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CD204-Targeted Liposomal Nanoparticles for Macrophage Repolarization in Cancer Immunotherapy: Current Approaches, Challenges, and Future Perspectives

Mennatallah Abdelmaqsoud
m36782595@gmail.com

ABSTRACT

Tumor-associated macrophages, predominantly exhibiting an M2-like phenotype, are considered a crucial component of the immunosuppressive tumor microenvironment, driving tumor progression, angiogenesis, and metastatic dissemination. CD204 (macrophage scavenger receptor 1, MSR1) is markedly upregulated on M2-like TAMs, functioning not only as a phenotypic marker but also as a critical modulator of immune suppression and tumor-supportive processes. Therapeutic targeting of CD204 offers a strategic way to reprogram TAMs toward a proinflammatory M1-like phenotype, thereby restoring anti-tumor immunity. Liposomal nanoparticles (LPs), engineered with surface functionalization such as anti-CD204 antibodies or mannose ligands, provide a selective and efficient delivery platform for therapeutic payloads. Among these, small interfering RNA (siRNA) enables precise intracellular gene silencing, inhibiting STAT6-mediated M2 polarization and reducing the secretion of immunosuppressive cytokines, including IL-10 and TGF-β. This combinatorial approach of receptor-targeted nanoparticle delivery and gene-silencing payloads effectively modulates TAM phenotype, reshapes the tumor immune milieu, and enhances cytotoxic T-cell-mediated antitumor responses. CD204-directed liposomal immunotherapy represents a promising paradigm in cancer treatment, offering the potential to overcome immune evasion mechanisms and improve clinical outcomes.

INTRODUCTION

Cancer remains one of the leading causes of death worldwide. This is mainly due to the difficulty of early detection and the ability of cancer cells to spread and develop rapidly. Conventional treatment strategies such as chemotherapy and radiotherapy have several limitations and side effects on the patients' health. Chemotherapy may cause severe side effects such as hair loss, fatigue, and general health problems. Radiotherapy influences the patient's health and may lead to damage of cells and tissues. Therefore, the development of more effective and targeted therapeutic strategies has become an important focus in cancer research. In this context, the tumor microenvironment plays a critical role in cancer development

and progression.

Tumor-associated macrophages are among the most abundant immune cell types in the tumor microenvironment. Macrophages have an essential role in the formation of the immunosuppressive microenvironment surrounding the tumor. Numerous studies have demonstrated that macrophages can be broadly classified into two main types: the M1-like macrophages and the M2-like macrophages. In many solid tumors, these macrophages predominantly exhibit an M2-like phenotype, which contributes to immune suppression, tumor progression, and metastasis. In contrast, M1-like macrophages exhibit pro-inflammatory and anti-tumor signals to activate cytotoxic T-cells. As a result, the balance between their percentages in the tumor microenvironment is crucial in determining the progression or repression of cancer. Therefore, tumor-associated macrophages have emerged as one of the most crucial therapeutic targets in cancer biology.

The immune system plays a dual role in cancer regulation. It can both suppress tumor growth and promote tumor progression under certain conditions. Within the tumor microenvironment (TME), numerous immune cells interact with cancer cells and other components to shape the tumor's development and response to therapy. Among these, tumor-associated macrophages (TAMs) represent one of the most abundant and influential immune cell types. TAMS exhibit functional plasticity, meaning they can adopt different phenotypes that either support tumor growth or enhance anti-tumor immunity. Their abundance makes them key regulators in the TME, influencing processes such as angiogenesis, immune suppression, and metastasis. Understanding the complex role of TAMs is therefore crucial for developing innovative cancer immunotherapies and designing strategies that can manipulate the immune system to improve patient outcomes.

Tumor-associated macrophages (TAMs) are very important cells in the tumor microenvironment. Some of these cells help the tumor grow, while others try to stop it. One receptor on TAMs, called CD204, is found a lot on the M2-like macrophages. This receptor is linked to worse outcomes for patients and makes the tumor stronger. Targeting CD204 could help change the M2-like cells into M1-like cells, which fight the tumor. This could make the body's immune system stronger against cancer and make treatments work better.

Nanotechnology can help deliver drugs directly to these macrophages. Liposomal nanoparticles are tiny carriers that can carry molecules like siRNA and protect them from breaking down in the blood. They can also be modified, for example by PEGylation, to stay longer in the body and avoid the immune system. Using these nanoparticles can make therapies more accurate and help change the macrophages in a way that supports the body in fighting cancer.

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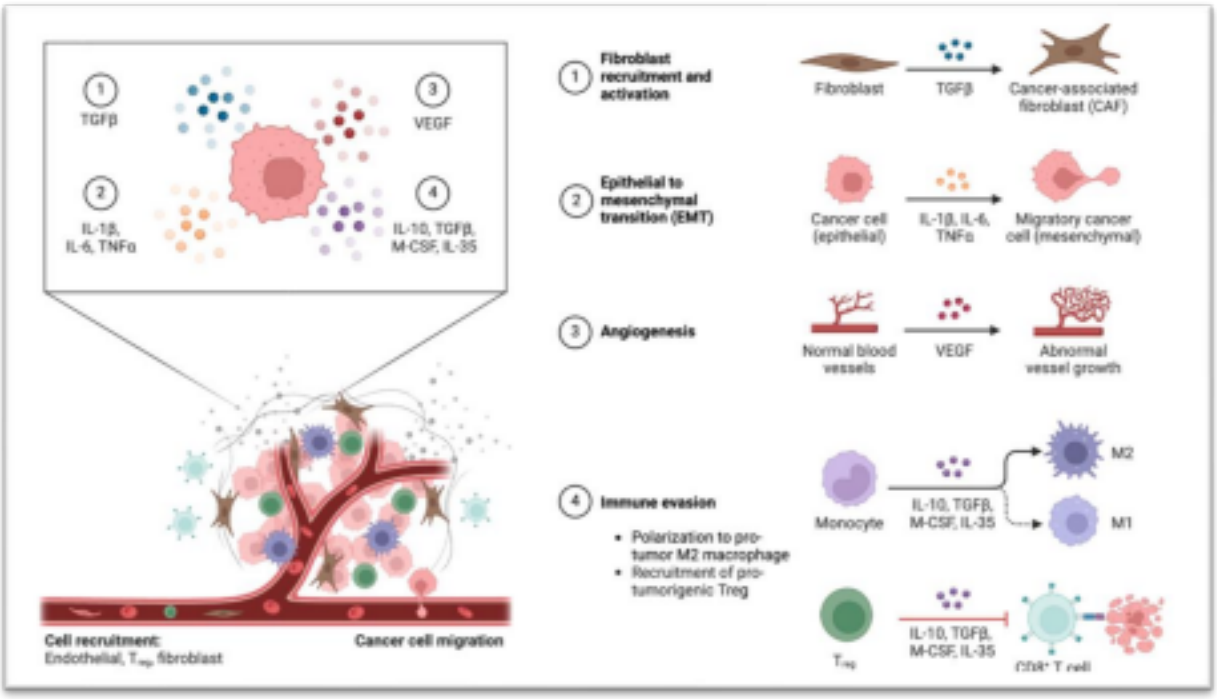

Figure 1. Overview of the tumor microenvironment (TME) and its role in cancer progression.
The TME consists of cancer cells, immune cells, fibroblasts, and endothelial cells that interact through signaling molecules such as TGF-β, IL-6, TNF-α, and VEGF. These interactions promote fibroblast activation, epithelial–mesenchymal transition (EMT), angiogenesis, and immune evasion. Tumor-associated macrophages (TAMs) are polarized toward a pro-tumoral M2-like phenotype, contributing to immunosuppression and tumor progression.

LITERATURE SEARCH METHODOLOGY

This narrative review was developed through a structured literature search conducted between December 2025 and April 2026. Relevant literature was identified using multiple scientific databases and academic search platforms, including PubMed and Google Scholar, together with additional full-text articles accessed through institutional library resources, including the Oberlin College Library as well as other scholarly databases.

The search strategy combined keywords and Boolean operators related to the main concepts of this review, including "*CD204*," "*SCARA1*," "*tumor-associated macrophages (TAMs)*," "*macrophage repolarization*," "*liposomal nanoparticles*," "*siRNA*," "*nanotechnology*", and "*cancer immunotherapy"*. Various keyword combinations were used to identify studies addressing macrophage-targeted drug delivery, intracellular gene silencing, and immunomodulatory strategies in cancer.

The reference lists of relevant review articles were also manually screened to identify additional eligible studies that may not have been retrieved during the initial database search.

A broad range of original research articles and review papers published in English were initially screened to ensure comprehensive coverage of the topic. Following critical evaluation for scientific quality, relevance, and recency, the most pertinent studies were selected and incorporated into this review. Priority was given to peer-reviewed studies investigating CD204-targeted therapies, macrophage biology, liposomal nanocarriers, and related signaling pathways. Conference abstracts, non-English publications, and studies not directly relevant to macrophage repolarization or CD204-targeted nanomedicine were excluded where appropriate.

LITERATURE REVIEW

Tumor-Associated Macrophages (TAMs):

Naturally, macrophages are cells found in the innate immune system and have an essential role in the host immune system. The tumor microenvironment, which surrounds the cancerous cells, is a complex and dynamic ecosystem that contains interacting components such as malignant cells, immune cells, extracellular matrix, signaling molecules, and blood vessels. Macrophages that infiltrate the tumor are known as tumor-associated macrophages (TAMs).

These cells aren't accumulated in the tumor microenvironment randomly. Cancer cells actively secrete chemokines that guide monocytes toward the tumor site. Among these molecules, C-C motif chemokine ligand 2 (CCL2) plays a crucial role in promoting immune cell infiltration. This recruitment is predominantly of pro-tumorigenic immune cells, as circulating monocytes are chemo-attracted to the tumor, where they differentiate into **TAMs** and are polarized towards a pro-tumorigenic phenotype.

The persistence of TAMs is driven by tumor-derived growth factors. Among these factors, colony stimulating factor 1 (CSF-1) significantly contributes to macrophage expansion and long-term maintenance within the tumor microenvironment.

Angiogenesis is the process through which tumors stimulate the formation of new blood vessels to supply the tumor with nutrients and oxygen. This environment significantly affects macrophage behavior. Macrophages participate in pathogen clearance, regulate inflammatory responses, and contribute to wound healing. One of the defining characteristics of macrophages is their remarkable

phenotypic plasticity. This characteristic enables them to alter their functional phenotype in response to the environmental signals. Tumors exploit this plasticity to support their progression.

TAMs represent a major immune cell population within many solid tumors. Currently, macrophages are broadly classified into two functional phenotypes, M1-like and M2-like phenotypes. Classically, M1 cells are stimulated by pro-inflammatory signals such as interferon-gamma (IFN-γ). They produce inflammatory cytokines, including interleukin-12 (IL-12) and tumor necrosis factor-alpha (TNF-α). These cells enhance antigen presentation and activate cytotoxic T cells. In contrast, M2 macrophages are induced by IL-4 and IL-13 production. These macrophages also secrete IL-10 and transforming growth factor-beta (TGF-β). Additionally, they promote angiogenesis and support tumor cell survival. They also suppress cytotoxic immune responses. Generally, in many solid tumor types, TAMs predominantly exhibit an M2-like phenotype. However, M1-like phenotypes may still be present at lower frequencies.

The predominance of M2-like TAMs contributes to immunosuppression, tumor progression, and metastasis in addition to remodeling of the tumor microenvironment. Immunosuppression is the reduction in cytotoxic immune cell activity. It also allows the cancer cells to evade immune attack, which facilitates local invasion and metastatic dissemination. Due to their abundance within tumors and their strong influence on immune regulation, TAMs have emerged as attractive therapeutic targets in cancer research.

CD204 receptor as a potential target on TAMs:

Macrophage scavenger receptor 1 (MSR1), which is also named CD204, is a class A scavenger receptor that is primarily expressed on the surface of macrophages. It is highly expressed on M2-like TAMs, contributing to an immunosuppressive tumor microenvironment, angiogenesis, and tumor progression. The CD204 receptor plays critical roles in immune regulation, including endocytosis, ligand binding, and lipid uptake. Through these mechanisms, CD204 contributes to macrophage-mediated clearance of modified lipoproteins and apoptotic cells, while also shaping immune signaling pathways within the tumor microenvironment. It forms homotrimeric structures on the cell surface and participates in multiple signaling pathways involved in immune regulation. This receptor is involved in processes such as atherosclerosis, innate and adaptive immunity, lung and liver disease, and more recently, cancer.

The immunosuppressive function of CD204-expressing TAMs is mediated through multiple molecular and cellular mechanisms within the tumor microenvironment. CD204 expression has been associated with a protumoral macrophage phenotype, where higher receptor levels are associated with increased M2-like polarization and enhanced secretion of anti-inflammatory cytokines.

CD204 is not merely a marker but also a functional driver of tumor progression. Recent studies suggest that targeting CD204 can alter macrophage polarization and potentially reprogram TAMs from a pro-tumoral M2-like phenotype toward a tumoricidal M1-like phenotype. High CD204 expression has been correlated with poor prognosis in several cancers. Elevated CD204 expression has been reported in multiple malignancies, including breast cancer, lung cancer, ovarian cancer, and glioma. It also helps

in tumor growth and metastasis. Elevated levels of CD204-positive TAMs are frequently observed in aggressive tumors.

These characteristics make it a suitable target for delivering nanoparticles or drugs to TAMs. Therefore, CD204 has emerged as a promising therapeutic target for macrophage-directed cancer immunotherapy and targeted nanomedicine strategies.

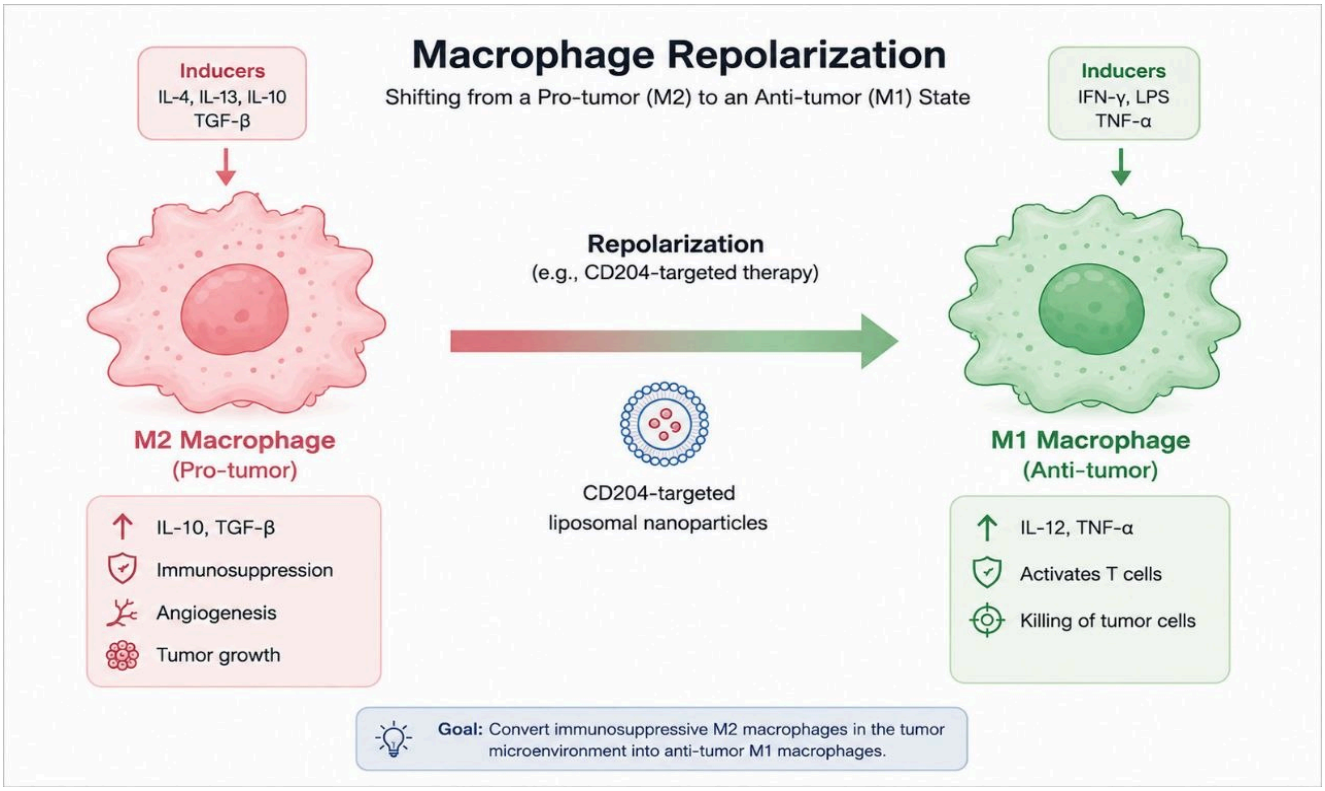

Figure 2. An overview of polarization of tumor-associated macrophages from an M1-like phenotype into an M2-like phenotype. Tumor-associated macrophages (TAMs) predominantly display an M2-like polarization within the tumor microenvironment (TME), producing high levels of IL-10, TGF-β, and arginase-1, which suppress cytotoxic T-cell activity and promote tumor progression. In contrast, M1-like macrophages exhibit a pro-inflammatory polarization, secreting IL-12 and TNF-α, enhancing antigen presentation, and activating cytotoxic T cells. CD204-targeted liposomal nanoparticles selectively deliver payloads to M2-like TAMs, modulating their polarization toward an M1-like phenotype, thereby restoring anti-tumor immune responses.

<u>Liposomal Nanoparticles in Cancer Immunotherapy:</u>

Liposomal Nanoparticles (LPs) are spherical, biocompatible vesicles composed of phospholipid bilayers

that can encapsulate therapeutic agents. Their structural versatility allows for functionalization with targeting ligands, enhancing selective delivery to specific cell populations such as TAMs. Functionalization, which is known as surface modification, is required to enhance their specificity toward target cells within the TME. Ligands are conjugated with the liposomal surface to help achieve selective targeting. These ligands bind to the overexpressed receptors on the M2-like phenotype.

Some conventional liposomes lack intrinsic cell specificity, so advanced surface functionalization approaches have been designed to improve selective targeting of TAMs by exploiting receptor overexpression patterns within the tumor microenvironment. By attaching anti-CD204 antibodies or specific peptides to the liposome surface, nanoparticles can bind to the TAMs and be internalized via receptor-mediated endocytosis. This enhances cellular uptake efficiency, improves target specificity, and reduces off-target toxicity.

On the one hand, M2 macrophages also hyperexpress the mannose receptor (CD206). Mannose-functionalized liposomes exploit this characteristic, leading to enhanced uptake by pro-tumoral macrophages. In addition, folate receptor targeting represents another strategy, as certain TAM populations and tumor cells express folate receptors. Folate-modified liposomes, therefore, improve tumor localization and intercellular internalization.

Despite the advantages of receptor-immediate targeting, unmodified liposomal nanoparticles are rapidly recognized and cleared by the mononuclear phagocyte system, significantly limiting their therapeutic efficacy. Therefore, PEGylation has been a good solution for such a problem. PEGylation is the attachment of polyethylene glycol (PEG) chains to the liposome surface. It has a critical role in the elongation of the period that liposomes can stay inside the body without being discovered by the immune system. It creates a hydrophilic steric barrier, reduces protein adsorption, decreases immune recognition, and prolongs circulation time. About **the Enhanced Permeability and Retention** effect (EPR) influence, the tumor blood vessels are leaky, so nanoparticles accumulate more in the tumor tissues. However, although PEGylation improves pharmacokinetic stability, repeated administrations may induce anti-PEG antibodies, potentially reducing long-term therapeutic efficiency.

Liposomal nanoparticles are not just for the transport of the payload to the tumor microenvironment; it is more than that. Beyond its surface engineering and circulation enhancement, the therapeutic efficacy of liposomal nanoparticles largely depends on the classification and nature of their encapsulated payload. Strategic payload design enables selective modulation of TAM function, particularly in shifting pro-tumoral M2-like macrophages toward an anti-tumoral M1-like phenotype. The payload is the most essential component in the liposomal nanoparticles. It is considered the active ingredient that is used to repolarize the TAMs from the M2-like phenotype toward the M1-like phenotype.

The first payload type can be cytokines such as IFN-γ or IL-12. Normally, M1-like macrophages are activated at the same time the STAT1 pathway is activated. The STAT1 pathway is activated by IFN-γ, which leads to T cell activation, antigen presentation, and secretion of high amounts of IL-12 and

TNF-α. Easily, IFN-γ can be injected directly into the blood, yet this leads to systemic toxicity. At the same time, the possibility that this load reaches the tumor microenvironment successfully is low. Using the same payload within a liposomal nanoparticle makes it arrive specifically in the tumor microenvironment.

The second type of payload is the small molecule inhibitors. This type of payload does not influence the M1-like macrophages. It only works on the M2-like macrophage. This inhibits the factors that enhance M2 polarization. M2 polarization occurs when IL-4 and IL-13 activate the STAT6 pathway. Inhibiting the STAT6 pathway or PI3K γ activation, the M2-like macrophage polarization will be reduced. This process occurs without any impact on M1-like macrophages.

Gene-silencing approaches represent a more precise strategy compared to conventional immunomodulation. Small interfering RNA (siRNA) is the payload used during this process. It is considered the most advanced type of payload in the main categories. The merit of this process is that it directly stops the responsible gene from working, compared to the other ways that target activation or inhibition of some substances.

Intracellular Reprogramming Mechanism:

Macrophage repolarization is governed by tightly regulated intracellular signaling pathways. Also, its phenotype is selected according to transcription factors. The M2 state is maintained through STAT6 activation, while the M1 state is driven by STAT1 signaling. Activation of STAT6 activates immunosuppressive genes that keep the M2 identity. Instead of activating pro-inflammatory pathways, gene-silencing approaches aim to suppress the molecular drivers that maintain the M2 macrophage.

Liposomal nanoparticles enter the macrophages via receptor-mediated endocytosis, such as CD204. Then, the liposomal nanoparticle stays inside the endosomes for a short period. After that, the siRNA payload escapes from the liposomal nanoparticle and reaches the cytoplasm of the cell in a process called endosomal escape. Following that, the siRNA payload binds with the RNA-induced silencing complex (RISC) protein. RISC protein uses siRNA as a guide to find the mRNA of the cell. Once the RISC complex identifies the target mRNA, it cleaves the sequence, leading to mRNA degradation. This also results in the failure of the gene that is responsible for the activation of M2-like macrophage polarization. siRNA is put in liposomal nanoparticles and not directly injected into the blood because it is very small and breaks down in the blood flow. Moreover, its negative charge makes it unable to go through the cytoplasm of the cell. Using the liposomal nanoparticle protects it from degradation and makes it easier to enter the cell.

IL-10, TGF-β, arginase-1, and STAT6 make M2 macrophages immunosuppressive and pro-tumoral. Reducing IL-10 production, decreasing arginase-1 activity, restoring pro-inflammatory responses, or attenuating STAT6 signaling leads to continuous actions such as inhibition of protein translation, decreased immunosuppressive signaling, reduced tumor support, and finally the conversion into an M1-like phenotype. This approach enables direct modulation of the intracellular signaling network

governing macrophage phenotype.

Therefore, combining CD204-targeted liposomal nanoparticles with siRNA-mediated gene silencing represents a promising strategy for selective reprogramming of tumor-associated macrophages and restoration of anti-tumor immune responses.

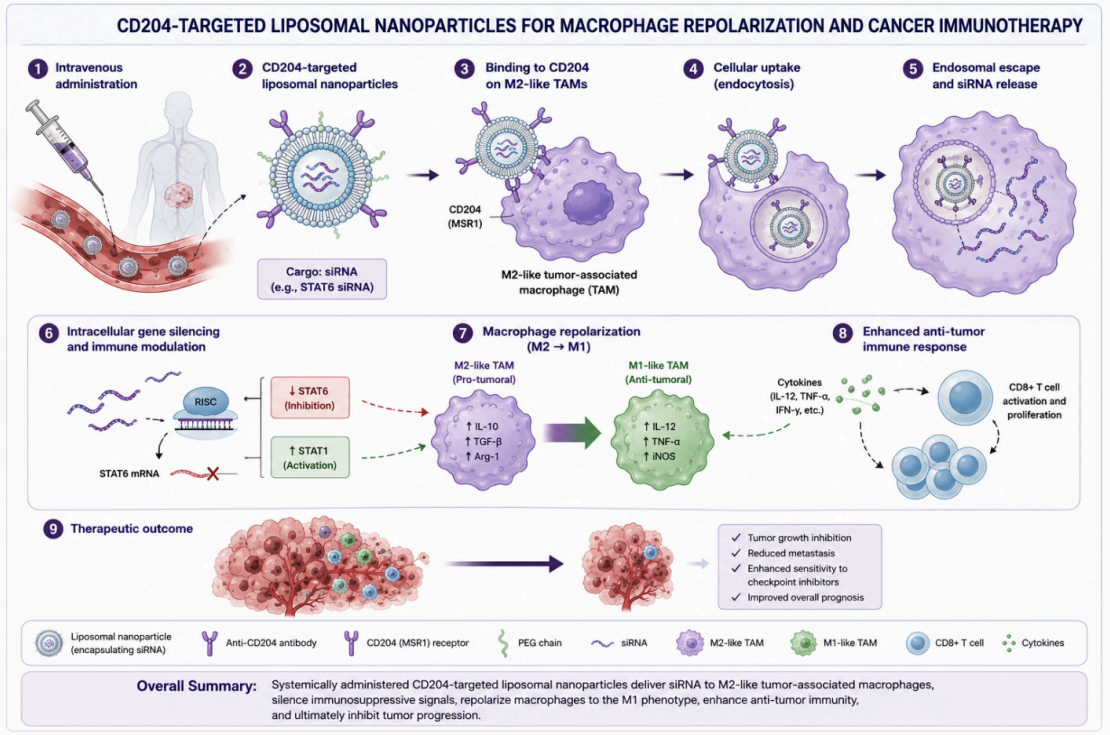

Figure 6. Overview of the therapeutic mechanism of CD204-targeted liposomal nanoparticles in cancer immunotherapy. Following systemic administration, CD204-targeted liposomal nanoparticles selectively deliver siRNA to M2-like tumor-associated macrophages, promoting macrophage repolarization, enhancing anti-tumor immunity, and inhibiting tumor progression.

DISCUSSION

Tumor-associated macrophages are among the most abundant immune cell types in the tumor microenvironment. Macrophages have an essential role in the formation of an immunosuppressive microenvironment. Numerous studies have demonstrated that macrophages can be broadly classified into two main types: the M1-like macrophages and the M2-like macrophages. In many solid tumors, these macrophages predominantly exhibit an M2-like phenotype, which contributes to immune suppression,

tumor progression, and metastasis. Therefore, tumor-associated macrophages have emerged as one of the most crucial therapeutic targets in cancer biology.

The surface of tumor-associated macrophages contains several structures, including receptors. Some of these receptors can be used as therapeutic targets in cancer biology. One of these receptors is the macrophage scavenger receptor 1 (MSR1), which is also known as CD204. The CD204 receptor is highly expressed on the surface of the M2-like macrophages. This receptor is associated with tumor progression and poor prognosis. In addition, it can be utilized in targeted drug delivery systems. Therefore, it is considered one of the most important receptors, which is related to TAMS.

Nanotechnology-based drug delivery systems, especially liposomal nanoparticles, have shown significant results in improving the precision and efficiency of cancer immunotherapy. Liposomal nanoparticles are nanocarriers that can encapsulate various molecules, including nucleic acids, cytokines, and many small-molecule inhibitors. In addition, they contain a phospholipid bilayer structure that provides protection for the fragile molecules, such as siRNA, from degradation in the bloodstream. Furthermore, some strategies, such as PEGylation, enhance their stability and prolong the circulation time in the body by reducing immune system recognition.

Among the various therapeutic payloads that have been used in TAM modulation, gene-silencing approaches using small interfering RNA (siRNA) represent one of the most precise strategies. Unlike the conventional therapies that suppress the immune responses or inhibit the activation of M1-like macrophages, siRNA-based therapies directly inhibit genes involved in macrophage repolarization. This occurs through inhibition of the STAT6 signaling pathway and activation of the STAT1 pathway. As a result, the M2-like phenotype is suppressed while the polarization of the M1-like phenotype is activated. Additionally, this shift can enhance cytotoxic T-cell responses and strengthen anti-tumor immunity.

Despite the promising results, several challenges and limitations remain and require further investigations and efforts in scientific research. These challenges include endosomal escape, tumor heterogeneity, efficient intracellular delivery, and the development of anti-PEG antibodies. However, the ongoing advances and developments in nanotechnology and immunotherapy may lead to the development of combination therapies, such as checkpoint inhibitors, which may influence cancer treatment effectively.

Although several macrophage-targeting receptors, including CD204, CD206, and the folate receptor, have been investigated for macrophage-targeted therapy, CD204 appears to offer several potential advantages because of its strong association with the immunosuppressive M2-like macrophage phenotype and its involvement in tumor progression. However, CD206 has also demonstrated encouraging preclinical results, although its expression is less restricted to tumor-associated macrophages, which may reduce targeting specificity. Similarly, folate receptor-targeted approaches have shown potential in selected tumor types but may be influenced by differences in receptor expression among cancers. Therefore, CD204-targeted liposomal nanoparticles may provide a more selective strategy for macrophage

repolarization. Nevertheless, current evidence for all of these approaches remains largely limited to preclinical studies, and further comparative investigations and well-designed clinical studies are required to determine the most effective strategy for future clinical translation.

LIMITATIONS

Although CD204-targeted liposomal nanoparticles have shown promising potential for macrophage repolarization, several challenges still need to be addressed. The heterogeneity of the tumor microenvironment and the variability of CD204 expression among different tumor types may affect the targeting efficiency of this strategy. In addition, efficient nanoparticle delivery and sufficient accumulation within tumor tissues remain major challenges despite the advantages of liposomal nanoparticles. Another important limitation is the difficulty of endosomal escape, which may reduce the intracellular release and activity of therapeutic payloads such as siRNA.
Furthermore, repeated administration of PEGylated liposomes may induce anti-PEG immune responses that could reduce therapeutic efficacy. Finally, most of the available evidence is still based on in vitro studies and animal models, while clinical studies evaluating CD204-targeted liposomal therapies remain limited. Therefore, further preclinical investigations and well-designed clinical studies are required to validate the safety, efficacy, and clinical applicability of this therapeutic strategy.

CONCLUSION

In conclusion, this literature review highlights the critical role of tumor-associated macrophages in shaping the tumor microenvironment, contributing to immunosuppression and tumor progression. Additionally, targeting the CD204 receptor represents a novel strategy for macrophage repolarization, primarily through the use of liposomal nanoparticles as targeted delivery systems for therapeutic payloads. The use of siRNA as a gene-silencing payload further represents a promising approach for regulating the genes involved in maintaining the pro-tumor M2 macrophage phenotype.

Current preclinical studies have demonstrated encouraging results regarding the potential of CD204-targeted liposomal nanoparticles to enhance macrophage repolarization and improve anti-tumor immune responses. However, the available evidence remains largely limited to in vitro studies and animal models, and further investigation is required before these findings can be translated into clinical practice. Future research should focus on addressing the current challenges associated with nanoparticle delivery, tumor heterogeneity, long-term safety, and clinical validation to fully determine the therapeutic potential of this strategy in cancer immunotherapy.

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