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Review article

Interleukin-enhanced CAR-engineered immune cells in tumor immunotherapy: current insights and future perspectives

Min Wang [a 1], Zixuan Wang [b 1], Guangji Zhang [c], Jia Fan [a]

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Highlights

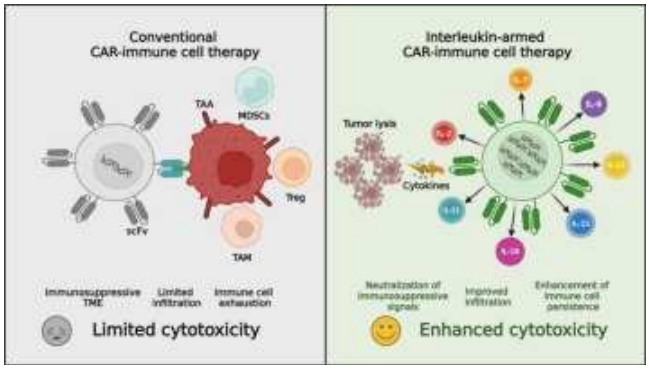
- IL-enhanced CAR cells overcome solid tumor barriers by secreting cytokines to boost infiltration, persistence & efficacy.
- Interleukins (IL-2, 7, 12, 15, 18, 21 & 23) enhance CAR immune cell activation, proliferation, persistence & cytotoxicity.
- IL-enhanced CAR cells combined with checkpoint inhibitors reprogram tumor microenvironment, amplifying anti-tumor responses.
- Targeted cytokine delivery and multi-specific CAR designs mitigate toxicities and antigen escape to optimize safety & efficacy.
- Controlled cytokine release, next-gen CAR designs & AI-driven personalization will refine precision immunotherapy.

Abstract

Despite the remarkable clinical success of chimeric antigen receptor (CAR)-T cell therapy in

hematologic malignancies, the therapeutic efficacy of conventional second-generation CAR-T cells in treating solid tumors remains suboptimal, primarily due to three major biological barriers: (1) the immunosuppressive tumor microenvironment (TME), (2) inadequate tumor infiltration capacity, and (3) T cell exhaustion mechanisms. To overcome these limitations, innovative fourth-generation “armored” CAR-T cell platforms have been engineered with integrated cytokine-secreting modules designed to potentiate anti-tumor responses through localized immunomodulation. These advanced cellular therapeutics achieve targeted delivery of various immunostimulatory cytokines directly within the TME, thereby orchestrating three critical therapeutic effects: (I) remodeling of the immunosuppressive niche, (II) enhancement of immune cell persistence, and (III) neutralization of immunosuppressive signaling networks. This comprehensive review systematically examines the translational applications of cytokine-secreting CAR-engineered immune cells, including CAR-T, CAR-NK, and CAR-iNKT cell platforms, in solid tumor immunotherapy, with particular emphasis on multiple classes of immunomodulatory cytokines that enhance cytotoxic potential, promote immune cell survival, and counteract TME-mediated immunosuppression. We critically evaluate preclinical and clinical evidence demonstrating the therapeutic efficacy of cytokine-armed CAR-engineered cells across various tumor models, including hematological malignancies, glioblastoma, and neuroblastoma. Furthermore, this review addresses current translational challenges, particularly cytokine-associated toxicity profiles and innovative strategies for achieving spatiotemporal control of cytokine release, while discussing their potential implications for advancing clinical outcomes in solid tumor immunotherapy.

Graphical abstract



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Introduction

The interleukin (IL) family of cytokines represents a crucial class of immunomodulatory molecules that orchestrate diverse aspects of immune cell biology, ranging from cellular development and differentiation to functional activation and homeostatic maintenance [1]. These pleiotropic signaling molecules, predominantly secreted by leukocytes, establish complex

cytokine networks regulating both innate and adaptive immunity. Through paracrine and autocrine signaling mechanisms, interleukins precisely modulate the behavior of various immune cell populations, including T lymphocytes, B cells, natural killer (NK) cells, and antigen-presenting cells [2]. For instance, IL-2 serves as a critical growth factor for T cell clonal expansion and survival, while IL-12 promotes Th1 polarization and enhances cytotoxic T lymphocyte (CTL) effector functions [3]. Furthermore, the interleukin family plays a pivotal role in maintaining immune homeostasis by regulating the delicate balance between immune activation and tolerance, thereby ensuring effective pathogen clearance while preventing autoimmune pathogenesis [4].

Chimeric Antigen Receptor T (CAR-T) cell therapy has revolutionized the treatment paradigm for hematologic malignancies, demonstrating unprecedented clinical responses in refractory B-cell leukemias and lymphomas [5]. However, translating this immunotherapeutic approach to solid tumors has encountered substantial biological barriers. The tumor microenvironment (TME) presents a multifaceted immunosuppressive landscape characterized by: (1) elevated levels of inhibitory cytokines (e.g., TGF-β, IL-10), (2) metabolic constraints (e.g., hypoxia, nutrient deprivation), (3) physical barriers (e.g., dense extracellular matrix), and (4) immune checkpoint molecule expression. These factors collectively contribute to CAR-T cell dysfunction through multiple mechanisms, including impaired tumor infiltration, limited persistence, and progressive exhaustion [6]. Consequently, there is an urgent need to develop innovative strategies to reprogram the immunosuppressive TME and enhance CAR-T cell functionality in solid tumor contexts.

This comprehensive review systematically examines the therapeutic potential of interleukin-mediated modulation in CAR-engineered immune cell therapy, with particular emphasis on overcoming the challenges associated with solid tumor treatment. We critically analyze the mechanistic roles of various interleukin family members (including but not limited to IL-2, IL-7, IL-12, IL-15, and IL-18) in enhancing the therapeutic efficacy of CAR-engineered immune cells through multiple mechanisms: (I) promoting cellular expansion and persistence, (II) enhancing tumor infiltration capacity, (III) augmenting cytotoxic effector functions, and (IV) reprogramming the immunosuppressive TME. By integrating recent advances in cytokine engineering and CAR-T cell technology, this review aims to provide a framework for developing next-generation cytokine-armed CAR-engineered immune cells with improved therapeutic potential against solid tumors.

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Section snippets

Interleukin

Interleukins (ILs), first identified in the 1970s as a family of cytokines, have emerged as pivotal regulators of immune responses due to their critical roles in immune cell activation, differentiation, and survival [1,7]. These multifunctional molecules bind to specific cell surface receptors, initiating intricate intracellular signaling cascades, including the JAK-STAT, MAPK, and NF-κB pathways [2,8,9]. These signaling events orchestrate essential immune processes such as cellular …

Advantages of interleukin-enhanced CAR-engineered immune cells

One of the key advantages of incorporating interleukins into CAR-engineered immune cell therapies is their ability to enhance cell activation and expansion. Cytokines such as IL-2, IL-7, and IL-15 have been shown to promote T cell survival, proliferation, and differentiation, thereby improving the persistence of CAR-T cells in vivo. For example, IL-15 has demonstrated particular efficacy in boosting the expansion and survival of CAR-NK cells without inducing excessive inflammation [135]. The …

Conclusion

Table1 summarizes key studies and clinical trials organized by cell type, interleukin, study design, cancer indication, and primary outcomes or trial status, while Table2 delineates the roles of diverse interleukins within the tumor microenvironment (TME) and their capacity to potentiate CAR-engineered immune cell functions. To complement these tables, we have incorporated a comprehensive schematic (Fig.1) that illustrates how cytokines—such as IL-2, IL-7, IL-12, IL-15, IL-18 and IL-21—modulate …

CRediT authorship contribution statement

Min Wang: Writing – original draft, Methodology, Formal analysis, Data curation. **Zixuan Wang:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Guangji Zhang:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Data curation. **Jia Fan:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition, Conceptualization. …

Ethics approval and consent to participate

Not applicable. …

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to improve the quality of

language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. …

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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Not applicable. …

Recommended articles

References (156)

J.J. O'Shea *et al.*
Cytokine signaling modules in inflammatory responses
Immunity (2008)

W. Liao *et al.*
IL-2 family cytokines: new insights into the complex roles of IL-2 as a broad regulator of T helper cell differentiation
Curr. Opin. Immunol. (2011)

M. Akdis
Interleukins (from IL-1 to IL-38), interferons, transforming growth factor β, and TNF-α: receptors, functions, and roles in diseases
J. Allergy Clin. Immunol. (2016)

C.A. Dinarello
Anti-inflammatory agents: present and future
Cell (2010)

T.A. Waldmann
The biology of IL-15: implications for cancer therapy and the treatment of autoimmune disorders

J. Investig. Dermatol. Symp. Proc. (2013)

A.N. Shouse *et al.*
Interleukin-2 signaling in the regulation of T cell biology in autoimmunity and cancer
Immunity (2024)

Y. Saito
Biochemical evidence for a third chain of the interleukin-2 receptor
J. Biol. Chem. (1991)

W. Liao *et al.*
Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy
Immunity (2013)

Y. Yuan
Therapeutic potential of interleukin-2 in autoimmune diseases
Trends Mol. Med. (2022)

V. Niederlova
IL-2-driven CD8+ T cell phenotypes: implications for immunotherapy
Trends Immunol. (2023)

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1 These authors contributed equally: Min Wang, Zixuan Wang.

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