Emerging nanomaterials targeting macrophage adapted to abnormal metabolism in cancer and atherosclerosis therapy (Review)

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Abstract. Macrophages, as highly heterogeneous and plastic immune cells, occupy a pivotal role in both pro-inflammatory (M1) and anti-inflammatory (M2) responses. While M1-type macrophages secrete pro-inflammatory factors to initiate and sustain inflammation, M2-type macrophages promote inflammation regression and uphold tissue homeostasis. These distinct phenotypic transitions in macrophages are closely linked to significant alterations in cellular metabolism, encompassing key response pathways such as glycolysis, pentose phosphate pathway, oxidative phosphorylation, lipid metabolism, amino acid metabolism, the tricarboxylic acid cycle and iron metabolism. These metabolic adaptations enable macrophages to adapt their activities in response to varying disease microenvironments. Therefore, the present review focused primarily on elucidating the intricate metabolic pathways that underlie macrophage functionality. Subsequently, it offers a comprehensive overview of the current state-of-the-art nanomaterials, highlighting their promising potential in modulating macrophage metabolism to effectively hinder disease progression in both cancer and atherosclerosis.

Contents

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1. Introduction

Macrophages can differentiate into distinct phenotypes in response to various stimuli. The two distinct polarized states of macrophages are M1-type and M2-type, each displaying unique functional characteristics. M1-type macrophages, activated by lipopolysaccharides (LPS) and interferon-gamma (IFN-γ), play an active role in promoting the formation and rupture of unstable atherosclerotic plaques, pathogen resistance and tumor control mainly through innate and adaptive immune responses (1,2). These macrophages upregulate inflammatory genes such as nuclear transcription factor-κB (NF-κB) signal expression, leading to proinflammatory responses and the release of cytokines like IL-1, IL-1β and TNF-α (3-6). By contrast, M2-type macrophages induced by IL-4 or IL-13 express high levels of the mannose receptor (MR, also known as CD206), IL-1 receptor (IL-IR), and C-C motif chemokine ligand 17 (CCL17). They also secrete pro-fibrosis factors and exhibit high arginase-1 (ARG-1) activity. The distinct characteristics of M2-type macrophages contribute to their involvement in various physiological and pathological processes, including pathogen and parasite clearance, anti-inflammatory reactions, wound healing, tissue remodeling and immune regulation (1,7-10). The plasticity of macrophages in the microenvironment underscores the critical role of their polarization state in determining their function in different diseases. Consequently, the regulation of macrophage polarization represents a significant therapeutic target for macrophage-based treatments across a range of diseases.

The polarization state of macrophages is intricately linked to alterations in various metabolic processes, including glycolysis, the pentose phosphate pathway (PPP), oxidative phosphorylation (OXPHOS), lipid metabolism (synthesis and oxidation

of fatty acids), amino acid metabolism, the tricarboxylic acid (TCA) cycle and iron metabolism. M1-type macrophages rely on glycolysis, PPP, heightened fatty acid synthesis (FAS), and iron retention to generate nitric oxide (NO) and sustain an inflammatory response. Nevertheless, their TCA cycle and OXPHOS are dysfunctional. By contrast, M2-type macrophages predominantly fulfill an anti-inflammatory role by enhancing fatty acid oxidation (FAO), OXPHOS and glutamine metabolism, while decreasing PPP activity (11,12).

Targeting macrophage in metabolic regulation has emerged as a pivotal strategy for addressing metabolic disorders. Advanced nanomaterials offer unique advantages in targeting macrophage metabolism for disease treatment, including independence from the microenvironment, enhanced immune activity and minimal side effects. These nanomaterials can be composed of organic materials (lipids, peptides, glycosylated compounds, hyaluronic acid, or nucleic acids), as well as metals, inorganic materials (iron oxides and gold), or combinations of these materials. The utilization of nanomaterials to regulate metabolic abnormalities, such as glycolysis, lipid metabolism, iron metabolism and glutamine metabolism, has emerged as a promising therapeutic strategy (13-16). For instance, polymer composites have been designed to modulate macrophage glycolysis signals, reverse the immunosuppressive phenotype of tumor-associated macrophages (TAMs), and regulate the immunosuppressive tumor microenvironment (TME) in the past few years (17). This approach introduces an innovative strategy for targeting macrophage metabolism using nanomaterials to treat diseases.

The present review provided a comprehensive overview of state-of-the-art nanomaterials targeting macrophage polarization for the treatment of metabolic diseases. More specifically, the intrinsic connection between macrophage metabolism and polarization was initially discussed. Subsequently, emphasis was given to describing how advanced nanomaterials are utilized to mitigate the progression of the disease including cancer and atherosclerosis by regulating macrophage metabolism.

2. Macrophage metabolism

Typically, M1-type macrophages exhibit elevated glycolysis, PPP activity, FAS and iron storage. Conversely, M2-type macrophages predominantly rely on OXPHOS, glutamine metabolism and fatty acid oxidation (FAO) (as shown in Table I). It is essential to target macrophage metabolism for regulating macrophages in the microenvironment of the lesion. In the following sections, a detailed review of the metabolic processes associated with macrophages will be provided.

Glycolysis. Glycolysis is a vital metabolic pathway in macrophages, responsible for converting glucose into lactic acid and generating a limited quantity of ATP through anaerobic metabolism. Glycolysis is indispensable for glucose metabolism and breakdown in macrophages, and the enhancement of glycolysis results in M1-type polarization. Following bacterial infection or activation by LPS, macrophages elevate glucose uptake, displaying augmented aerobic glycolysis. Within the cytoplasm, glucose undergoes enzymatic processing, ultimately resulting in the generation of pyruvate and ATP (18).

Pyruvate can be further converted to lactic acid by lactate dehydrogenase (LDH), or enter the mitochondria to participate in TCA cycle (19). In the TCA cycle, pyruvate is transformed into citrate, which is subsequently transported to the cytoplasm to generate acetyl-CoA, a precursor molecule that enhances the expression of genes encoding inflammatory molecules through histone acetylation (20). The metabolic transition from OXPHOS to glycolysis is evident in classically activated M1-type macrophages, promoting lactic acid synthesis and the secretion of inflammatory mediators, thereby contributing to the inflammatory response (21,22).

Lactic acid, a byproduct of glycolysis, has the potential to enhance pyruvate kinase activity and facilitate the polarization of macrophages toward a reparative phenotype (23). Elevated lactic acid concentrations have the capacity to hinder glycolysis in immune cells, decrease the extracellular acidification rate, and augment the oxygen consumption rate. Lactic acid may additionally impede the activation of YAP and NF-κB in the inflammatory process through GPR81-mediated signaling, thus inhibiting the pro-inflammatory response of LPS-stimulated macrophages (24).

The flux of glycolysis is regulated by a range of enzymes, including glycolytic enzyme and pyruvate kinase (PKM1/PKM2). Hypoxia-inducible factor 1α (HIF-1α) is a metabolic regulator that, when overexpressed, increases the expression of glycolysis-related genes. It upregulates glucose uptake by stimulating the expression of glucose transporters (such as GLUT1), as well as genes involved in glycolysis, such as hexokinase 2, PK and LDHA. Ultimately, HIF-1α mediates M1 type polarization of macrophages (25,26).

PPP. The PPP is a metabolic pathway that plays a critical role in nucleotide synthesis and the generation of NADPH (nicotinamide adenine dinucleotide phosphate). NADPH functions as a crucial cofactor in diverse cellular processes, encompassing lipid biosynthesis and the production of NO and reactive oxygen species (ROS). Activated by LPS and IFN-γ, the PPP is upregulated, leading to increased synthesis of NADPH in macrophages. The enhanced PPP activity in activated macrophages supports their heightened phagocytic function. NADPH derived from the PPP is particularly essential for cholesterol metabolism and FAS, these pathways are crucial for macrophage function. Additionally, the increased synthesis of NADPH through the PPP contributes to the expansion of the Golgi apparatus and endoplasmic reticulum in macrophages. This expansion facilitates the secreted production of inflammatory cytokines, further promoting the immune response (27).

OXPHOS. OXPHOS plays a critical role in inflammation resolution, and its reduction in M1-type macrophages contributes to the accumulation of TCA cycle intermediates such as citrate, succinate, fumarate and malate. Toll-like receptor 4 (TLR4) is involved in OXPHOS regulation with the PI3K/Akt axis playing a crucial role in this process. On the other hand, in M2-type macrophages, OXPHOS is upregulated to support ATP production, which is essential during the tissue repair phase and serves as the main functional pathway.

Lipid metabolism. Lipid metabolism is a pivotal aspect of macrophage function, integral to the modulation of

Table I. Classical metabolism pathway in M1-type and M2-type macrophage.

	M1-type macrophages	M2-type macrophages
Glycolysis PPP	Enhanced glycolysis	/
OXPHOS	Inhabited OXPHOS	Increased OXPHOS
Amino acid metabolism	Express iNOS to NO from arginine; Glutamine metabolism promote the synthesis of succinic acid;	Hydrolyzed arginine to ornithine and urea by arginase; Glutamine metabolism drive M2-polarization;
TCA cycle	Rupture after citrate and succinate	Entire TCA cycle
Iron metabolism	High levels of ferritin and iron deposition	Decrease in intracellular iron level

PPP, pentose phosphate pathway; OXPHOS, oxidative phosphorylation.

inflammatory responses and phagocytosis (28). In classically activated macrophages (M1), stimulation by LPS enhances *de novo* lipogenesis (DNL) by converting the cytosolic pool of glucose-derived citrate into acetyl-CoA, a key component of FAS (29). The increased biosynthesis of fatty acids in these macrophages results in the esterification of fatty acids into triglycerides, serving as a storage form of lipids (30). Consequently, LPS-activated macrophages increase glucose utilization to support DNL and triglyceride synthesis, which is crucial for maintaining the connection between the actin cytoskeletal network and the plasma membrane, promoting enhanced macrophage phagocytosis (30). In non-inflammatory-activated macrophages (M2), the upregulation of FAMIN protein expression establishes a connection between DNL and FAO, intensifying the flow of oxidative metabolism in macrophages following IL-4 activation (31,32).

FAO. Fatty acid metabolism like FAS and FAO serves distinct roles in M1-type and M2-type macrophages, respectively (33,34). FAS is intricately linked to the pro-inflammatory function of macrophages, whereas M2-type macrophages rely more on FAO for energy acquisition (34,35). In M1-type macrophages, when the TCA cycle is disrupted, citrate accumulates and is transported from the mitochondria to the cytoplasm, where it is converted to acetyl-CoA through the ATP citrate lyase (ACLY). This sequence of events stimulates the *de novo* synthesis of fatty acids (36). The *de novo* synthesis pathway of fatty acids is interconnected with glucose and lipid metabolism, further supporting M1-type macrophage polarization (37-40).

Saturated fatty acids (SFAs) have been demonstrated to induce NF-κB activation and the expression of inflammatory markers in macrophages through the activation of TLR signaling by SFA metabolites. This process results in macrophage inflammation, with the NLRP3 inflammasome orchestrating the activation of caspase-1 and the release of pro-inflammatory factors (IL-1β and IL-18) (41). Mitochondrial uncoupling protein-2 has been found to upregulate FASN-dependent lipid synthesis and positively regulate NLRP3 inflammasome-mediated caspase-1 activation in macrophages (42,43). On the other hand, M2-type macrophages exhibit an increased reliance on FAO (32). FAO generates acetyl-CoA, NADH and FADH2, which are utilized in the TCA cycle to produce abundant ATP (44,45). In macrophages treated with LPS, there is a notable reduction in the ability to oxidize fatty acids to CO_2 due to decreased expression of proteins such as CPT1α and CPT1β, which are responsible for facilitating the entry of fatty acids into the mitochondria for oxidation. The FAO pathway diminishes NLRP3 activation causing the suppression of the inflammatory response in macrophages (46,47).

Cholesterol metabolism. Cholesterol is a critical lipid in macrophages, essential for maintaining the integrity, fluidity and functionality of the macrophage membrane. Precise regulation of intracellular cholesterol is pivotal for the effective execution of a range of macrophage functions. Macrophages can synthesize cholesterol, and it can also be directly imported through the internalization of lipoproteins (48). Excessive cholesterol accumulation in macrophages can result in profound cellular dysfunction and the activation of inflammatory pathways, leading to IL-1β-mediated inflammation (49). The expression of cholesterol biosynthesis is regulated by the transcription factor sterol regulatory element-binding protein 2 (SREBP2). Cholesterol 25-hydroxylase (CH25H) is particularly important in inflammation and macrophage biology and responsible for producing 25-hydroxycholesterol (25HC), which is considered an interferon regulatory gene (50).

During the inflammatory response to viruses and certain microorganisms, changes in cholesterol homeostasis observed in macrophages are often caused by upregulation of CH25H mediated by interferon and the subsequent increase in 25HC production (51). Interferon signaling and pattern recognition receptors (PRRs) that induce IFN responses, such as TLR3-TRIF signaling, downregulate cholesterol biosynthesis and promote cholesterol storage in the form of cholesterol esters (50,52,53). The synthesis of cholesterol in macrophages is not directly linked to alterations in the overall level of intracellular cholesterol. Interferon-stimulated macrophages, instead of altering cholesterol biosynthesis, respond to interferon through other mechanisms, including increased cholesterol uptake or reduced cholesterol efflux (50,54).

Conversely, MyD88-dependent PRRs, such as TLR-2, TLR-7 and TLR-9, result in increased cholesterol biosynthesis and overall cholesterol content in macrophages (50). Macrophages preferentially acquire cholesterol through receptor-mediated endocytosis of cholesterol-rich lipoproteins. The transport of cholesterol out of macrophages relies

on transport proteins ABCA1 and ABCG1. Stimulation of macrophages with LPS can decrease the activity of ABCA1 and ABCG1, impairing cholesterol efflux and leading to intracellular cholesterol accumulation. Excessive cholesterol accumulation in macrophages can promote inflammatory responses. In mice lacking ABCA1 and ABCG1, macrophages exhibit enhanced cholesterol levels, and the immune response is heightened when stimulated by TLRs. This is due to the accumulation of cholesterol potentially causing the formation of cholesterol crystals, which can activate macrophage inflammasomes or act as phagocytic targets, triggering inflammatory responses (55,56).

Amino acid metabolism. The availability of amino acids is crucial for maintaining proper immune cell function during the immune response. Insufficient amino acids supply can lead to deficiencies in immune cell activity. Macrophages, in particular, depend on amino acid catabolism to support immune activation and swiftly adjust to fluctuating nutrient sources (55). Amino acid metabolism plays a significant role in regulating various macrophage response pathways, such as mTOR signaling and NO production. Moreover, amino acid metabolites possess immunomodulatory properties that influence macrophage response. For instance, in LPS + IFN-γ-stimulated macrophages, glutamine is essential for LPS-induced IL-1β secretion, while arginine is metabolized by inducible NO synthase (iNOS) to produce NO, which acts as both an antimicrobial agent and a signaling molecule involved in vasodilation, angiogenesis and insulin secretion. Macrophages can polarize into an anti-inflammatory M2 phenotype, leading to significant alterations in amino acid metabolism, including arginine and proline metabolism, alanine, aspartic, and glutamic acid metabolism, cysteine and methionine metabolism, and taurine metabolism (56). By contrast, M1-type macrophages rely on glutamine metabolism (57,58). In the following section, the present review will delve into how arginine metabolism and glutamine metabolism processes govern macrophage function.

Arginine metabolism. Arginine metabolism indeed serves as a prominent example of macrophage amino acid metabolism, with ARG-1 being a classical marker of the M2 phenotype. The metabolic fate of arginine regulates the polarization of M1-type and M2-type macrophages. In macrophages stimulated by LPS + IFN-γ, there is an overexpression of iNOS, which results in citrulline production. Arginine succinate synthase 1 converts citrulline into arginine succinate, which is rapidly broken down to regenerate arginine and sustain NO production. This conversion of arginine to citrulline and NO through iNOS promotes the loss of mitochondrial complex at the later stage of M1 polarization (59). On the other hand, anti-inflammatory M2 macrophages consistently express ARG-1, which is involved in arginine catabolism. During this process, ornithine is produced, which can control cell growth and promote tissue repair when converted to polyamines by ornithine decarboxylase (60,61). These metabolic pathways highlight the dynamic regulation of arginine metabolism in macrophage polarization. The balance between the production of NO and the metabolism of arginine plays a crucial role in determining the M1 or M2 phenotype of macrophages.

Glutamine metabolism. Different pathways of glutamine metabolism contribute to the polarization of macrophages into distinct phenotypes upon activation. Glutamine metabolism in M1-type macrophages promotes the synthesis of succinic acid by entering the TCA cycle. Simultaneously, glutamine metabolism also drives M2 polarization (62,63). The degradation of glutamine generates α-ketoglutaric acid (αKG), which plays a critical role in OXPHOS and FAO processes in M2-type macrophages. αKG can also facilitate macrophage epigenetic reprogramming, thereby promoting the M2 phenotype (64). The production of α-KG from glutamine decomposition is influenced by the SENP-Sirt3 signaling pathway, which deacetylates GLUD1, increasing its activity in glutamine decomposition and promoting αKG production (65). This mechanism further modulates M2 polarization by controlling the αKG/succinic acid ratio. A high ratio favors M2 phenotype, while a low ratio strengthens the pro-inflammatory phenotype in classically activated (M1) macrophages. Consequently, αKG contributes to endotoxin tolerance following M1 activation (64).

Additionally, glutamine metabolism contributes to the UDP-GlcNAc synthesis pathway, which experiences upregulation in M2-type macrophages. Glutamine serves as a substrate for glutamine synthetase (GS), which is highly expressed in M2 macrophages. GS induces the synthesis of intracellular glutamate and ammonia, leading to the production of glutamine. The ablation of GS in TAMs results in reduced expression of M2-type markers, such as ARG1 and CD206 (66,67). These findings elucidate the intricate interplay between metabolic and epigenetic reprogramming through glutamine metabolism in customizing the immune response of macrophages.

TCA cycle. The TCA cycle, commonly referred to as the Krebs cycle, serves as the central pathway for the oxidation of carbohydrates, fatty acids and amino acids. It plays a crucial role in cellular anabolism (such as gluconeogenesis and lipid synthesis) and catabolism (including glycolysis) (68). Research has revealed that the TCA cycle is disrupted at various nodes in M1-type macrophages, resulting in the accumulation of specific metabolites such as citrate, itaconic acid and succinate (69,70). By contrast, M2-type macrophages demonstrate an intact TCA cycle, accompanied by increased OXPHOS and ATP levels (71).

The production and transformation of citrate are intricately linked to both mitochondrial and cytoplasmic metabolism. Citrate is generated via the condensation of oxaloacetic acid and acetyl coenzyme A in the TCA cycle. In macrophages activated by LPS, the expression of the mitochondrial citrate carrier (CIC/SLC25a1) mRNA and protein significantly increases. Citrate output supports FAS, which is essential for the production of prostaglandin E2 (PGE2), as well as the reduction of $NADP^+$ to NADPH (72,73).

Itaconic acid, generated by the upregulation of aconitic acid decarboxylase 1 in classically activated macrophages, acts as a key regulator of macrophage function. Itaconic acid exits the TCA cycle and has demonstrated the ability to diminish the production of proinflammatory mediators in LPS-treated macrophages. Additionally, it contributes to maintaining the stability of the anti-inflammatory transcription factor nuclear factor erythroid 2-related factor 2 (NRF2).

Succinate, another metabolite, accumulates during macrophage activation and exhibits proinflammatory properties. LPS-induced macrophage activation leads to intracellular buildup of succinate and the activation of the γ-aminobutyric acid shunt pathway. In response to inflammatory signals, macrophages express GPR91, a receptor for succinate. Succinate triggers GPR91-mediated signaling, maintaining a proinflammatory phenotype, and facilitating the production of IL-1β. GPR91 is expressed in diverse cell types and responds to extracellular succinate (74,75). This process has been implicated in diseases such as diabetic retinopathy (76), diabetic nephropathy (77), hypertension (78) and atherothrombotic thrombosis (79).

Iron metabolism. Iron plays a crucial role in the development, differentiation and function of macrophages. Macrophages are essential for maintaining systemic iron homeostasis. The characteristics of M1 and M2 macrophages are closely linked to their iron status. M1-type macrophages have high levels of ferritin and are prone to iron accumulation, while M2-type macrophages can metabolize and export iron, leading to a decrease in intracellular iron levels. Macrophages acquire iron directly through transporters and receptors such as LDL-related receptor 1, transferrin receptor 1 and the hemoglobin-haptoglobin receptor (CD163). Intracellular iron homeostasis in macrophages is regulated post-transcriptionally by the iron regulatory protein (IRP)/iron-responsive element (IRE) system. Iron regulation in macrophages is intricately connected to immune function, with intracellular iron levels directly impacting macrophage polarization (80-82). The mechanisms through which iron mediates macrophage polarization involve modulation of intracellular signaling pathways such as NF-κB, MAPK and ROS generation (83).

Iron storage in macrophages is primarily achieved through ferritin binding. In M1-type macrophages, iron overload leads to abundant iron storage due to higher expression of hepcidin (Hamp) and ferritin heavy (FTH)/ferritin light (FTL), and lower expression of hepcidin-ferroportin (FPN) and IRP1/2 (84). Iron-overloaded macrophages are often accompanied by increased expression of various M1-type cytokines, including IL-1β, TNFα and IL-6, as well as decreased levels of the M2-type marker TGM2 (85). This iron accumulation in macrophages is associated with increased glycolytic metabolism and p53 acetylation (86,87). Additionally, iron-overloaded macrophages manifest increased ROS production (87) and lipid peroxidation through the Fenton reaction, leading to iron-induced cell death (88). Specific cytokines released by macrophages can either induce or inhibit iron-induced cell death through diverse mechanisms. For instance, TNF-α upregulates enzymes such as ACSL3 and ACSL57, which participate in acyl coenzyme A synthesis, fostering lipid accumulation in macrophages and establishing conditions for iron-induced cell death. IL-1β, a typical inflammatory cytokine, enhances the expression of phosphorylated c-Jun N-terminal kinase and its substrates (c-Jun and b-Jun), leading to FPN degradation and iron-induced cell death in macrophages (89,90). Conversely, macrophages deficient in FPN show increased iron accumulation and elevated expression of inflammatory cytokines (91). Both TNF-α and IL-1β have proinflammatory functions and play important roles in promoting iron-induced cell death in macrophages. iNOS, a hallmark of M1-type macrophages, has been found to induce lipid peroxidation in macrophages, which has a protective function against iron-induced cell death (92,93). Alterations in iron metabolism in macrophages are closely associated with macrophage polarization, production of inflammatory factors, lipid processing, angiogenesis and iron sequestration, all of which impact the progression of various diseases including cancer and atherosclerosis.

3. Nanomaterials regulate macrophage metabolism to treat diseases

Nanomaterials have emerged as promising therapeutic agents for addressing metabolic disorders, owing to their distinctive size and physicochemical characteristics. Their expansive specific surface area, high bioavailability, targeting capabilities and adjustable release rates make them valuable tools for regulating metabolic abnormalities in diseases. This article provides a comprehensive review of the current status and prospects of using nanomaterials to target the abnormal metabolism of macrophages for the treatment of cancer and atherosclerosis (Fig. 1).

Cancer. Tumors are intricate multicellular systems, and among the constituents of the TME, TAMs assume a pivotal role. TAMs exhibit heightened metabolic activity in pathways such as glycolysis, FAS, FAO, as well as altered glutamate metabolism and aberrant iron uptake. These metabolic alterations contribute to the tumor-promoting functions of TAMs. In this section, the unique metabolic pathways observed in TAMs were discussed and the utilization of advanced nanomaterials to modulate these pathways was examined.

TAMs, being the predominant immune cell population within tumors, have an immunosuppressive role during tumor progression. Cancer cells fulfill their energy demands for rapid proliferation by consuming large amounts of glucose and relying on glycolysis. Consequently, TAMs must shift to alternative metabolic pathways such as OXPHOS and FAO to meet their energy requirements and maintain an immunosuppressive phenotype in the glucose-deficient TME (94). Reprogramming TAMs using nanodrugs to enhance glycolysis or inhibit OXPHOS and FAO in the TME holds promise for mitigating tumor development. For instance, Jiabao *et al* (95) employed LDH mimicking SnSe nanosheets equipped with carbonic anhydrase IX inhibitors to shift TAM metabolism from mitochondrial OXPHOS to glycolysis. This approach activated TAMs into M1-like macrophages and enhanced the efficacy of TAM-based antitumor immunotherapy (Fig. 2).

Previous studies have revealed that TAMs exhibit higher glucose uptake and elevated levels of glycolytic metabolism (96-98), though the specific mechanisms underlying these observations require further investigation. The downstream metabolite of TAM glycolysis is lactate. M1-like TAMs are predominantly found in the normoxic tumor regions, while M2-like TAMs are concentrated in the hypoxic regions. Hypoxia, characterized by low oxygen levels, enhances the tumor-promoting activities of TAMs. The transcription factor HIF-1α plays a crucial role in regulating glycolysis under hypoxic conditions. Within TAMs, HIF-1α activates pyruvate dehydrogenase kinase 1, leading to the inactivation of

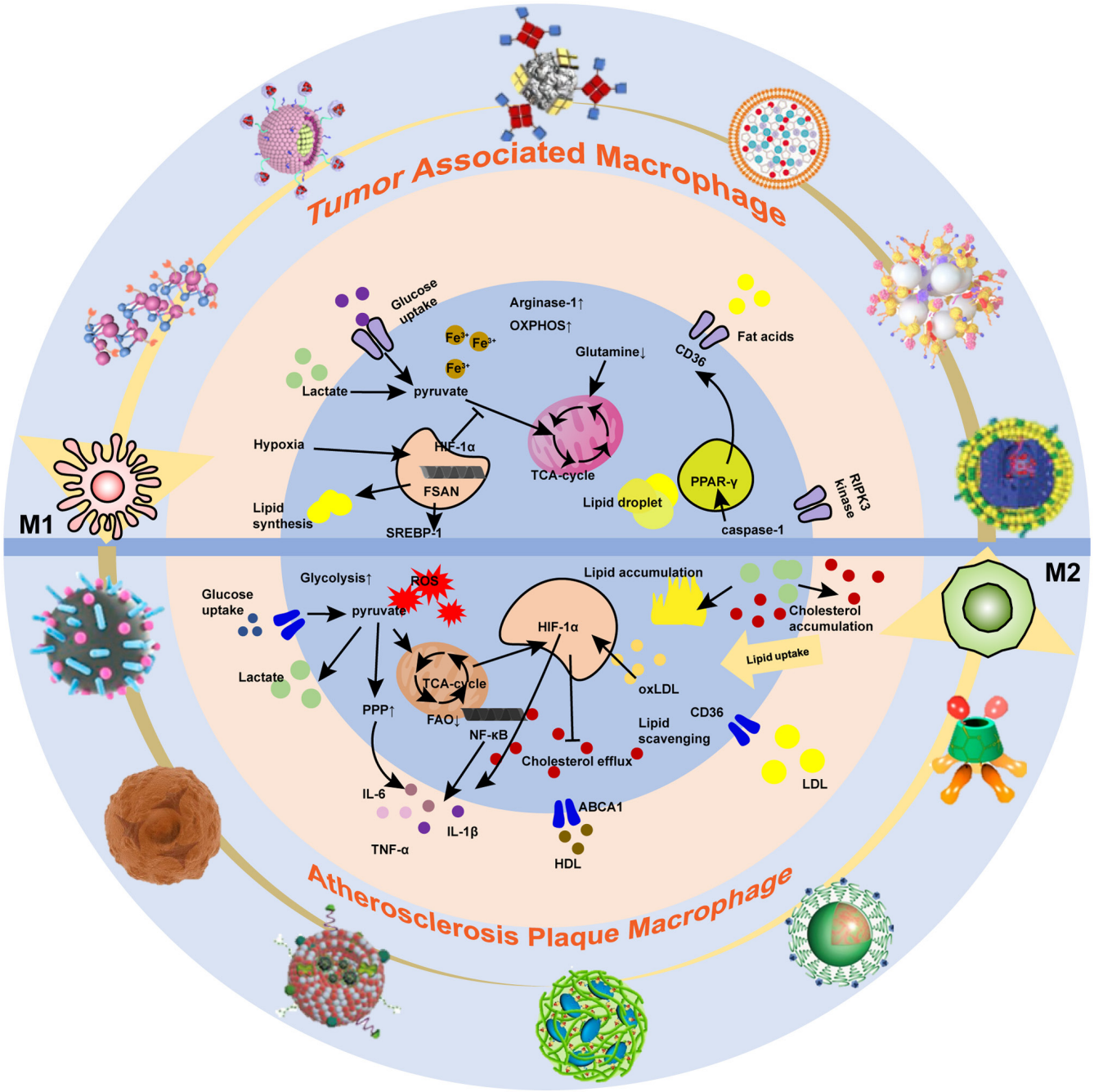

Figure 1. Nanomaterials targeting macrophages for metabolic therapy in cancer and atherosclerosis.

pyruvate dehydrogenase (PDH) and preventing pyruvate from entering the TCA cycle, resulting in lactic acid accumulation. TAMs predominantly rely on glycolysis as their primary metabolic pathway, which distinguishes them from the traditional M2-type macrophages. In M2-type macrophages, pyruvate is converted to lactic acid by LDHA. The excessive accumulation of lactic acid promotes cancer cell proliferation and favors the polarization of macrophages towards an immunosuppressive M2 phenotype in the TME (99-104). Sustained lactic acid release in malignant tumors is associated with cancer progression, and lactic acid polarizes macrophages towards M2-like phenotypes by regulating the acetylation level of macrophage histones, thereby promoting TAM polarization (105-108). Lactate secreted by breast cancer cells has been found to increase ROS levels in macrophages via NRF2, inducing M2-type macrophage polarization, VEGF expression, and promoting epithelial-mesenchymal transition in cancer cells (109). Increased availability of lactic acid in the TME facilitates the catabolism of arginine by ARG-1 and ARG-2 in macrophages, inhibiting the secretion of anticancer substances such as NO and citrulline (110). This results in the production of tumor-supporting cytokines such as ornithine and polyamines by TAMs (111). Consequently, preventing lactic acid efflux from cancer cells has emerged as an important strategy to regulate the immunosuppressive TME. Li *et al* (112) developed a nano-cascade platform that responds to the weakly acidic TME and high glutathione (GSH) levels in tumor cells. This platform enables the sustained release

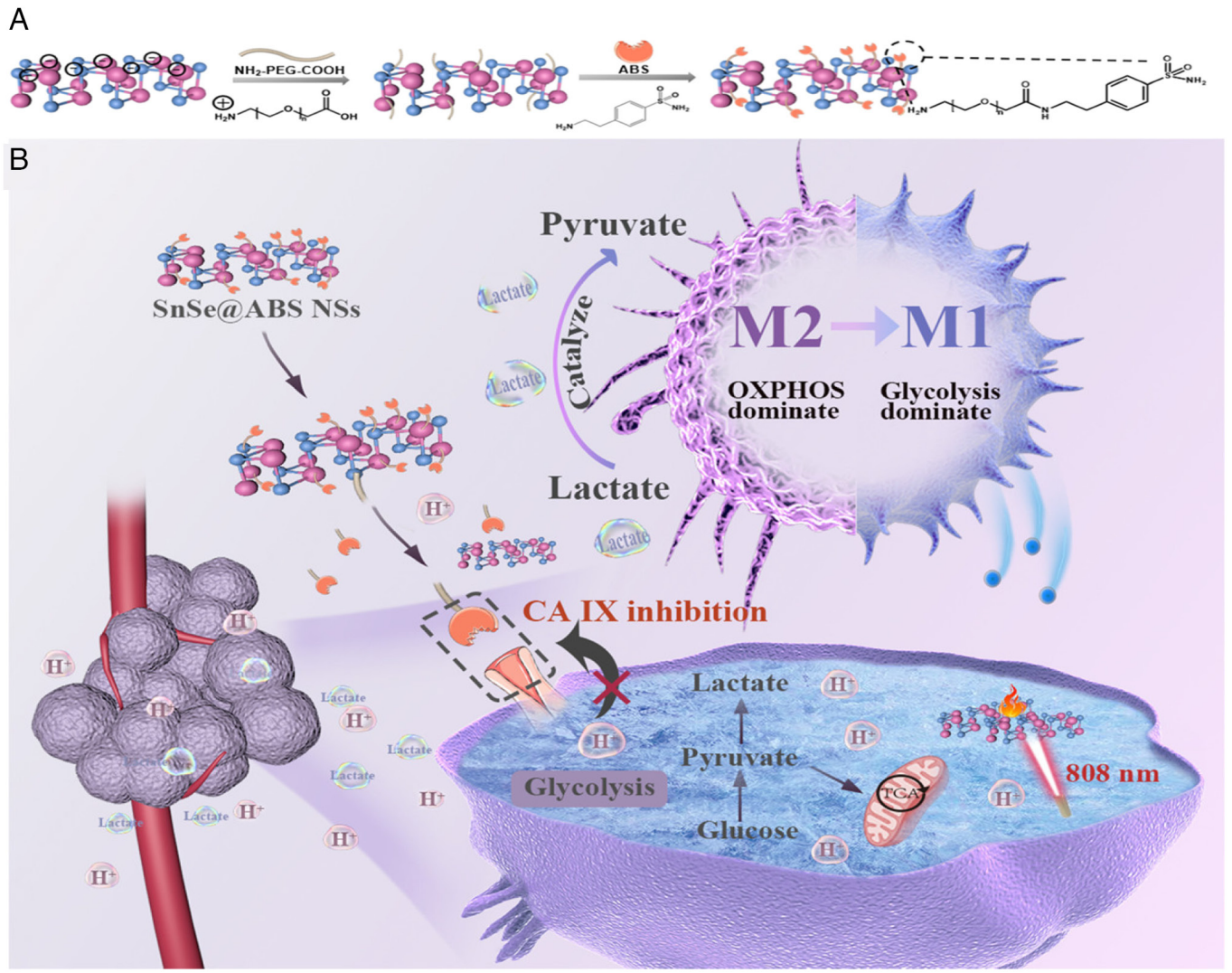

Figure 2. (A) Schematic illustration of SnSe@ABS NSs. (B) Lactic acid dehydrogenase-mimicking SnSe manosheets loaded with CAIX inhibitor (SnSe@ABS NSs) for the therapeutic modulation of acidic tumor microenvironment and repolarization of tumor-associated macrophages [Reprinted with permission from Ref. (95); Copyright (2022) American Chemical Society]. CAIX, carbonic anhydrase IX; TCA, tricarboxylic acid; OXPHOS, oxidative phosphorylation.

of hydroxycamptothecin and siMCT-4, inhibiting intracellular lactate efflux. By combining chemotherapy with lactate efflux modulation, this nanoplatform effectively reshapes the immunosuppressive TME, repolarizes TAMs from the M2 phenotype to the M1 phenotype and significantly inhibits tumor growth (Fig. 3A). Currently, advanced nanomaterials primarily target the consumption of lactic acid accumulated in the TME, assuming that this lactic acid originates from tumor cell secretion (112-115) (Fig. 3). Nonetheless, the exploration of other metabolic pathways in TAMs, such as amino acid and iron metabolism, remains a promising direction for the development of new nanomaterials in the comprehensive study of macrophage metabolism within the TME.

As aforementioned, reprogramming the metabolic processes of TAMs has emerged as a promising approach to modulate their tumor-promoting function. One of the metabolic pathways closely related to TAM polarization is OXPHOS. Inhibition of the OXPHOS pathway has been explored as a strategy to promote the transition of M2-type TAMs to the M1 phenotype. Yang *et al* (116) developed nano-ultrasound contrast agents (Pt(IV)/CQ/PFH NPs-DPPA-1) that could reprogram the metabolic processes of TAMs, enhancing glycolysis and reducing OXPHOS. This reprogramming increased the proportion of pro-inflammatory macrophages and enabled combined chemical and immunotherapy using Pt (IV) and anti-PD-L1 peptide (DPPA-1) (Fig. 4).

In addition to enhancing glycolysis and inhibiting OXPHOS, the development of FAO inhibitors to induce phenotypic transformation of macrophages and inhibit tumor development is also a promising avenue of research. TAMs utilize FAO as an energy source through the scavenger receptor CD36, mediating lipid uptake and catabolism (117). In the TME, activation of the RIPK3 kinase in cancer cells promotes lipid accumulation in TAMs by activating PPAR-γ via caspase 1 (118,119). Macrophages with increased lipid content and endoplasmic reticulum (ER) stress promote tumor development through the combination of β-Glucoceramide with receptors on TAMs, triggering stress responses in the ER tubular organelles (120). Hypoxia, a characteristic feature of solid tumors, activates HIF, which upregulates SREBP1 (121,122). Activated FASN, the main transcriptional regulator of FASN genes, promotes *de novo* lipid synthesis under hypoxia stress, leading to the

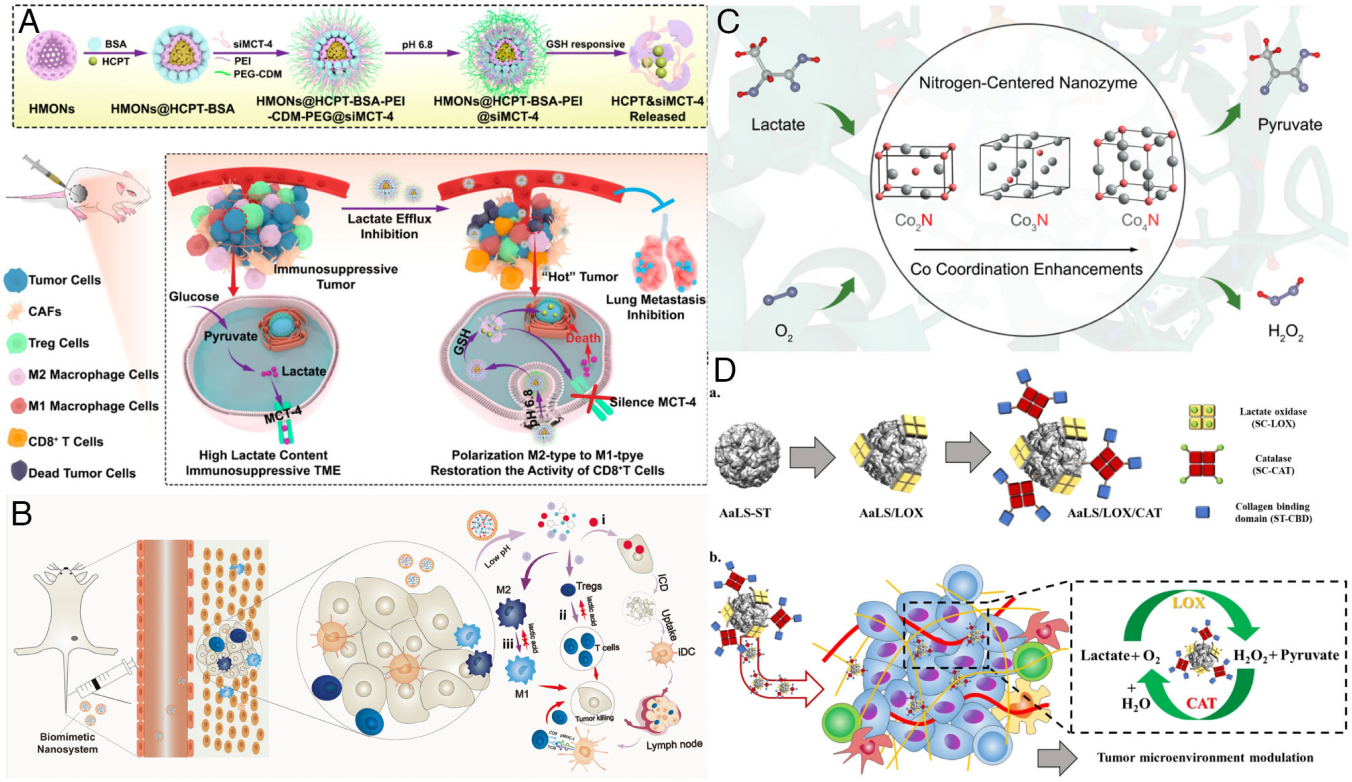

Figure 3. (A) The nanoplatform directly induces tumor cell apoptosis though HCPT and the increased intracellular lactate, then transforms immunosuppressive tumors to 'hot' tumors, polarizes the tumor-associated macrophages' phenotype from M2 type to M1 type, and restores CD8 T cell activity via inhibiting lactate efflux [Reprinted with permission from Ref. (112); Copyright (2020) American Chemical Society]. (B) Biomimetic metal organic framework nanosystems regulate the metabolism of immunosuppressive tumor microenvironment to amplify immunotherapy by consuming lactic acid and amplifying ICD-induced immunotherapy [Reprinted with permission from Ref. (114); Copyright (2023) Springer Nature]. (C) Nitrogen-centered lactate oxidase nanozyme for tumor lactate modulation and microenvironment remodeling [Reprinted with permission from Ref. (115); Copyright (2023) Elsevier]. (D) Schematic illustration of constructing AaLS/LOX and AaLS/LOX/CAT and their application to the TME modulation. (D-a) Polyvalent immobilization of LOX onto the surface of AaLS and subsequent CAT immobilization using a SpyTag/SpyCatcher ligation system. (D-b) Schematic illustration of AaLS/LOX/CAT delivery to the tumor sites and their subsequent TME modulation by the effective consumption of lactate and H_2O_2 [Reprinted with permission from Ref. (113); Copyright (2023) American Chemical Society]. HCPT, hydroxycamptothecin; TME, tumor microenvironment; GSH, glutathione.

accumulation of lipids stored as lipid droplets, which support biofilm formation, energy production and protein modification (123,124). Accumulated lipid droplets in macrophages can induce TAM polarization toward the M2 phenotype by regulating the catabolism of unsaturated fatty acids in mitochondrial respiration (117). Targeting lipid synthesis is a promising strategy for tumor treatment (125). Jiang *et al* (126) developed a nano-emulsion containing α-tocopherol, encapsulating the IRE1-XBP1 pathway inhibitor KIRA6, to inhibit ER stress and oxidative stress. This dual inhibitory effect reprogrammed M2-type TAMs by increasing glycolysis and inhibiting FAO, thereby delaying tumor growth (Fig. 5A). Hou *et al* (127) constructed a hollow mesoporous Prussian blue (HMPB) nano-system with mannose modification and hydroxychloroquine (HCQ) adsorption. They combined macrophages and thylakoid (TK) membranes on the surface of the nanoparticles, resulting in TK-M@Man-HMPB/HCQ, which effectively alleviated TAM polarization induced by the hypoxic microenvironment and promoted cytotoxic T lymphocyte (CTL) infiltration, leading to significant inhibition of cancer growth (Fig. 5B). Yang *et al* (128) developed a novel poly (vinylpyrrolidone) (PVP)-modified $BiFeO_3/Bi_2WO_6$ (BFO/BWO) with a p-n-type heterojunction that catabolizes H_2O_2 to produce O_2, thereby alleviating tumor hypoxia and enhancing the sensitivity of photodynamic therapy (PDT) and radiotherapy (RT). The PVP-modified BFO/BWO nanoparticles also reduced the expression of HIF-1α and promoted the polarization of TAMs toward the antitumor M1 phenotype (Fig. 5C).

Iron metabolism is another important aspect of TAM function, as M2-type TAMs are key players in iron uptake, metabolism, storage and export. TAMs provide iron to promote tumor growth through multiple transport routes, making targeting TAM iron delivery systems a potential strategy to enhance the anti-tumor immune response (129). Macrophages regulate intracellular iron levels by modulating hepcidin/iron transporters. When this balance is disrupted, excess iron is exported, resulting in tissue iron overload and iron-induced cell death. Inducing iron-mediated cell death in TAMs can inhibit tumor development by transforming or sacrificing them. Zhang *et al* (130) developed a biomimetic magnetosome using Fe_3O_4 magnetic nanoclusters as the core, bearing PD-1 antibodies on the membrane surface and loaded with a TGF-β inhibitor. This biomimetic magnetosome induced TAM polarization from M2 to M1, resulting in increased release of Fe ions and subsequent hydrogen peroxide production, which induced iron-induced cell death in tumor cells. Iron overload stress can also modulate TAM signaling activation and metabolic

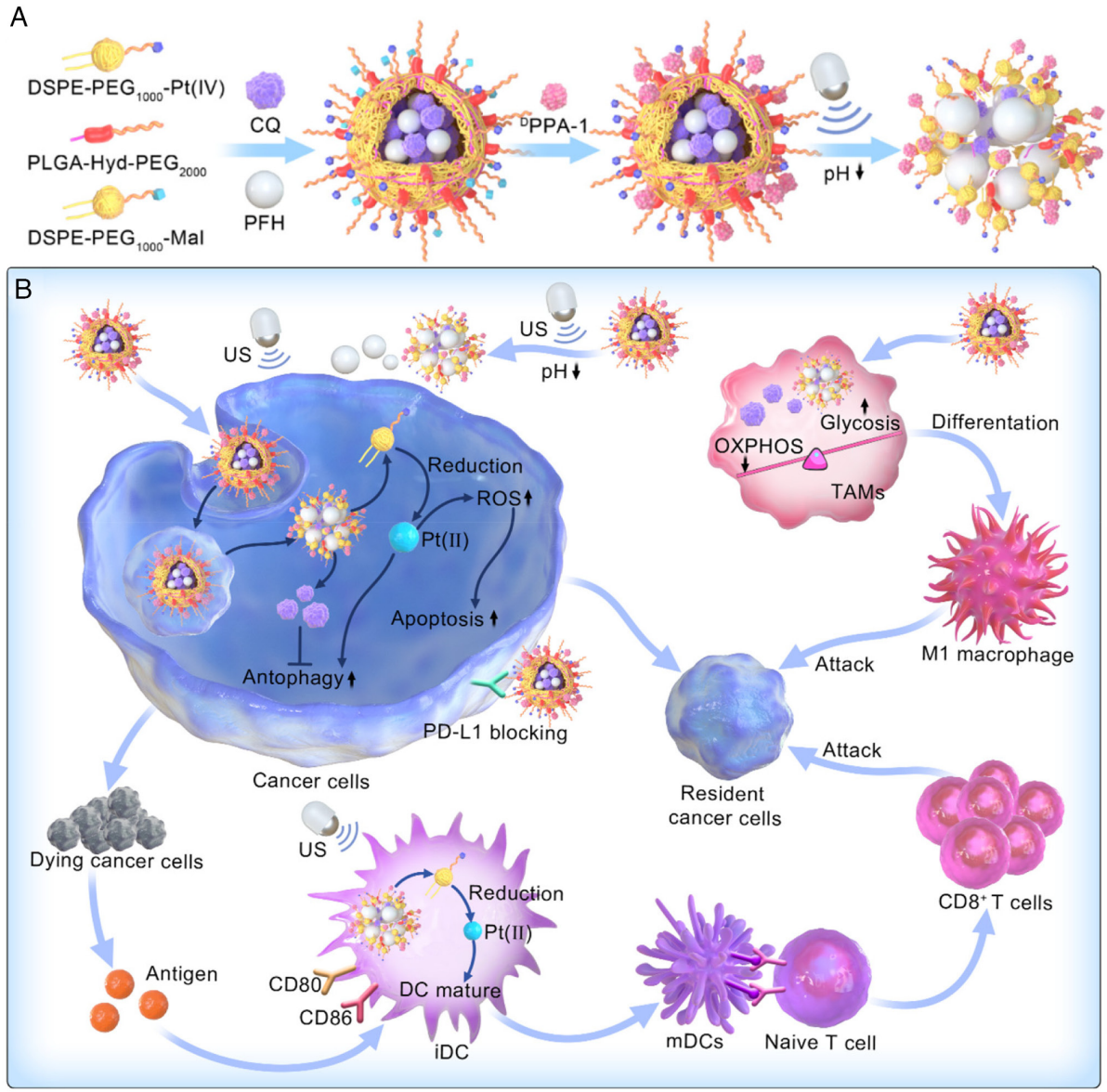

Figure 4. (A) Synthesis process used to prepare NPs. (B) Schematic illusion of Pt (IV)/CQ/PFH NPs-DPPA-1 assisted by ultrasound for augmenting chemoimmunotherapy of breast cancer, which ameliorate the tumor microenvironment by immune metabolism to promote the ratio of mature dendritic cells and M1 macrophages [Reprinted with permission from Ref. (116); Copyright (2022) American Chemical Society]. NPs, nanoparticles; OXPHOS, oxidative phosphorylation; TAMs, tumor-associated macrophages; ROS, reactive oxygen species.

function, offering a promising antitumor therapeutic approach. Gu *et al* (131) developed iron-based metal-organic framework nanoparticles equipped with an iron death inducer. These nanoparticles synergistically enhanced TAM mitochondrial glycolysis, promoted macrophage M1 activation and increased the secretion of antitumor cytokines, thereby strengthening the tumoricidal activity of macrophages (Fig. 6).

In addition to the previously discussed abnormalities in glycolysis, lipid metabolism and iron metabolism, M2-TAMs significantly contribute to the immunosuppressive TME through their amino acid metabolism. Amino acids play a crucial role in the survival of TAMs, with glutamine being a key amino acid for cancer cells and immunosuppressive TAMs (132,133). *In vitro* experiments have demonstrated that glutamine ligase promotes the polarization of TAMs towards the M2 phenotype by catalyzing the conversion of glutamate to glutamine. Inhibiting the uptake of glutamine by TAMs can repolarize them towards the M1 phenotype, enhancing their antitumor function. An effective approach for tumor immunotherapy involves targeting macrophages through nanomaterial delivery and regulating their glutamine metabolism. Certain studies have employed small molecule inhibitors of glutamine metabolism, such as the prodrug of small molecule-6-diazo-5-oxo-L-demethylleucine, to target glutamine metabolism and increase the population of inflammatory TAMs, thereby inhibiting tumor growth (134).

Du *et al* (135) conducted a study involving an endogenous stimulus-responsive nano-delivery system (DOX@HFn-MSO@PGZL). This innovative system incorporated L-methionine sulfoxideimine (MSO) to disrupt the glutamate metabolism of TAMs in tumor-bearing mice. This disruption promoted the formation of the M1 phenotype, stimulated M1-TAMs to restore their antigen presentation function, and synergistically interacted with mature dendritic cells to

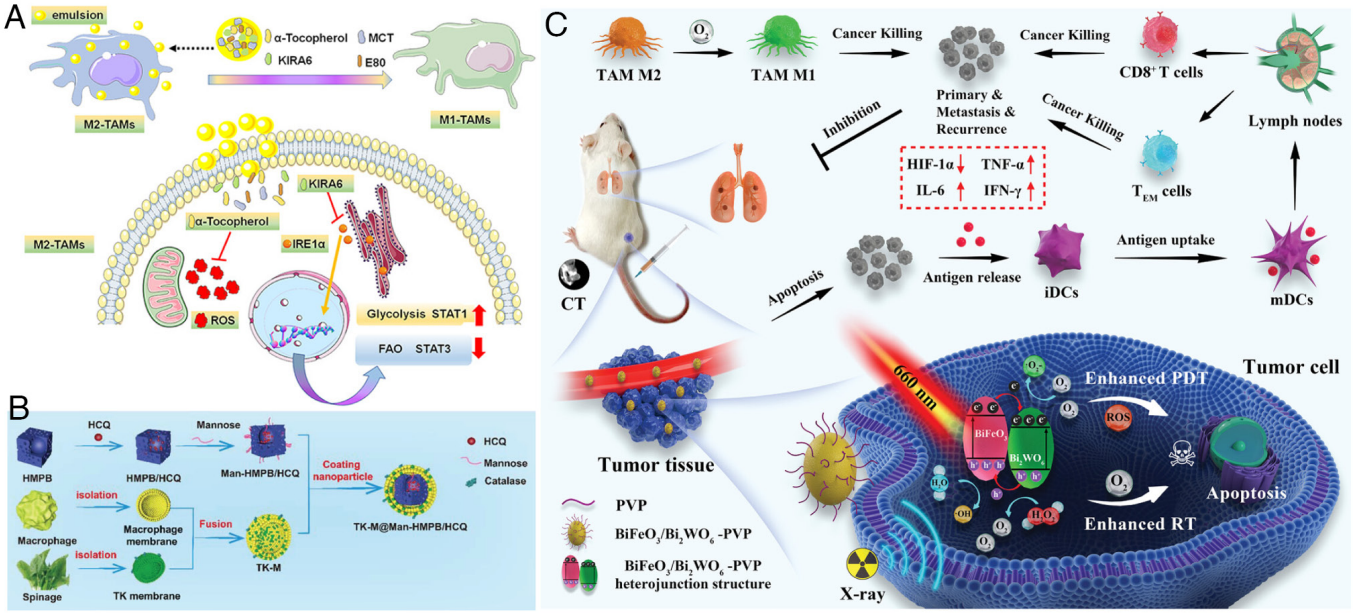

Figure 5. (A) Dual inhibition of endoplasmic reticulum stress and oxidative stress successfully manipulated the repolarization of M2-TAMs, achieved by inducing the metabolism shift of macrophages from FAO to glycolysis [Reprinted with permission from Ref. (126); Copyright (2021) American Chemical Society]. (B) Schematic diagram of Man-HMPN/HCQ camouflaged by TK-M hybrid membrane for cancer immunotherapy [Reprinted with permission from Ref. (127); Copyright (2022) Wiley-VCH GmbH]. (C) Schematic illustration of BFO/BWO-PVP NPs for CT-imaging-guided O_2 self-supplying photodynamic therapy/radiotherapy synergistic antitumor immunity therapy [Reprinted with permission from Ref. (128); Copyright (2022) Wiley-VCH GmbH]. TAMs, tumor-associated macrophages; HCQ, hydroxychloroquine; FAO, fatty acid oxidation; TK, thylakoid; ROS, reactive oxygen species.

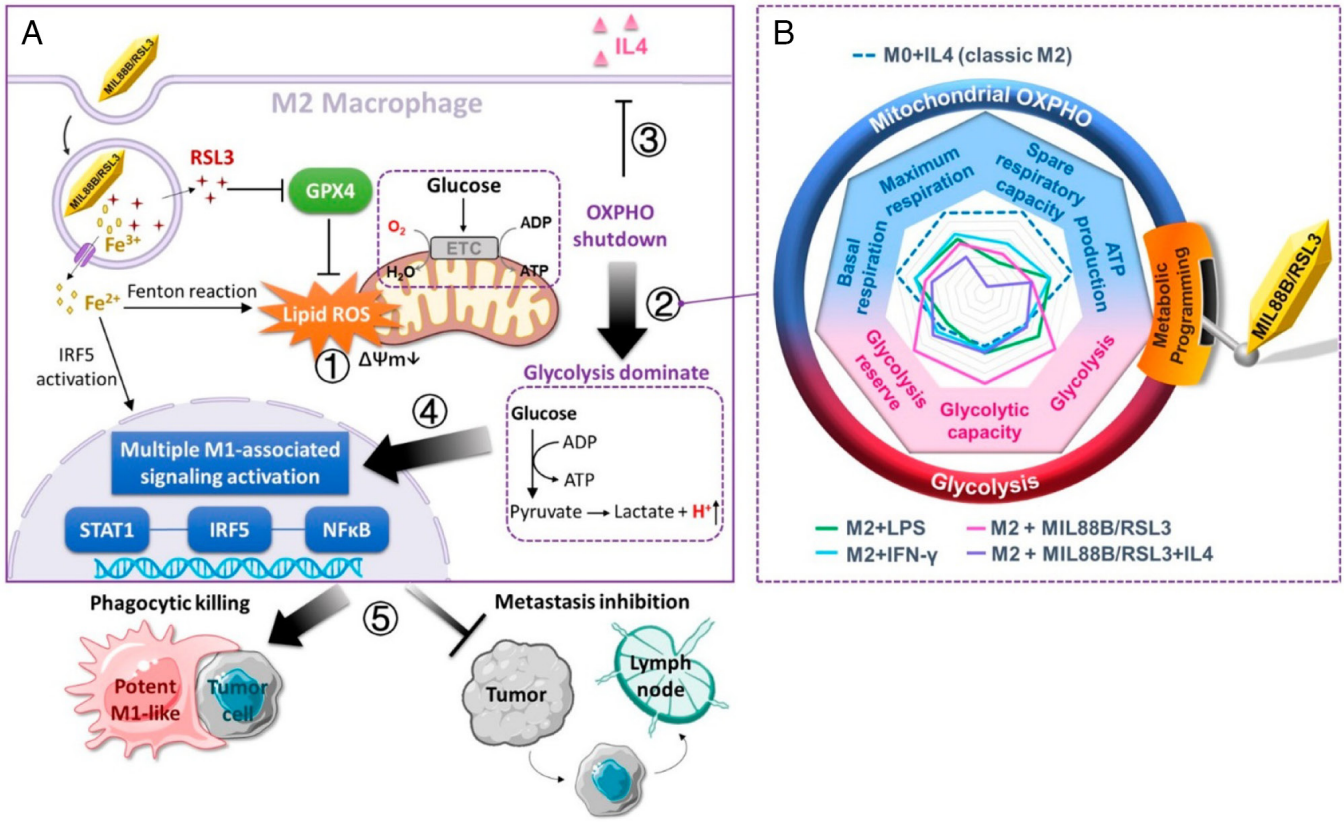

Figure 6. MIL88B/RSL3-Induced metabolic programming and tumoricidal macrophage polarization. (A) When M2 macrophages are treated with MIL88/RSL3, the iron species and RSL3 synergizes to induce ferroptosis-associated lipid peroxidation, which disrupts mitochondrial activity ①, embodied in the loss of membrane potential. The shutdown of OXPHOS forces macrophage metabolism to shift to glycolysis for ATP ② and effectively counteracts the stimulation of M2 anti-inflammatory cytokine ③. This MIL88/RSL3 drives potent M1 polarization via activation of multiple M1-associated nuclear transcriptional factors ④. Collectively, MIL88/RSL3 significantly promotes M1 population in breast cancer tumors and elicits excellent tumoricidal activities ⑤ including phagocytic killing and metastasis inhibition. (B) MIL88B/RSL3 shifted M2 macrophages from OXPHOS to glycolytic metabolism, dramatically elevating the level of glycolysis, glycolytic capacity and glycolysis reserve, and lowering mitochondrial basal respiration, maximum respiration, spare respiratory capacity and ATP production [Reprinted with permission from Ref. (131); Copyright (2021) American Chemical Society]. OXPHOS, oxidative phosphorylation.

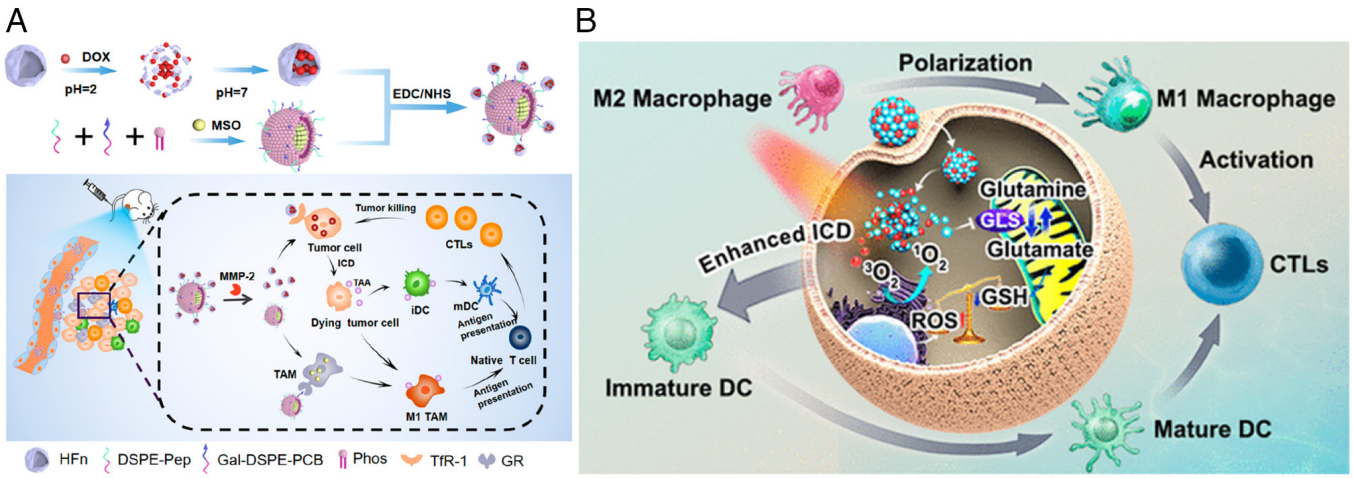

Figure 7. (A) Synthesis and Mechanism of DOX@HFn-MSO@PGZL nanoparticles for the antitumor immunotherapy [Reprinted with permission from Ref. (135); Copyright (2021) American Chemical Society]. (B) Schematic illustration of antitumor synergistic immunotherapy mediated by C9SN with laser irradiation via increasing tumor immunogenicity and reversing immunosuppressive tumor microenvironment [Reprinted with permission from Ref. (140); Copyright (2023) American Chemical Society]. DC, dendritic cell; MSO, L-methionine sulfoxideimine; CTL, cytotoxic C lymphocyte; ROS, reactive oxygen species; GSH, glutathione.

enhance antigen presentation efficiency. Consequently, this activation of tumor-killing T cells resulted in a potent anti-tumor effect (Fig. 7A). Furthermore, the use of glutamine enhances the pro-inflammatory response induced by FAO and optimizes the NAD/NADH ratio of glutamine-producing lactic acid, contributing to antitumor immunity. CD40, strongly expressed by macrophages and other antigen-presenting cells, has been targeted for the phenotypic re-education of TAM in tumor-bearing mice (136-138). Activation of CD40-mediated signaling with agonistic anti-CD40 monoclonal antibodies has been shown to promote macrophage glutamine and fatty acid metabolism, thereby facilitating epigenetic reprogramming of pro-inflammatory genes and antitumor phenotypes in ACLY-dependent macrophages (139).

The immunotherapeutic effect of PDT can be attenuated by tumor defense mechanisms associated with glutamine metabolism. To overcome this, Mai *et al* (140) developed a carrier-free immunotherapy enhancer, C6SN, with a dual synergistic effect. This enhancer combines the self-assembly of glutamine inhibitor compound 9 (C968) and the photosensitizer Chlorin e6 (68) to block glutamine metabolism in macrophages and polarize TAM towards the M1 phenotype. Consequently, it further recruits and activates CTL while remodeling the immunosuppressive TME (Fig. 7B).

In summary, the metabolic processes of TAMs drive their immunosuppressive functions, including increased glucose and lipid uptake, as well as glutamine and glutamic acid accumulation during tumor growth. These insights highlight the potential of designing nanodrugs specifically tailored to target macrophage-specific metabolic changes, offering a promising avenue to enhance anti-tumor immunotherapy.

Atherosclerosis. Macrophages within atherosclerotic plaques often exhibit metabolic abnormalities, including dysregulated glycolysis, PPP, iron overload, excessive intracellular lipid accumulation and reduced cholesterol efflux. This section delves into the atherosclerotic microenvironment and the concomitant metabolic aberrations. Additionally, nanomaterials that target these abnormal metabolic processes, ranging from the modulation of macrophage cholesterol efflux and lipid accumulation to the inhibition of macrophage foam cell formation and plaque injury, were briefly discussed.

Firstly, a concise overview of the microenvironment within the atherosclerotic plaque and the metabolic characteristics of macrophages dwelling within it was provided. During the early stage of atherosclerosis, monocytes are attracted to the arterial wall through chemokine-receptor interactions and the secretion of intercellular adhesion molecule-1 and vascular adhesion molecule-1 by endothelial cells (141). Subsequently, these monocytes differentiate into macrophages, acquiring either pro-inflammatory or anti-inflammatory phenotypes under the influence of the local microenvironment (142). Pro-inflammatory macrophages are predominantly found in early plaques and exhibit a heightened affinity for oxidized low-density lipoprotein (oxLDL) via scavenger receptor CD36, as opposed to the LDL receptor (143,144). This leads to the accumulation of lipids within macrophages, resulting in the formation of foam cells characterized by excessive cholesterol and triglyceride storage in cytoplasmic lipid droplets. Cholesterol accumulation within macrophages triggers Toll-like receptor signaling, NF-kB-mediated NLRP3 inflammasome activation and the promotion of macrophage inflammation, thereby exacerbating the chronic inflammatory state associated with atherosclerosis (145). Moreover, untreated cholesterol overload induces macrophage toxicity and apoptosis while impairing their capacity to migrate and remove plaques. High-density lipoprotein (HDL) levels in the bloodstream are inversely correlated with the risk of atherosclerosis, primarily through the process of reverse cholesterol transport, which facilitates the transport of excess cholesterol from surrounding cells and tissues back to the liver while regulating inflammation to prevent lipid accumulation (146). However, in the inflammatory environment of atherosclerosis, increased macrophage myeloperoxidase (MPO) activity leads to HDL oxidation, causing partial loss of its functionality. Furthermore, MPO-mediated oxidation of the cholesterol

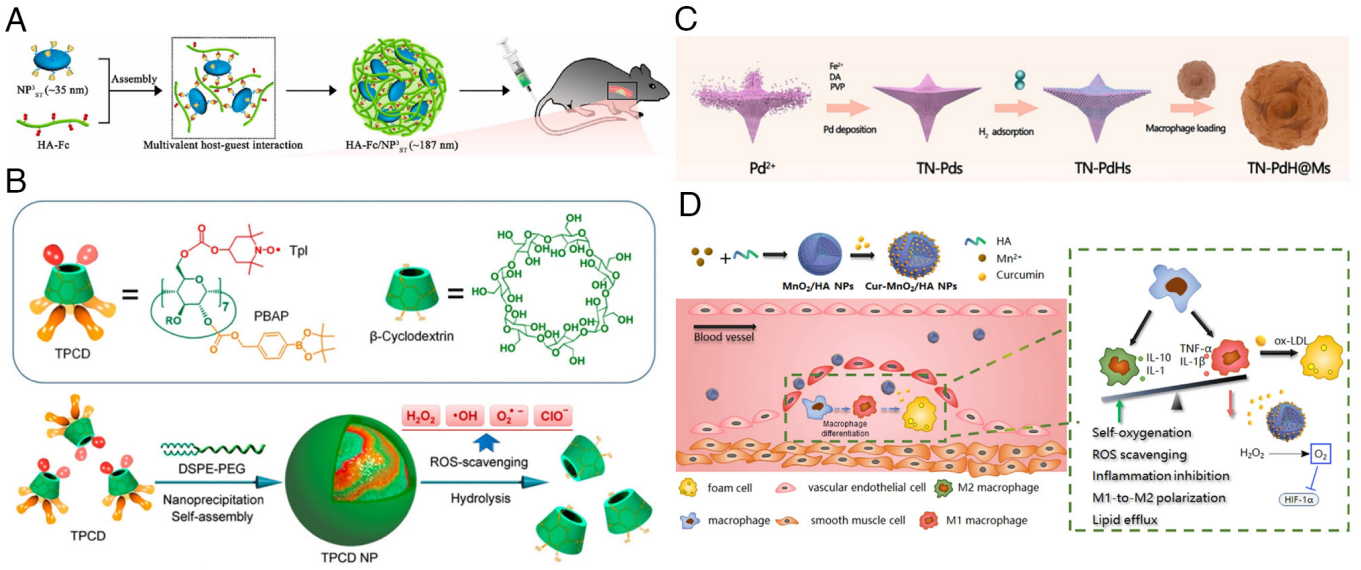

Figure 8. (A) Small-sized NP3ST is crosslinked by HA-Fc conjugates to large-sized HA-Fc/NP3ST nano-assemblies through multivalent host-guest interactions between β-CD/Fc [Reprinted with permission from Ref. (150); Copyright (2023) Elsevier]. (B) Chemical structure of a broad-spectrum ROS-eliminating material TPCD and development of a TPCD nanoparticle (TPCD NP) [Reprinted with permission from Ref. (151); Copyright (2018) American Chemical Society]. (C) Schematic illustration of synthetic procedure of TN-PdH@Ms, and autophagy-synergetic multiple effects for treating atherosclerosis as enabled by the engineered TN-PdH@Ms [Reprinted with permission from Ref. (152); Copyright (2022) American Chemical Society]. (D) A scheme illustration the preparation of the Cur loaded MnO2/HA for targeting delivery in atherosclerotic lesions, and the mechanisms for anti-AS therapy [Reprinted with permission from Ref. (152); Copyright (2022) Spring Nature]. ROS, reactive oxygen species; TPCD, cyclic polysaccharide β-cyclodextrin; PDH, pyruvate dehydrogenase; NP, nanoparticle; oxLDL, oxidized LDL; HIF-1α; hypoxia-inducible factor 1$^{\alpha}$.

transport receptor ABCA1 impairs cholesterol excretion by macrophages. Therefore, it is crucial to target macrophages within the plaque environment, modulate their lipid metabolism, and regulate cholesterol influx and efflux for the progression of atherosclerosis (147).

Given that the inability to efflux cholesterol from macrophages within atherosclerotic plaques is a major contributor to disease progression, numerous therapeutic strategies focus on restoring cholesterol efflux capacity. Consequently, various nanomaterials have been designed to target diseased macrophages and plaques by addressing the underlying metabolic abnormalities and metabolites in this environment. In the subsequent section, the review shall focus on the nanomaterials designed to facilitate cholesterol efflux from macrophages, mitigate inflammation in atherosclerosis, and ameliorate the disease.

In the atherosclerotic plaque environment, the abnormal accumulation of cholesterol in macrophages triggers local inflammation by promoting the production of ROS and the secretion of inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6, IL-8 and TGF-β. These inflammatory responses further attract immune cells to the site (148,149). Given the unique characteristics of the atherosclerotic plaque environment, which is characterized by high levels of ROS, environmentally responsive nanomaterials have been developed to modulate the abnormal lipid metabolism in macrophages.

For instance, He *et al* (150) reported the development of a nano-module called HA-Fc/NP3ST, comprising disc-shaped high-density lipoprotein, hyaluronic acid-ferrocene conjugate anchored by β-cyclodextrin. This nanomaterial exhibits ROS responsiveness and undergoes size reduction. In atherosclerotic mice, it demonstrates a potent therapeutic effect by releasing HDL in response to excessive ROS. This deepens plaque penetration and targets cholesterol efflux from macrophages, leading to a significant reduction in plaque area and lipid deposition (Fig. 8A).

Wang *et al* (151) prepared nanoparticles by covalently coupling superoxide dismutase simulator tempol and pinacol phenylborate, which are hydrogen peroxide elimination compounds, to cyclic polysaccharide β-cyclodextrin. This nanomaterial effectively inhibits the internalization of oxLDL, thus preventing the formation of foam cells in macrophages and vascular smooth muscle cells. By significantly reducing ROS-induced inflammation and apoptosis in macrophages, it stabilizes atherosclerotic plaques and reduces the necrotic core (Fig. 8B).

Another innovative approach was introduced by Hu *et al* (152), who developed a unique quadruped needle-like PDH nano-enzyme that is loaded into macrophages and specifically targets arterial plaques. This nanomaterial demonstrates ROS scavenging activity, anti-inflammatory properties and the activation of autophagy. It yields highly favorable outcomes in the management and treatment of atherosclerosis by concurrently addressing multiple facets of the disease (Fig. 8C).

Additionally, Sun *et al* (153) have developed a nano-drug based on MnO_2, which is used to reprogram macrophages and target atherosclerosis. The incorporation of curcumin (Cur) with antioxidant and anti-inflammatory properties into MnO_2 enables the polarization of M1 macrophages into the M2 phenotype. MnO_2 also inhibit HIF-1α and restores the lipid efflux function of macrophages, thereby suppressing foam cell formation and removing lipids and ROS from cells. This nanomaterial exhibits a robust anti-atherosclerotic effect (Fig. 8D).

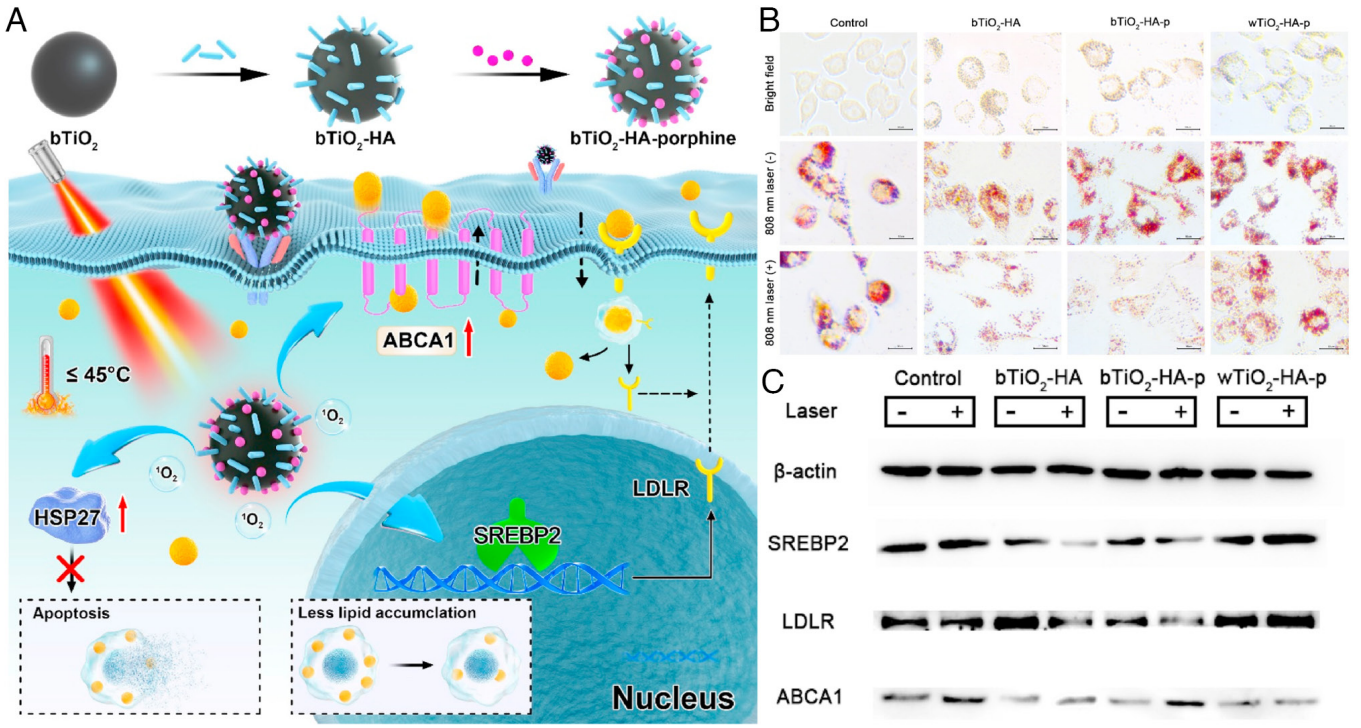

Figure 9. (A) Schematic illustration of lipid metabolism in foam cells after phototherapy with $bTiO_2$-based nanoprobes irradiated by 808 nm NIR laser. (B) Effects of mild phototherapy on the intracellular lipid burden. (C) Examination of the mechanism underlying the effects of mild phototherapy on lipid metabolism [Reprinted with permission from Ref. (155); Copyright (2022) Elsevier].

The use of photosensitizers engulfed by cells in combination with near-infrared light irradiation can generate ROS or heat, which regulates the cholesterol efflux capacity of macrophages in the plaque and affects necrosis, apoptosis and autophagy of foam cells in atherosclerotic plaques, thereby slowing down the progression of atherosclerosis. For instance, upconversion fluorescent nanoparticles encapsulating chloroproteins e6 (UCNPs-Ce6) were used to mediate PDT, enhancing the cholesterol efflux ability and inducing autophagy in THP-1 macrophage-derived foam cells (154). In another study, Dai *et al* (155) designed a nanoprobe that combines photothermal therapy and PDT by loading hyaluronic acid and porphyrin onto black TiO_2. This nanomaterial effectively targets macrophage foam cells in atherosclerotic plaques without inducing extensive apoptosis and necrosis that could damage the plaque. Through the SREBP2/LDLR pathway, it reduces cholesterol production and excess cholesterol uptake in cells while initiating ABCA1-mediated cholesterol efflux, thus inhibiting lipid accumulation in foam cells (Fig. 9).

Apart from the surge of ROS, another characteristic of atherosclerotic lesion environment is acidic pH. The acidic microenvironment in atherosclerotic plaques is primarily caused by the accumulation of lactic acid secreted by macrophages due to enhanced glycolysis. The underlying mechanisms were described in detail.

During the development of atherosclerotic plaques, oxygen consumption in the vascular wall increases, but the narrow vascular lumen leads to insufficient oxygen supply, resulting in tissue hypoxia in the plaque lesions. This hypoxic condition stabilizes the HIF-1α transcription factor in macrophages, activating the glycolysis pathway to generate energy. Therefore, the accumulation of lactic acid within plaques is a byproduct of macrophage glycolysis. Increased glucose uptake by macrophages and enhanced glycolytic metabolism in atherosclerotic vascular walls contribute to increased inflammatory burden and plaque progression. The mechanism involves increased glucose uptake and glycolytic flux, which generate mitochondrial ROS, promoting the phosphorylation of PKM2 and transcription factor STAT3. This leads to the production of inflammatory cytokines such as TNF-α, IL-6 and IL-1β. A significant portion of macrophages in atherosclerotic plaques originate from the proliferation of resident macrophages within the plaques. Increased activity of PPP is crucial for the synthesis of proteins in inflammatory macrophages and the amino acids required for RNA and DNA synthesis. Glycolysis provides fuel for the PPP, and its activation leads to the removal of electrons and production of ROS through mitochondrial and phagosome NADPH oxidase. ROS contribute to oxidative stress in atherosclerotic plaques by oxidizing proteins and fatty acids.

Excessive lactic acid plays a role in promoting angiogenesis and vascular calcification within atherosclerotic plaques. Moreover, accumulated lactic acid can increase cholesterol accumulation inside and outside cells through various mechanisms, including inducing extracellular acidification, enhancing lipoprotein retention and modification, and reducing apolipoprotein E secretion. Therefore, inhibiting the process of glycolysis, preventing lactic acid accumulation and promoting lactic acid consumption will be effective ways to alleviate atherosclerosis. However, there are limited nanomaterials that target these processes. Moreover, corresponding nanomaterials with acidic pH responsiveness have emerged as an effective platform for the on-demand release of anti-atherosclerotic drugs in the inflammatory microenvironment.

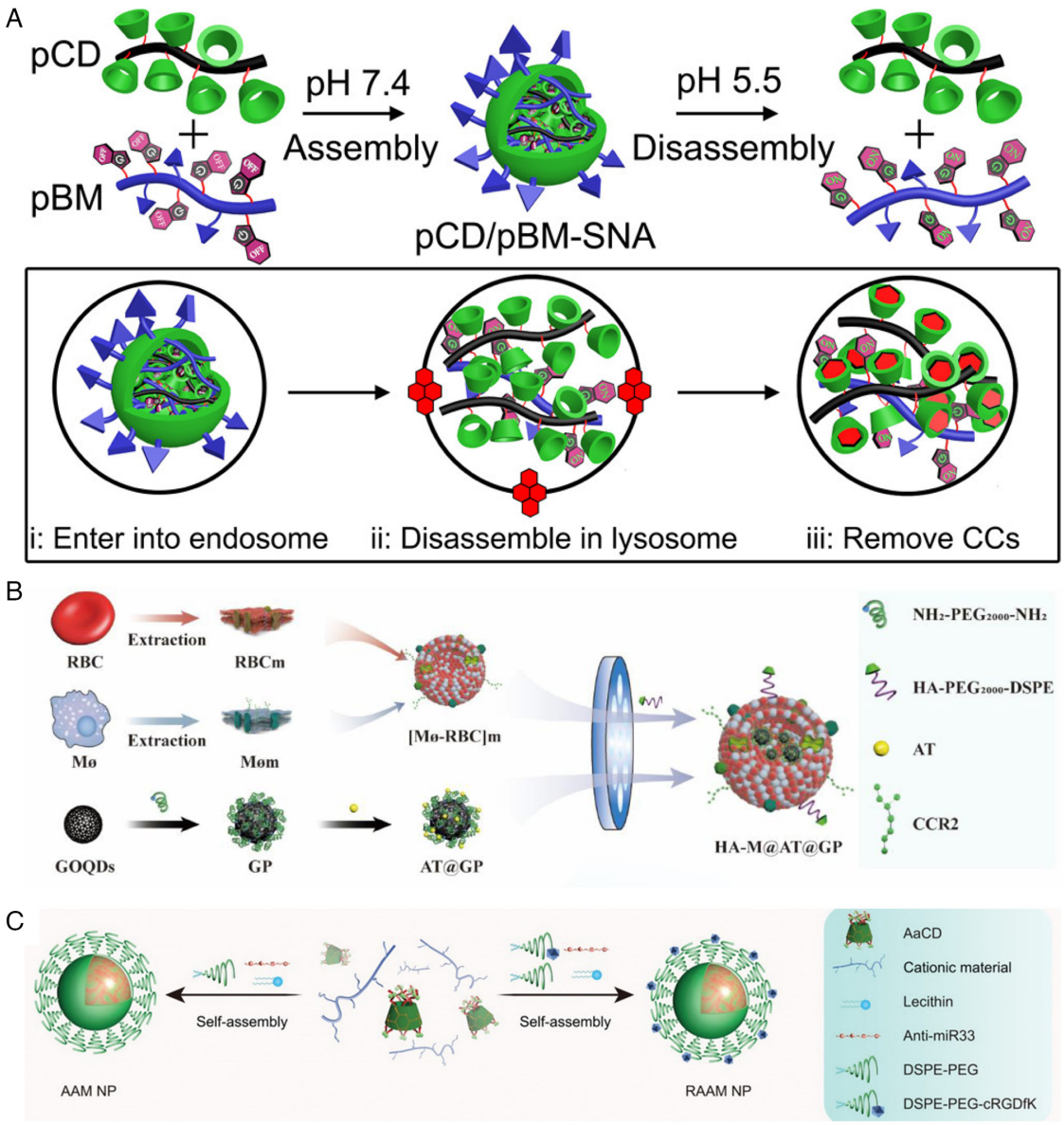

Figure 10. (A) Schematic diagram of the poly-β-cyclodextrin supramolecular nanoassembly as a pH-sensitive lysosomal cholesterol crystal remover for antiatherosclerosis [Reprinted with permission from Ref. (156); Copyright (2021) American Chemical Society]. (B) Schematic illustration of the fabrication of hybrid membrane camouflaged nanosystem (HA-M@AT@GP) and therapy performance in atherosclerosis [Reprinted with permission from Ref. (157); Copyright (2022) Elsevier]. (C) The composition and preparation of designed anti-miR33 nano-therapies AAM and RAAM [Reprinted with permission from Ref. (158); Copyright (2022) Wiley]. pCD, poly-β-cyclodextrin; BM, benzimidazole.

These pH-responsive nano-materials have been designed for controlled drug release and imaging diagnostic applications in atherosclerosis. Drugs such as metformin, pioglitazone and statins have shown efficacy in regulating macrophages and mitigating the progression of atherosclerosis. Nonetheless, using pure drugs lacks targeting specificity. Therefore, numerous studies have utilized the acidic environment to design nano-drug delivery systems with pH-responsive properties, specifically targeting diseased macrophages for the treatment of atherosclerosis.

For instance, Zhang *et al* (156) employed poly-β-cyclodextrin as a cholesterol crystal solubilizer and benzimidazole-grafted dextran sulfate as a pH-sensitive switch to form a supramolecular nano-assembly. This system enhanced cholesterol efflux and promoted the regression of atherosclerosis (Fig. 10A). You *et al* (157) reported a hybrid nanomaterial composed of a mixed membrane-coated graphene oxide quantum dot loaded with atorvastatin. This hybrid membrane included hyaluronic acid. This formulation effectively suppressed the inflammatory state of diseased macrophages, reduced lipid influx, enhanced autophagy to promote cholesterol efflux, and significantly inhibited plaque development (Fig. 10B). Li *et al* (158) designed pH-responsive and integrin-targeted nanoparticles derived from cyclodextrin and microRNA-33 (anti-miR33) antisense oligonucleotide for the precise treatment of atherosclerosis. This approach significantly promoted reverse cholesterol transport, alleviated atherosclerosis in mice, and markedly reduced vulnerable plaque (Fig. 10C).

Advanced atherosclerosis is characterized by the presence of extensive necrotic cores, increased apoptosis, and the accumulation of oxLDL, all of which promote the transformation of macrophages into foam cells. This

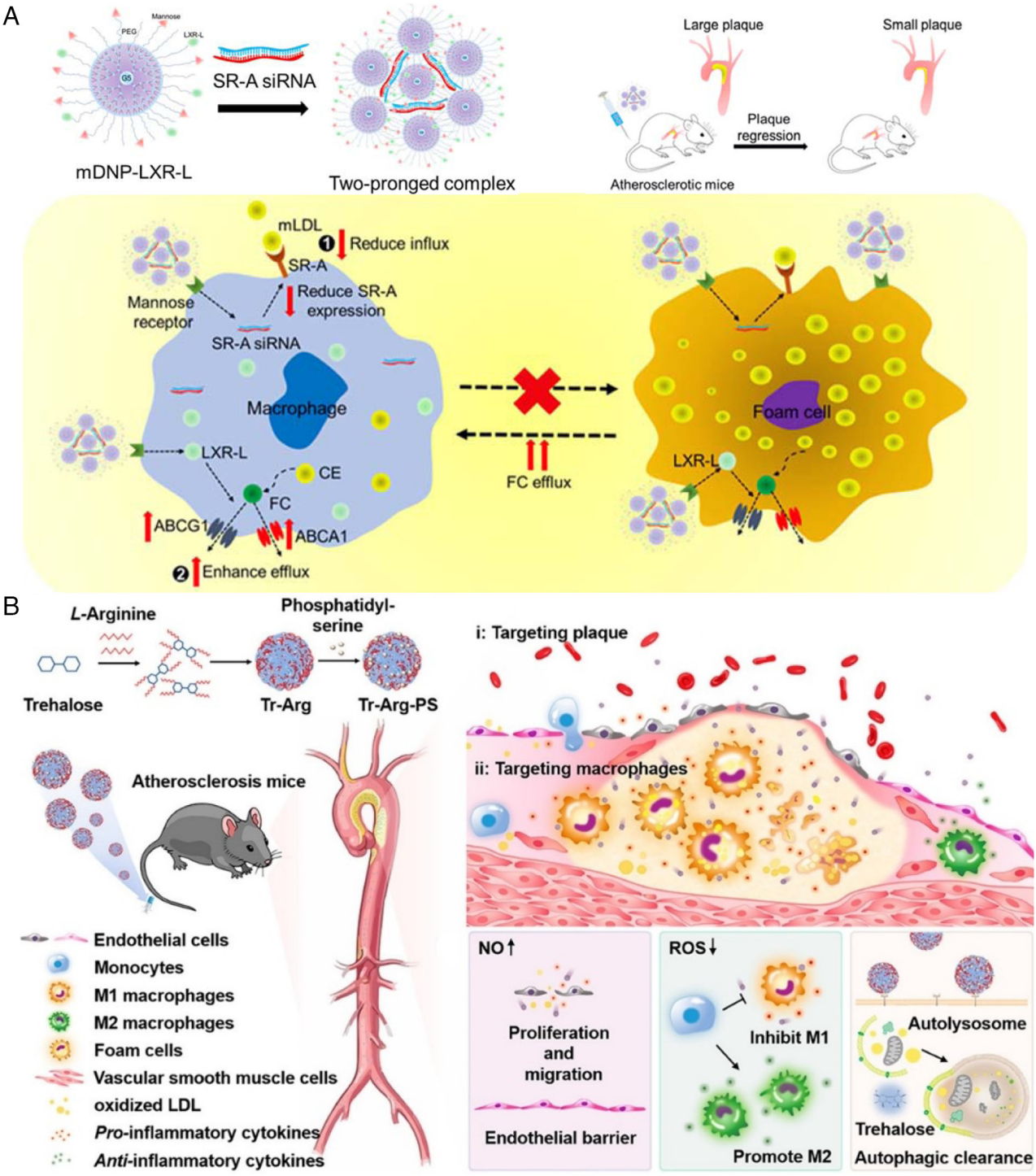

Figure 11. (A) 'Two-pronged complex' is constructed by combining the anti-atherogenic platform of mDNP-LXR-L with SR-A siRNA [Reprinted with permission from Ref. (159); Copyright (2020) Elsevier]. (B) Schematic illustration of the synthetic process of Tr-Arg-PS (TAP) nanomotors and the two-stage-targeted strategy for comprehensive treatment of AS [Reprinted with permission from Ref. (160); Copyright (2022) American Chemical Society]. mDNP, mannose-functionalized dendritic polymer nanoparticles; SR-A, scavenger receptor-A; LXR-L, liver X receptor ligand.

process contributes to plaque instability and poor prognosis. In the late stage of atherosclerosis, macrophage function becomes impaired, hindering the clearance of necrotic cells and resulting in the outflow of lipid-laden necrotic cells and infiltration of inflammatory cells. Therefore, the induction of macrophage autophagy to rectify irregular lipid metabolism has emerged as a pivotal therapeutic strategy for alleviating arterial congestion.

A recent study harnessed optimized mannose-functionalized dendritic polymer nanoparticles to simultaneously deliver scavenger receptor-A siRNA (to reduce LDL uptake) and liver X receptor ligand (to stimulate cholesterol outflow). This approach effectively reduced the cholesterol content of macrophages, promoted the regression of atherosclerotic plaques and facilitated plaque stabilization (159) (Fig. 11A). Wu *et al* (160) developed a carrier-free nanomotor driven by NO based on

the reaction between trehalose (one of the mTOR-independent autophagy inducers), L-arginine and phosphatidylserine. This nanomotor precisely targeted macrophages in atherosclerotic plaques, regulated their polarization to the M2 phenotype, promoted lipid excretion and facilitated the reconstruction of the endothelial barrier, enabling multifaceted treatment of atherosclerosis (Fig. 11B).

In addition to abnormalities in lipid metabolism and glycolysis, amino acid metabolism and iron metabolism also play important roles in atherosclerosis. The immunomodulator ARG1, crucial in macrophages, regulates atherosclerotic plaque progression by inhibiting NO-mediated cytotoxicity through L-arginine consumption, primarily in anti-inflammatory macrophages within the plaques. This modulation decelerates plaque progression, promotes the formation of fibrous caps and increases plaque stability. NO and ARG1 are commonly used as indicators to assess changes in macrophage phenotype. Glutamine, another extensively studied amino acid in atherosclerotic macrophages, has been found to stabilize inflammation. Anti-inflammatory macrophages exhibit increased uptake of glutamine. Iron overload in macrophages within atherosclerosis contributes to their transformation into foam cells, exacerbates glycolysis and macrophage inflammation, and worsens the severity of the disease.

Although advanced nanomaterial development has primarily focused on addressing lipid metabolism, inhibiting foam cell formation and reducing the expression of inflammatory factors, there is a pressing need to explore the potential of nanomaterials in addressing iron metabolism and amino acid metabolism. These areas hold great promise as therapeutic targets in the comprehensive study of macrophage metabolism within the atherosclerotic plaque environment, thus warranting the development of new nanomaterials.

4. Conclusion

In the present review, the typical metabolic pathways of macrophages were comprehensively outlined, highlighting their inherent relationship with macrophage polarization and functional activation. Furthermore, the aberrant metabolic processes in macrophages associated with cancer and atherosclerosis were illustrated. Additionally, an overview of recent advancements in nanomaterials aimed at reprogramming macrophage metabolism, contributing to disease progression inhibition, was provided. At present, in the context of immunosuppressive TAMs, nanomaterials are primarily engineered to restrain glucose and lipid uptake, while also curbing the accumulation of glutamine and glutamate. In the case of atherosclerosis, nanomaterials are specially formulated to enhance cholesterol efflux and inhibit lipid accumulation, mitigating the formation of macrophage foam cells and plaque damage.

Nevertheless, there remain pressing issues within the realm of nanomaterials aimed at regulating the aberrant metabolism of macrophages in cancer and atherosclerosis. Firstly, although metabolic pathways such as glycolysis, OXPHOS, FAO and amino acid metabolism have received extensive scrutiny in the context of tumors and atherosclerosis, certain abnormal metabolic processes, such as those associated with iron and glutamine metabolism in atherosclerosis, remain inadequately understood. This knowledge gap holds paramount importance for the development of precise nanomaterials. Currently, these unelucidated abnormal metabolic processes lack corresponding nanomaterial interventions and thus demand further investigation.

Secondly, the prolonged biosafety of nanomaterials designed to target the abnormal metabolism of macrophages in cancer and atherosclerosis is a significant concern within this discipline. Consequently, the ongoing development of next-generation nanomaterials, including those based on proteins and DNA, is imperative.

In conclusion, the advent of advanced nanomaterials has expedited the advancement of therapeutic approaches targeting abnormal macrophage metabolism in cancer and atherosclerosis. It is evident that by harnessing the capabilities of nanomaterials and furthering the understanding of macrophage metabolism, the path for innovative immunotherapies and personalized treatments can be paved, effectively modulating macrophage function in a range of diseases.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

MMX and YC contributed equally to the conception of the review, wrote the original draft, edited and critically revised the manuscript. SYW, XLC, YYC, SJT, AQY and WWC contributed equally to data curation. LXW approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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