delivery systems (DDSs) to achieve localized and sustained release within the TME offers a promising avenue to maximize efficacy while minimizing systemic toxicities. Innovative approaches, such as nanoparticle-based or stimuli-responsive DDSs, could ensure precision delivery and optimize therapeutic impact. Zhu et al.'s engineered IL-21 receptor platform underscores the potential for tailored cytokine delivery to empower adoptive T-cell therapies. This approach addresses critical challenges in treating solid tumors by enabling persistent IL-21 signaling and enhanced functionality. Expanding its application to other tumor types and integrating it with checkpoint inhibitors and DDS technologies could redefine immunotherapy paradigms.

By addressing these challenges and building on IL-21's dual role as a cytotoxic reprogramming agent and immune enhancer, the field is poised to revolutionize cancer treatment. Integrating IL-21 into novel immunotherapeutic platforms and technologies can deliver more effective, durable, and personalized therapies, transforming outcomes for patients across a broad spectrum of malignancies.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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