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MANIFESTATION OF THE PARTICULARITIES OF SOME KEY ISSUE ASPECTS OF NEW IMMUNOTHERAPY CHALLENGES AND PERSPECTIVES BY CAR-T CELL THERAPY

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იმუნოთერაპიის ახალი გამოწვევებისა და პერსპექტივების ზოგიერთი ძირითადი ასპექტის მახასიათებლები CAR-T უჯრედული თერაპიის გამოყენებით

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რეზიუმე

კვლევის მიზანს წარმოადგენდა იმუნოთერაპიის ახალი გამოწვევებისა და პერსპექტივების ზოგიერთი ძირითადი ასპექტის მახასიათებლების შესწავლა CAR-T უჯრედული თერაპიის გამოყენებით. კიბოს იმუნოთერაპია მოიცავს თერაპიული მიდგომების ფართო სპექტრს, რომელთაგან თითოეული მიმართულია იმუნური სისტემის ან სიმსივნის მიკროგარემოს ცალკეული კომპონენტებისკენ. იმუნოთერაპიის ძირითადი კატეგორიები მოიცავს: მონოკლონურ ანტისხეულებს (mAbs): ეს ინჟინერიული ანტისხეულები მიზნად ისახავს კიბოს უჯრედების ანტიგენებს, რაც იწვევს იმუნური შუამავლობით დესტრუქციას ისეთი მექანიზმების მეშვეობით, როგორიცაა ანტისხეულზე დამოკიდებული უჯრედული ციტოტოქსიკურობა (ADCC) და კომპლემენტზე დამოკიდებული ციტოტოქსიკურობა (CDC).

CAR-T უჯრედების თერაპია, წარმოადგენს კიბოს რევოლუციური მკურნალობის მიმართულებას და იწვევს პოტენციურად ხანგრძლივ პასუხს მძიმე ჰემატოლოგიური კიბოს მქონე პაციენტებში, პაციენტის საკუთარი T უჯრედების გენეტიკურად მოდიფიცირებით, რათა გამოხატონ ქიმერული ანტიგენის რეცეპტორები (CAR), რაც მათ იდენტიფიცირების საშუალებას აძლევს და ხდება შეტევა კიბოს უჯრედებზე ძირითადი ჰისტოთავსებადობის კომპლექსის (MHC) შეზღუდვების გარეშე.

Background: Immunotherapy encompasses a diverse array of treatment modalities aimed at harnessing the immune system to recognize and eliminate cancer cells. The fundamental principle underlying cancer immunotherapy is to leverage the inherent capabilities of the immune system to mount a specific and durable anti-tumor response. Unlike conventional treatments, such as chemotherapy and radiation therapy, which directly target cancer cells, immunotherapy aims to activate or modulate the immune system to selectively target tumor cells while sparing normal tissues. Key principles of cancer immunotherapy include enhancing immune recognition of tumor cells, overcoming immunosuppressive mechanisms within the tumor microenvironment, and promoting durable anti-tumor immune responses. Targeting tumor-specific antigens: Immunotherapies, such as checkpoint inhibitors and CAR-T cell therapy, target antigens expressed specifically on cancer cells, thereby minimizing off-target toxicity [1-3].

Aim of the research was to study and analyze particularities of some key issue aspects of new immunotherapy challenges and perspectives by CAR-T Cell Therapy.

Methodology: The material of the article was the revised data from scientific publications, which were processed, analyzed, overviewed and reviewed by generalization and systematization. Research studies are based on a review/overview assessment of the development of critical visibility and overlook of the modern scientific literature. Use the following databases (for extensive literature searches to identify the particularities of some key issue aspects of new immunotherapy challenges and perspectives by CAR-T cell therapy): PubMed, Scopus, Web of Science, Clinical key, Tomson Reuters, Google Scholar, Cochrane Library, and Elsevier Foundations.

Results and Discussion. The inception of chimeric antigen receptor (CAR) T cell therapy has its roots deeply embedded in the pioneering strides made within the realms of immunology and genetic engineering, heralding a transformative era in the landscape of cancer therapeutics. While conventional treatment modalities such as chemotherapy and radiation have long served as the linchpins of oncological care, their efficacy is often constrained by formidable limitations, compounded by the burdensome toll of adverse effects, particularly evident in cases of advanced or recalcitrant disease. The quest for more efficacious and less deleterious therapeutic alternatives has thus catalyzed a profound exploration into the promising domain of immunotherapy, which leverages the innate potential of the body's immune system to selectively target and eliminate malignant cells [4,5].

CAR-T cell therapy, emerging from the intricate domains of T cell biology and cancer immunology, stands as a testament to the transformative potential inherent in this innovative therapeutic paradigm. T cells, the quintessential vanguards of the adaptive immune system, unparalleled capacity to discern and eliminate aberrant cells. By ingeniously engineering T cells to express synthetic receptors endowed with the unique ability to recognize tumor-specific antigens, researchers have embarked on a monumental quest to augment the precision and potency of the immune response against cancer. CAR-T cell therapy, a revolutionary cancer treatment, offers potentially long-lasting response in patients with challenging hematologic cancers, by genetically modifying a patient's own T cells to express chimeric antigen receptors (CARs), enabling them to identify and attack the cancerous cells without major histocompatibility complex (MHC) restrictions [6,7].

The research endeavors are exploring CAR-T cell therapy in various hematologic malignancies and solid tumors. Despite hurdles linked to tumor heterogeneity and immune resistance, early studies showcased prospective expansion for CAR-T cell therapy from hematological malignancies to the domain of solid tumor oncology [8,9].

CAR-T cell therapy hinges upon sophisticated engineering methods to furnish T cells with chimeric antigen receptors (CARs), enabling them to identify tumor antigens. These CARs are artificial receptors made up of different functional segments, including an extracellular antigen binding sector, a hinge and transmembrane domain for structural support, and intracellular signaling domain for cell activation. The antigen binding domain typically contains a single chain variable fragment (scfv) sourced from a monoclonal antibody. This allows CAR-T cells to recognize tumor associated antigens (TAAs) without relying on the major histocompatibility complex (MHC), ensuring precise and efficient targeting. CAR-T cell therapy's success depends on selecting specific target antigens expressed on tumor cells while avoiding heathy tissues. Ideal antigens possess high expression levels in cancer cells, minimal presence in normal tissues, and essential in oncogenesis.

CD19 is among thoroughly investigated target antigens in CAR-T cell therapy, notably for hematologic malignancies like B-cell acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). As a B cell specific surface antigen expressed across all stages of B cell development, CD19 presents an attractive target for CAR-T cell therapy [4,7,9]. After recognizing antigens and receiving co-stimulatory

signals, activated CAR-T cells undergo clonal expansion to produce a strong effector cell population, capable of exerting cytotoxic activity against tumor cells.

CAR-T cells exert their anti-cancer impacts through diverse mechanisms, such as direct cell killing, release of cytokines, and attracting immune cells. When they encounter tumor cells displaying specific antigens, CAR-T cells activate various actions to eradicate cancerous cells and prompt tumor shrinkage. CAR-T cells demonstrate bystander killing effects, where nearby tumor cells without the target antigen are eradicated via a phenomenon called antigen spreading. This process is triggered by the release of cytokines and the presentation of tumor antigens by antigen-presenting cells (APCs), resulting in the activation of the body's own immune effector cells against the tumor cells. Although CAR-T cells exhibit strong antitumor capabilities, they can face resistance mechanisms within the tumor microenvironment. These include immunosuppressive cell populations like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), as well as inhibitory cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10). To counteract these resistance mechanisms, strategies involve employing combination therapies with immune checkpoint inhibitors, cytokine modulators, and targeted therapies aimed at disrupting immunosuppressive pathways.

Conclusion: CAR-T cells utilize a diverse array of effector mechanisms to specifically target and eradicate tumor cells, presenting a powerful and precise strategy for cancer immunotherapy.

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SUMMARY

Aim of the research was to study and analyze particularities of some key issue aspects of new immunotherapy challenges and perspectives by CAR-T Cell Therapy. Cancer immunotherapy encompasses a broad spectrum of therapeutic approaches, each directed towards distinct components of the immune system or the tumor microenvironment. Major categories include: Monoclonal Antibodies

(mAbs): These engineered antibodies target cancer cell antigens, inducing immune mediated destruction through mechanisms like antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). CAR-T cell therapy, a revolutionary cancer treatment, offers potentially long-lasting response in patients with challenging hematologic cancers, by genetically modifying a patient's own T cells to express chimeric antigen receptors (CARs), enabling them to identify and attack the cancerous cells without major histocompatibility complex (MHC) restrictions.

Keywords: New Immunotherapy, Challenges, Perspectives, CAR-T Cell therapy