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Cellular backpacks for macrophage immunotherapy- A Review

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Abstract

Worldwide, the most feared disease is cancer and more than 10 million people fall prey to it every year. For curing a disease, destroying the agent causing disease is required in the host, within the same environment. The utmost promising treatment is immunotherapy for cancer, and it has set a new pattern leading to many breakthroughs. Compared with norms of care such as chemotherapy, radiotherapy and surgery; immunotherapies like adoptive cellular immunotherapy, antibodies, vaccines, immune checkpoint inhibitors have achieved great heights in terms of its success rate and has brought remarkable growth in terms of quality of life and survival. There are limitations like adverse effects, inconsistent efficiency, and with regards to cancer low resistance and antitumor response rate, despite all the progress made. Between the in-built and adaptive immunity, co-operation is very crucial, for a long-lasting and efficacious antitumor response. Therapeutic approaches combined or based with macrophages were made in order to bypass these challenges, for the better treatment of various therapies to cure and reduce the severity of cancer. The role of macrophages and backpacks with the advancement of nanotechnology in current immunotherapy is vital for drug administration and will be an asset in the present era.

Keywords: Cellular Backpacks; Macrophages; Immunotherapy; Chimeric antigen receptor (CAR) -T cell therapy

1. Introduction

A revolutionized clinical approach to cancer treatment is made by immunotherapy. CAR T-cell therapy is the best example, that expresses CARs consisting of engineered T-cells. It is on the tip of a clinical revolution [1], by providing complete recovery to 90% patients suffering from leukaemia [2]. The positive results of this therapy depend on (i) previous learning and tumor-specific immunogens being present, (ii) liquid tumors and (iii) organizing and expanding the population of cell [3]. In order to succeed, cancer cells are killed by macrophages where tumor-specific immunogens are excess or unfamiliar and T-cell therapies are short in number [4]. However, the macrophages acceptance is decreased in immunotherapy once injected into the body by the shift of the protumoral phenotypes.

Here, in modern oncological medical chemotherapy, the clinical applications having a wide range are observed, reviewed and analyzed in detail. The types of cellular backpacks, macrophages, immunotherapy, their roles, advantages, limitations, and recent advances for macrophage drug delivery systems are defined and elaborately specified for better understanding about cancer immunotherapy.

2. Immunotherapy

In 2013, cancer immunotherapy was regarded as 'breakthrough of the year' and it has reformed the field of oncology [5]. It uses the immune system's specificity and killing mechanisms to target and eliminate cancerous cells.

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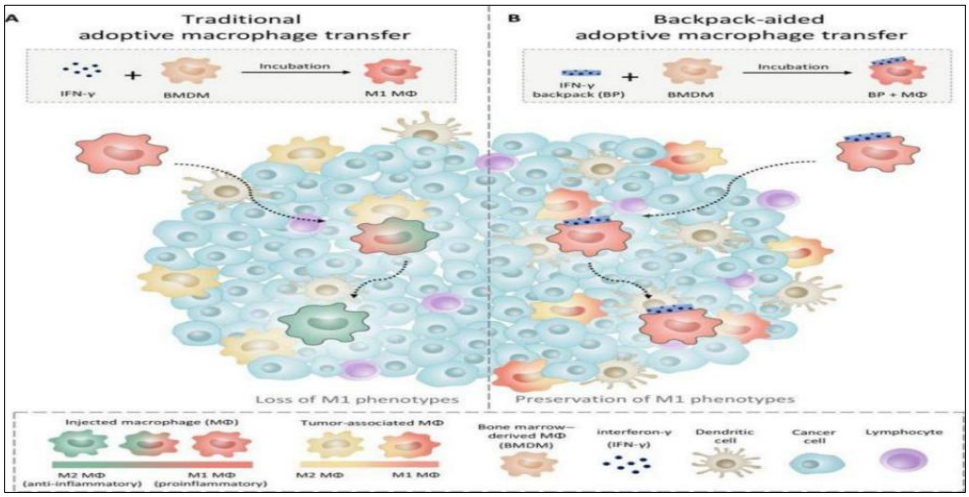
There are six pillars of immunotherapy, and the approach to use one or more kinds have led to Food and Drug Administration acceptance recently against many suggestions [6].

- Direct immune modulators: Immunomodulators by activating immune cells aids in protection and memory. To safeguard or for regeneration of tissues in case of autoimmune diseases, allergies, transplantation, recovery from an injury, to stop immune cell stimulation in an uncontrollable environment, immunomodulators can be utilized.
- Monoclonal antibodies: Nivolumab and Rituximab direct cell-intermediated toxin and is used to treat B-cell lymphoma, cyclophosphamide combination with these monoclonal antibodies led to elimination of tumor in bone marrow by macrophage activation [7].
- Checkpoint inhibitors: Anti-PD-1 and Anti-PD-L1 are generally used immune inhibitor therapies. To speed up T cells anti-tumor function, blocking these pathways with inhibitors is one way, which made progress in the malignancies resolution [8].
- Oncolytic viruses: Organisms that offer stabilization to the immune system, by an antitumor response are known as oncolytic viruses [9]. Viral vectors that treat cancer are adenoviruses that attach with great affinity to codocytes receptor [10]. They are used to treat prostate cancer, by using monotherapy and combination therapy with anti-PD-1or anti-PD-L1 inhibitors [11].
- Vaccines: To treat virus or bacterial infections, HBV and HPV are used as preventative vaccines that induces humoral immunity. Therapeutic vaccines such as artificial polypeptides, conjugated proteins, whole tumor cells, nucleic acids or bacteria were chosen as vaccines to stimulate T-cells through accessory cells [12].
- Adoptive-cellular therapies: Tumor regression is promoted by moving immune cells to the cancer-bearing host. To gain enough number in an artificial environment before administration they are controlled to hold intracellular functions in general [13].

2.1. Cellular backpacks

Here in cancer, TAMs adopt M2phenotypes because of the solid tumors immunosuppressive microenvironment [14], which is related to tumor growth, angiogenesis, metastasis, and chemotherapy resistance [15]. Macrophages revert to M2 phenotypes, once they are embedded into TME and the approaches that were made failed (Fig. 1A). To modulate the adoptively transferred macrophages phenotypes *in vivo*, strategies must be developed for therapeutic effects of macrophages.



Source: Shields CW 4th, Evans MA, Wang LL, Baugh N, Iyer S, Wu D, Zhao Z, Pusuluri A, Ukidve A, Pan DC, Mitragotri S. Cellular backpacks for macrophage immunotherapy. Sci Adv. 2020 Apr 29;6(18): eaaz6579. doi: 10.1126/sciadv. aaz6579. PMID: 32494680; PMCID: PMC7190308

Figure 1 Cellular backpacks for upholding pro-inflammatory nature of adoptive macrophage therapies. (A) After solid tumor penetration, macrophages diverged with IFN-γ in an artificial environment shift from proinflammatory to anti-inflammatory phenotype. (B) IFN-γ–loaded backpacks carried by macrophages to keep their proinflammatory phenotypes in the tumor micro-environment, changing the intrinsic TAMs phenotype

To modulate the adoptively transferred macrophages phenotypes *in vivo*, strategies must be developed for therapeutic effects of macrophages. "Backpacks" are soft disc-like particles that control the macrophages composition in vivo (Fig.1B). For durable storage, easy preparation, metabolic clearance for clinical translation backpacks were made from the biodegradable polymers and is organized with two surfaces of bio-compatible polymer poly(lactic-co-glycolic) acid,

by an inner 'filling' of polyvinyl alcohol and the cytokine interferon-gamma (IFNγ). It is selected, as it encourages pro-inflammatory response in macrophages and in several tumors where it reduces their sizes [16]. To make the backpacks more adherent, cell-adhesive layer was added at the end of the whole process.

Cellular backpacks are of different types, out of which a few were loaded with 'catalase' due to its antioxidant qualities and treats inflammation of brain [17–20]. Neurodegenerative diseases like Parkinson's and Alzheimer's, HIV-related neurocognitive disorders [21, 22], and stroke [23, 24] are dealt by macrophage based formulations. The different kind that is used in lymphoid tissue engineering as defined by Suematsu is an injectable backpack system [25].

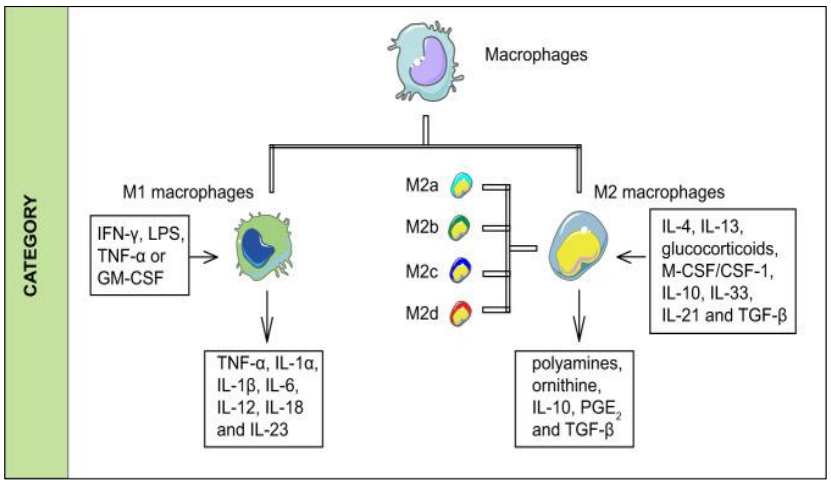
The cellular backpacks on macrophages are an experimental approach, that delays phagocytosis through disrupting the disease treatment, which is more precise than the small molecular drugs and discloses an engineered particle "BACKPACK" which a) adheres strongly to the surface of macrophage and regulates cellular make-up in the lab b) avoids endocytosis for many days c) secretes cytokines macrophages polarization in anti-tumor, antiviral, and auto-immunological ailments d) supports macrophages transfer to keep the phenotypes inside the solid neoplasms of immunosuppressive environment.

2.2. Macrophages

Macrophages are immune effector cells whose functional flexibility initiates protumor and antitumor functions which destroy the tumor-associated macrophages (TAMs). The macrophage [26], which protects against pathogens and maintains body equilibrium in the tumor microenvironment (TME), is the important part of mononuclear phagocyte system and TAMs helps in metastasis and growth of tumor by boosting proliferation of cancer cells, immunosuppression, invasion, tumor microenvironment regulation, and angiogenesis. TAMs increases tumor hypoxia and glycolysis [27], that are angiogenesis causing reasons [28, 29]. M2 macrophages release exosomes, responsible for metastasis in cancer cells by transferring miRNAs in colon cancer and ductal adenocarcinoma of pancreas [30, 31].

2.3. Categories

Macrophages are categorized into M1 (proinflammatory, traditionally activated macrophages) and M2 (anti-inflammatory, alternatively activated macrophages) based on composition and roles (Fig.2). Their phenotypic plasticity makes them a preferred candidate for addressing diseases of wide range [4]. Reactive oxygen species, nitric oxide, interleukin-12(IL-12), tumor necrosis factor-α (TNF-α), and other cytokines that generates inflammation are produced by M1 macrophages [32]. IL-1α, IL-1β, TNF-α, IL-6, IL-12, IL-18, and IL-23 are examples of cytokines secreted by M1 macrophages that increase inflammatory responses [33, 34]. A surplus of M1 macrophage responses cause damage of tissues, the reason of arterial sclerosis and other chronic inflammation [35, 36, 37]. Cytokines can stimulate M2 macrophages like IL-13, IL-4, M-CSF/CSF1, IL-10, IL-33, IL-21, glucocorticoids, and TGF-β [34-40]. M2a, M2b, M2c, and M2d are subcategories of M2 macrophages [41]. Macrophages promote pathogenesis when there are dysfunctional tissues to develop phenotypes [42].



Source: Duan Z, Luo Y. Targeting macrophages in cancer immunotherapy. Signal Transduct Target Ther. 2021 Mar 26;6(1):127. doi: 10.1038/s41392-021-00506-6. PMID: 33767177; PMCID: PMC7994399

Figure 2 Categories of macrophages

2.4. Advances in macrophage drug delivery systems

New self-assembling carriers for nanoscale drug delivery were recently designed to reduce constraints, escape detection by the mononuclear phagocyte system and extend circulation time. RBC, macrophages, neutrophils, lymphocytes, and tumor cells were used by humoral drug delivery has drawn attention [43,44], as they attack blood vessels during immune system clearance, stays inactive in the circulation, delivering nutrients to tissues, pathogen elimination, and delivering specific drugs [45].

2.5. Applications

- Anti-Inflammatory treatment: To attack inflammatory areas and normalize the inflammatory response macrophages were utilized as medicated agents or drug carriers.
- Therapeutic agents: Septic mice survival that are earlier injected into serous membrane with *E. coli*, can be improved when macrophage membrane-coated empty nanoparticles (NPs) are used as therapeutic agents [46].
- Anti-tumor therapeutic agents: TNF-α expressing macrophage membranes were encapsulated with empty chitosan NPs and the resultant particles hindered proliferation of tumor [47].
- Tumor imaging: Fluorescence-based imaging is to detect cancer in its initial stages and for the study of cancer metastases. Macrophage vesicles wrapping upconversion with NPs allows macrophage adhesion and targets the tumor [48].
- Anti-tumor therapy: Clinical anti-tumor drugs now causes side effects and do not target tumors. Anti-tumor medications such as Paclitaxel and Doxorubicin have been encapsulated into macrophages to decrease disadvantages [49, 50, 51].
- Anti-tumor drug delivery: Breast cancer lung metastasis is effectively inhibited by macrophage liposomes and resonating bismuth selenide nanoparticles [52, 53].
- Treatment of other diseases: For the intracellular parasite treatment Amphotericin-B was encapsulated in macrophage membrane vesicles [54]. A significant role in the compulsive course of atherosclerosis, is played by macrophages [55].

2.6. Advantages

2.6.1. Drug half-life prolongation and circulation time

- NPs encapsulated micro-vesicles: Rheumatoid arthritis target treatment stayed at the lesion site for more than 24 hours which indicates that it extends the drug's half-life [56].
- Gold nanoshells: This improves tumor photo-thermal treatment [57].
- Naked nanoshells: Disappears from the blood 24 hours' post-injection.

2.6.2. Biodegradability and biocompatibility

Polymer based nano-drug delivery systems: Until 30 days after IV, iron oxide NPs coated with macrophage membranes had not altered the weight or blood biochemistry of ICR mice, and pathology revealed no evident damage to major organs [58].

2.6.3. Improved medication stability and reduced immunogenicity

Nanocapsules encapsulated macrophages: Mesoporous silica nanocapsules is loaded with doxorubicin and encased by macrophage cell membranes, allowed nanoparticles for evading immune response and reduced drug uptake [59].

2.6.4. Sustained drug release

Macrophage-nanozyme delivery system: In Parkinson's disease treatment, naked catalase degraded rapidly, while the enzyme catalase that is loaded into macrophage-nanozyme delivery system permitted to release in a fast and active form for more than a day.

2.6.5. Improvement of drug targeting ability

Macrophage-mediated drug delivery system: Drug incorporated with liposome in a macrophage cell membrane that was twice that of naked liposomes showed anti-tumor breast activity [60].

2.6.6. Delivery of Various Substances:

Macrophages can also be incorporated with nanozymes and variety of natural small-molecule medicines while maintaining biological function.

3. Discussion

Altogether, these studies might shortly pave ways to a new scientific direction within the higher prognosis successful treatment of human malignancies, a dreadful curse to the global population, with the help of adoptive cellular immunotherapy. Future enthusiastic researchers, have a great opportunity for the investigation of the optimal loading of IFN-γ into cellular backpacks for the therapeutic beneficiary. Macrophage drug delivery systems has more advantages over standard drug delivery, but many of them used to form these delivery systems reduced their clinical use and macrophages storing is a big obstacle for mass- production. To make progress, these tasks have to be looked upon to bring the macrophage delivery systems faster to the clinic in future.

4. Conclusion

In the long run of cancer immunotherapy, backpacks may be combined with adjuvant therapies to reduce side effects, improve therapeutic effects, and improve the target therapy. Cancer immunotherapy could depend on combination therapy using checkpoint inhibitors, personalized cancer vaccines and novel target therapies directed on the tumor microenvironment. It is believed that tumor associated macrophage cure is essential to immunotherapy with an insightful learning about variety of macrophages by single-cell sequencing and different techniques. Innovations in these particular fields probably expand in next-generation immunotherapies for dealing with types of diseases and scenarios in wound healing, oncology, autoimmunity, transplantation of organs, communicable diseases, drug resistance, and regenerative medicine.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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