Nanomedicines for dysfunctional macrophage-associated diseases

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Abstract

1Introduction

2Nanomedicines and approaches for homing to macrophage

3 Nanomedicines targeting dysfunctional macrophage in diseases

3.1 Dysfunctional macrophages in cancer

3.2 Dysfunctional macrophages in atherosclerosis

3.3 Dysfunctional macrophages in rheumatoid arthritis (RA)

3.4 Dysfunctional macrophages in inflammatory bowel disease (IBD)

3.5 Dysfunctional macrophages in obesity and ensuing insulin resistance for type 2 diabetes

3.6 Dysfunctional macrophages in HIV/AIDS

4 Concluding remarks and future perspectives

Reference

Figures

Abstract

Dysfunctional macrophages have significant pathophysiological roles in diseases, including malignant tumors, inflammatory diseases (rheumatoid arthritis and inflammatory bowel disease), metabolic diseases (atherosclerosis, diabetes and obesity) and major infections like HIV/AIDS. Developing nanomedicines to target dysfunctional macrophages within diseases' foci is a promising approach to treating those diseases with better outcomes. This review discusses the roles dysfunctional macrophages have in cancerous, metabolic and infectious diseases and reviews the latest advances on nanomedicine-based therapies for treating diseases associated with dysfunctional macrophages.

Keywords: dysfunctional macrophages; nanomedicines; cancer; atherosclerosis; RA; IBD; obesity; diabetes; HIV

1 Introduction

Macrophages originate from the differentiation of blood-derived monocytes and mainly reside within tissues throughout the body. Macrophages respond to alterations in their microenvironment by producing a wide variety of products to mediate inflammation, tissue injury, homeostasis and immunity [1, 2]. Granulocyte/monocyte precursor cells develop into monocytes induced by endogenous stimuli such as macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-3 (IL-3). De novo monocytes leave the bone marrow, enter the bloodstream and approximately one day later migrate into tissues where they differentiate into tissue macrophages (called resident macrophages). They have different names based on their locations such as Kupffer cells in the liver, alveolar macrophages in lungs, red pulp macrophages in spleen, and sinus histiocytes in lymph nodes [2, 3]. Although those tissue macrophages are anatomically distinct from one another and have diverse functional capabilities and transcriptional features, they are invariably essential in maintaining the physiological function and homeostasis of organism (Fig. 1) [2, 4].

When some parts in our body (like tissues) get damaged as a result of infection or injury, circulating blood monocytes are recruited from the circulation and differentiate into macrophages once they migrate into the affected tissues [1, 5]. Macrophages can recognize pathogen-associated molecules and apoptotic cells-associated endogenous ligands through receptor-mediated recognition patterns. Those recognition events are generally ended with pathogen clearance by phagocytosis and consequent infection alleviation. However, when macrophages are inappropriately activated, an uncontrollable inflammatory response would be initiated, and their homeostatic and reparative functions would be subverted, thus resulting in a causal association of macrophages with disease states [6, 7], including growth and metastasis of malignant tumors [8-10], inflammatory diseases (rheumatoid arthritis [11-14] and inflammatory bowel disease [15, 16]), metabolic diseases (atherosclerosis [17-19],

diabetes[20-22] and obesity[23, 24]) and severe infections like HIV/AIDS[25, 26]. Therefore, based on their pathophysiological roles in diseases, targeting the recruitment, activation and regulation of dysfunctional macrophages within those diseases' foci have emerged as a promising therapeutic strategy[5, 7, 27]. Although many molecular-base therapies have been developed to target dysfunctional macrophages to restore their protection functions, the lack of macrophage-specific targeting greatly restricts the application of treatments with minimized adverse side-effects[27, 28]. Emergence and advancement of nanotechnology have given rise to specific targeting nanomedicines, and opened up new opportunities for treating diseases associated with dysfunctional macrophages[27-31]. This review discusses how macrophages play roles in various pathophysiological diseases and reviews how nanomedicines are utilized to treat dysfunctional macrophage-associated diseases.

2 Nanomedicines and approaches for homing to macrophages

Nanomedicines, the application of nanotechnology to medicine, is highly anticipated to help us solve a number of concerns associated with conventional therapeutic agents, including poor water solubility (for most new molecule entity), lack of targeting specificity, nonspecific distribution, systemic toxicity, and low therapeutic index[31-33]. Over the past several decades, remarkable progress has been achieved in the development and application of engineered nanoparticles to treat various diseases[34]. The most popular engineered nanoparticles (Fig. 2) include polymeric nanospheres, lipid structured carriers (liposomes and emulsions), polymeric micelles, dendrimers, inorganic nanoparticles (mesoporous silica nanoparticle, gold nanoparticles, quantum dots and carbon nanotubes)[35-37]. Additionally, the different types of nanoparticles with focus on material, cargo attachment, and their various advantages and disadvantages are summarized in Table 1.

Table 1 Summary of different types of engineered nanoparticles

Types	Size (nm)	Compositions	Cargo loading manner	Advantages	Disadvantages	Ref.
Nanospheres	10-1000	Solid hydrophobic nanoparticles based on polymer matrix	Embedded in the polymer matrix or loaded within the core	High loading capacity and controllable release	Difficult to purify and poor stability	[38, 39]
Liposomes	100-1000	Self-assembly of lipid bilayer	Encapsulated within the hydrophilic core and hydrophobic bilayer	Easily fabrication, better biocompatible and suitable for both hydrophobic and hydrophilic drug loading	Stability issues like cohesion and drug leakage	[40-42]
Emulsions	100-1000	Amphipathic surfactant embedding inner hydrophobic core	Encapsulated within the hydrophobic core	Highly hydrophobic drug loading	Stability issue like flocculation, coalescence and aggregation	[43, 44]
Micelles	10-100	Hydrophobic core surrounded by amphipathic polymer	Encapsulated within the hydrophobic core	Small size and able to incorporate highly hydrophobic cargo	Highly sensitive to structural changes below CMC and poor release profiles	[45, 46]
Dendrimers	10-100	Highly and uniformly branched polymer	Embedded inside the branches, conjugated to the surface chemical group, or electronic complex with gene/siRNA	Highly water soluble and functionalized surface groups.	Concerns about toxicity from highly positive surface charge and biocompatibility	[47-49]
Mesoporous silica nanoparticles	20-200	Mesoporous form of silica with nanosize	Encapsulated within the mesopores by hydrophobic interaction	High loading capacity, and homogenous distribution for guest molecules into porous	Low drug release; lack of <i>in vivo</i> studies on PK/PD, bio-distribution and clearance	[50, 51]
Gold nanoparticles	2-100	Solid gold particles within nanometer	Attached to the surface/surface coating	Innate optical and photothermal properties	No inner loading cavity; poor biocompatibility and biodegradability.	[52-54]
Quantum dots	2-10	Typically cadmium selenide core with a zinc selenide cap	Attached to the surface or surface coating	Innate optical properties and high extinction coefficient.	No inner loading cavity and toxicity issues	[55, 56]
Carbon nanotubes	1-5 diameter 1-150 length	Graphite arranged in either a sheet or cylindrical structure	Entrapped inside the carbon backbone	Innate optical and electrical properties, and high surface drug loading	Expensive production, poor biodegradability and organ accumulation	[57, 58]

In comparison to traditional formulations, nanoparticle-based nanomedicines offer many distinctive characteristics, including: 1) improved delivery of drugs with poorly water solubility; 2) extended plasma half-life of the drug in the systemic circulation through better protection of the drug from harsh environments in physiological conditions (such as high levels of proteases or other types of enzymes in the blood stream and the highly acidic environment in the stomach or the lysosomes of a cell) before they can reach the targets; 3) controlled drug release over a manageable period of time at precise doses; 4) co-delivery of multiple types of drugs and/or diagnostic agents (like contrast/imaging agents) for combination therapy and real-time readout on the treatment efficacy; and 5) targeted drug delivery in

a cell-specific or tissue-specific manner so that the treatment efficacy can be maximized while systemic side effects are minimized[32, 35]. These advantages have already made several excellent nanomedicines available on market or in clinic trials[34, 36, 59, 60], and also can be utilized to provide better therapeutic solutions to diseases arising from dysfunctional macrophages.

To further enhance the specificity to those dysfunctional macrophages in diseases' foci, active targeting approaches can be achieved based on the surface modification of the nanoparticles with moieties (such as ligand, antibody and peptide, etc.) that have selective affinity for recognizing and interacting with certain receptors on the surface of macrophages[28, 31, 61-64]. Table 2 briefly describes some receptors that are overexpressed on the surface of macrophages and have been utilized for actively targeting macrophages, including mannose receptor, scavenger receptors, dectin-1 receptor, tuftsin peptide, CD44 receptor, folate receptor beta (FR-b) and phosphatidylserine receptor.

Table 2 Examples of receptors targeting macrophages

Macrophage-targeted receptors	Brief description	Ref.
Mannose receptor	Cluster of Differentiation 206, CD206; A C-type lectin primarily present on the surface of macrophages can recognize mannose terminal, N-acetylglucosamine and fucose residues molecules with high affinity.	[65-68]
Scavenger receptor	A group of receptors (categorized into classes A, B, and C) that highly recognize modified low-density lipoprotein (LDL) such as SR-A and CD36.	[69-73]
Dectin-1 receptor	A non-opsonic β -glucan receptor, overexpressed in macrophages, is essential for the phagocytosis of yeast by macrophages through the recognition of β -glucans, a cellular component of yeast.	[74-76]
Tuftsin peptide	Tetra-peptide sequence l-Thr-l-Lys-l-Pro-l-Arg (TKPR); Synthesized by the enzymatic processing of the Fc fragment of the heavy chain of IgG molecule; Activates macrophage and enhances their phagocytic ability.	[77-79]
CD44 receptor	Cell-surface glycoprotein involved in cell-cell interactions, cell adhesion and migration; Distinctive receptor for hyaluronic acid and can also interact with other ligands, such as osteopontin, collagens, and matrix metalloproteinases (MMPs).	[80-82]
Folate receptor beta (FR-b)	FR-b is specifically expressed by activated macrophages and shows a high affinity for folic acid (FA).	[83-86]
Phosphatidylserine receptor	Responsible for clearance of apoptotic cells overexpressing phosphatidylserine on the outflow of membrane.	[87, 88]

3 Nanomedicines targeting dysfunctional macrophage-associated diseases

Dysfunctional macrophages have common pathological features and critical implications in the pathogenesis of many disorder conditions of various diseases, and therefore dysfunctional macrophage could serve as a potential target for the prevention and treatment of these diseases. We highlight the characteristics and some potential therapeutic strategies of dysfunctional macrophage-associated diseases (Fig.3 and Table 3), along with some selected examples from recently reported nanomedicine-based therapies [1, 5, 7].

Table 3 Overview of major dysfunctional macrophage-associated diseases and selected nanomedicines

Disease type	Involvement of dysfunctional macrophage	Potential therapeutic strategies for dysfunctional macrophage	Selected nanomedicines based on dysfunctional macrophage
Cancer	Macrophage within the tumor microenvironment, termed as tumor associated macrophages (TAMs), facilitate angiogenesis, extracellular matrix remodeling and promote tumor cell metastasis.	Inhibiting macrophage recruitment and activation; Suppressing TAMs survival; Enhancing M1-like tumoricidal activity of TAMs and blocking M2-like tumor-promoting activity of TAMs.	[89-93]
Rheumatoid arthritis	The abundance and activation of macrophages in the inflamed synovial membrane/pannus lead to inflammation and ensuing osteoclasts.	Reduce the numbers of activated macrophages to inhibit activation signals and/or their specific products that amplify the disease.	[94-97]
Inflammatory bowel disease	A change in flora or a defect in microbial clearing processes can lead to uncontrolled microbial growth in the lamina propria, thus stimulating recruitment and activation of inflammatory macrophages	Use of receptor agonists or antagonists that stimulate intestinal immune responses to achieve the required response, thus inhibiting the recruitment of macrophage from blood.	[98-101]
Atherosclerosis	Under stimulus from oxLDL, the recruited monocyte differentiates into macrophages that overexpress scavenger receptors, which internalize excessive oxLDL in an unregulated manner, thus propagating the inflammatory cascade and leading to neointimal plaques	Alleviate the inflammation in intima to stop the monocyte recruitment; Inhibit lipid accumulation in macrophage to stop the foam cell formation; Enhance the removal of cholesterol ester from the existing plaque.	[102-106]
Diabetes	Pro-inflammatory cytokines produced by M1-like macrophages abundant in adipose tissue inhibit insulin receptor signaling and lead to insulin resistance.	Anti-inflammatory treatments; Transition in macrophage polarization from M1-like state back to M2-like state	[107-109]
Obesity	Adipose tissue is intimately characterized by infiltration of large number of pro-inflammatory macrophages (termed as adipose tissue macrophages, ATMs)	Anti-inflammatory treatments; Transition in macrophage polarization from M1-like state back to M2-like state	[110-113]
HIV/AIDS	Macrophages not only act as the HIV antigen presenting cells and also disseminate HIV-1 viral throughout the body	Targeting HIV-1 reservoir in macrophages; Sensitive the antigen presenting capacity for macrophage;	[114-117]

3.1 Dysfunctional macrophages in cancer

3.1.1 Involvement of tumor-associated macrophages in cancer development

Accumulating evidences from clinical and experimental studies indicate that macrophages in tumor tissues, namely tumor-associated macrophages (TAMs), have important roles in progression and

metastasis of solid tumors [118-120]. TAMs are the main population of inflammatory cells in solid tumors and the cytokines released from them possess diversified roles in tumor advancement. Specifically, macrophages are first derived from blood-derived monocyte, activated by some chemotactic factors within tumor microenvironment and then actively provide many trophic functions that facilitate tumor progression and metastasis. Many studies have already demonstrated that the majority of TAMs are activated M2-like macrophages, with anti-inflammatory properties that very differ from the pro-inflammatory M1-like macrophages which are usually resident in tissue areas with acute inflammation. Once being activated, M2-like TAMs highly express amount of tumor-promoting cytokines and growth factors (such as endothelial growth factor, angiopoietin, matrix metalloproteinase 9 and TNF- α , etc.), and thus facilitate tumor promotion, angiogenesis, progression and metastasis, matrix remodeling and immune evasion (Fig. 4). Additionally experimental investigations indicate that TAMs also contribute to drug-resistance and radioactivity-protective effects, and clinical evidences show that an elevated number of TAMs and their M2-like profile are positively correlated with poor prognosis and therapeutic failure in cancer patients [91, 121]. Therefore specific TAMs-targeted drug delivery, depletion of TAMs and conversion from tumor-promoting M2 subtype to tumor-suppressing M1 subtype have now been considered as potential targets for adjuvant anti-cancer therapy.

3.1.2 Tumor-associated macrophages as a therapeutic target for cancer treatment

Recently, TAMs-targeted strategies have achieved significant progress and some works got encouraging results. Based on the proposed involvement of TAMs in tumor, those strategies are generally classified into the four categories: (1) inhibiting recruitment and activation of monocyte-derived macrophage [122]; (2) repressing survival of TAMs [123]; (3) enhancing the anti-tumor activity of M1-like TAMs [74]; (4) suppressing the tumor-promoting activity of M2-like TAMs [124-126].

Although the clinical application of molecular-based TAM targeting approach is still far from success, a number of experimental studies have collectively shown the utility of this approach on effective tumor suppression and well therapeutic outcomes, which sheds inspiration all light on further clinical trials. Several excellent reviews [118, 119, 124-127] have been written on targeting tumor-associated macrophages in cancer therapy, but with a few focuses on the field of nanomedicines targeting TAMs. So here we aim to briefly review with particular emphasis on recent developments and applications of TAMs-targeting nanomedicines for anticancer therapy.

Since unlike the tumor-promoting M2-like macrophage, the pro-inflammatory M1-like macrophages in the tumor exert anti-proliferative and cytotoxic activities against the progression of tumor, which is due to their ability to secrete oxygen species and reactive nitrogen (such as hydrogen peroxide, NO, peroxynitrite, and superoxide, etc.) and some pro-inflammatory cytokines (such as TNF- α , IL-1, and IL-6) [128-130]. Hence, reprogramming the TAMs from M2-like subtype to M1-like subtype could be an efficient strategy for anticancer therapy. Song et al. developed mannan-conjugated MnO₂ particle with hyaluronic acid (HA) modification (Man-HA-MnO₂ NPs), where mannan was utilized as a macrophage targeted ligand, MnO₂ was used as tumor hypoxia alleviator by highly reacting with hydrogen peroxide in tumorous hypoxic area for simultaneous production of O₂ and regulation of pH and HA modification was to reprogram anti-inflammatory, pro-tumoral M2 TAMs to pro-inflammatory, antitumor M1 macrophages to further enhance the ability of MnO₂ NPs to lessen tumor hypoxia and also modulate chemoresistance (Fig 5). The results showed that this multifunctional nanoparticle significantly increased tumor oxygenation and M1-like population in tumor. Combination treatment of the tumors with Man-HA-MnO₂ NPs and doxorubicin significantly inhibited tumor growth in comparison to free doxorubicin alone. Besides, the ability of Man-HA-MnO₂ NPs to react with endogenous H₂O₂ highly enhanced T1- and T2-MRI performance for better tumor imaging application [131].

In order to actively targeted delivery of anticancer agents to the TAMs but reduce the non-specific uptake by some normal organs, Zhu et al. reported a PEG-sheddable and mannose-modified nanoparticle that efficiently targeted TAMs via mannose receptor after shedding acid-sensitive PEG coating in the acidic tumor microenvironment, while reduced the unwanted uptake by normal macrophages in the mononuclear phagocyte system (MPS) organs due to effective PEG shielding at neutral pH condition. Animal studies showed this novel modified-nanoparticle possessed higher tumor accumulation but lower undesired normal tissues accumulation than the unmodified one, likely due to smart PEGylation shielding/shedding and mannose modification [132]. Niu et al. also demonstrated combination of mannose modification and acid-sensitive sheddable PEGylation TAMs highly delivered doxorubicin (DOX) to TAMs in triple-negative breast cancer, animal studies showed that a single intravenous injection of functionalized nanoparticles significantly reduced macrophage population in tumors within 2 days, and the repeated injections of nanoparticle could help keep the population of the macrophages at a lower level even for 9 days after the first injection [133].

Due to the widely observed serious side effects and bad patient compliance of traditional chemotherapeutic drugs, bioactive macromolecules (such as peptides and gene) such as gene and present a promising direction in future [134-136]. Yu et al. designed and characterized pH-responsive polymeric micelles that were mannosylated using “click” chemistry to achieve CD206 (mannose receptor)-targeted delivery siRNA to TAMs. Results showed that the mannosylated nanoparticles improved the delivery of siRNA into primary macrophages by 4-fold higher compared with the delivery of a non-targeted carrier. Further, after 24 h treatment with the mannose-targeted siRNA carriers, $87 \pm 10\%$ knockdowns of a model gene was observed in primary macrophages, a typical cell difficult to transfect, which suggested this polymeric micelles could be used as a promising gene vector targeting TAMs [100]. Cieslewicz et al. designed a novel peptide, called M2pep, which could strongly bind to and

be internalized into M2-like macrophages responsible for tumor growth and metastasis while minimal interaction with M1-like macrophage responsible for anti-tumor property. They used M2pep to carry a pro-apoptotic peptide to TAMs and demonstrated that selective reduction of M2-like TAMs resulted in improved survival in tumor-bearing mice[90].

3.1.3 Macrophage membrane-camouflaged nanomedicines for cancer treatment

Recently, bio-mimetic strategies, that nanoparticles are engineered to mimic the cellular functions, are attracting close attentions for drug delivery application. The innate tumor homing capacity of macrophages can be employed as a ‘Trojan horse’ to camouflage the nanoparticles containing anti-cancer agents and then specifically deliver loaded agents to the tumor[137-140]. Cao et al. used macrophage membrane to decorate liposomes to improve tumor-metastasis targeting capability (though $\alpha 4$ integrin-VCAM-1 interactions between macrophages and metastatic cancer cells) and suppress lung metastasis of breast cancer (Fig. 6). Macrophage membranes were first isolated from murine monocyte/macrophage cell line RAW 264.7 cells with high expression of $\alpha 4$, and then coated the emtansine liposome with the isolated macrophage membrane to generate a macrophage membrane-coated emtansine liposome. The results showed that this macrophage membrane decoration increased cellular uptake of the emtansine liposome by metastatic 4T1 breast cancer cells and had significant inhibitory effects on cell viability. *In vivo*, the macrophage membrane-coated liposome targeted metastatic cells and then produced an obvious inhibitory effect on lung metastasis of breast cancer[89].

Xuan et al. used macrophage cell membrane (MPCM) to decorate gold nanoshells (AuNS) that can serve as a new generation of photothermal conversion agents for *in vivo* photothermal cancer therapy. The resulting MPCM-coated AuNSs exhibited good colloidal stability and kept the original near-infrared adsorption of AuNS. Because AuNS carried high density coverage of MPCM, the totally functional portions of macrophage cell membrane were grafted onto the surface of AuNS. This surface

functionalization provided active targeting ability by recognizing tumor endothelium and thus improved tumor accumulation in comparison to the red blood cell membrane coating approach. These biomimetic nanoparticles significantly enhanced *in vivo* blood circulation and local accumulation at the tumor after being systematically administered. Upon laser irradiation, local heat generated by the MPCM-coated AuNS achieves high efficiency to suppress tumor growth and selectively ablate cancerous cells within the illuminated zone[141].

Those strategies all employed physical interactions between isolated macrophage membrane fragments and inner nanostructured core, the stability issue in circulation will post a big challenge, as complex components in blood may competitively replace the coated macrophage membrane and bind to the surface of inner core, thus leading to unexpected shed off of macrophage membrane and ensuing off-target accumulation. Hence, how to obtain stable macrophage membrane-derived coating will be a highly concerned point. Our lab exploited click reaction on the basis of bioorthogonal chemistry to get a very stable conjugation bond between macrophage and nanoparticles. For instance, Xu et al. previously fed the RAW 264.7 with azido sugar to let cells express azides on the surface; meanwhile succinimidyl ester DIBO alkyne was coupled to amine-terminated PAMAM dendrimer G4.0 to make clickable dendrimers, and then hybridized macrophage with PAMAM dendrimer was formed via copper-free click reaction. Efficient and selective cell surface modification by dendrimers was confirmed by confocal microscopy. Viability and motility of RAW hybrids remain the same properties as untreated RAW cells according to a series of bioassay. Therefore, this concept shows the feasibility of applying bioorthogonal chemistry to create cell membrane-nanoparticle hybrids and could provide new approach for the nanoparticle surface engineering via cell membrane[142].

In addition to recent advances on TAMs-targeted nanomedicines, novel immunotherapy-based TAMs depletion has also been widely investigated and some of them already entered clinic, which could

provide us with some powerful support and reference for the design of TAMs-targeted nanomedicines[119, 125, 126, 143].

3.2 Dysfunctional macrophages in atherosclerosis

3.2.1 Involvement of macrophages in the development of atherosclerosis

During the development of atherosclerosis, macrophages have multiple functions in all phases of atherosclerosis, from development of the fatty streak to ultimate plaque rupture[144, 145]. Both the leakiness of endothelial cell junctions in areas of low shear stress and some injury of endothelial cell junction in areas of high shear stress permit excessive blood-derived low-density lipoprotein (LDL) to enter the intima, where it is converted to oxidized LDL (oxLDL). oxLDL initiates inflammation and upregulates adhesion molecules, such as P-selectin, intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1), to recruit leukocytes, like monocytes. Recruited monocytes will adhere to various leukocyte adhesion molecules on the activated endothelial layer, and migrate into the tunica intima, innermost layer of the arterial wall. Once arrive the arterial intima, monocytes acquire stimulus from oxLDL, undergo a series of morphological changes and ultimately transform into macrophage. Macrophages inside the intima overexpress scavenger receptors (such as the SRA and CD36) and internalize excessive oxLDL through those receptors in an uncontrolled fashion, thus leading to formation of foam cell and ensuing necrotic lipid core, which constitute the early atherosclerotic lesion and further propagate the inflammatory cascade (Fig. 7)[146]. Moreover, many evidences based on animal studies have strongly demonstrated that macrophage depletion is highly resistance to development of atherosclerosis. Hence macrophages already became a promising target for new interventions against atherosclerosis[19, 147, 148].

3.2.2 Dysfunctional macrophages as a therapeutic target for atherosclerosis treatment

Based on the vital roles of macrophage during progression of atherosclerosis, there are following aspects that could be considered as potential therapeutic targets to modulate functions of macrophage [18, 149-152], thus preventing development of atherosclerosis: 1) inhibiting leukocyte adhesion [104, 153]; 2) inhibition of LDL oxidation to retard the macrophage activation, for instance, angiotensin-converting enzyme (ACE) inhibitors are reported to increase the resistance of circulating LDL to oxidation and reduce the development of atherosclerosis in *Apoe*^{-/-} mice independently out of their blood pressure-lowering effects [154, 155]; 3) suppression of macrophage scavenger receptor activity could potentially reduce the uptake of oxLDL and thus reduce the foam cell formation [105, 156] and 4) regulation of cholesterol homeostasis in macrophage, for example, reduction of cholesterol ester accumulation and increment of cholesterol ester efflux in macrophage within plaques [157, 158].

Many reports proved that modulating the polarity of macrophages (M1/M2-like macrophages) toward a less inflammatory direction may be a potential strategy to prevent plaque destabilization and rupture [106, 147, 159, 160]. Nakashiro et al. prepared biodegradable poly(lactic-co-glycolic-acid) nanoparticles (NPs) containing pioglitazone (clinically approved potent agonist of peroxisome proliferator-activated receptor- γ to affect macrophage polarity), and found that intravenous administration of NPs incorporated with fluorescein isothiocyanate was almost accumulated in circulating monocytes and aortic macrophages proved by flow cytometry, which suggested the macrophage-targeting property. Additionally, weekly intravenous administration of pioglitazone-NPs (7 mg/kg per week) for 4 weeks significantly decreased buried fibrous caps, a surrogate marker of plaque rupture, in the brachiocephalic arteries of *Apoe*^{-/-} atherosclerotic mice mainly through suppressing the recruitment of inflammatory monocyte and activating the production of anti-inflammatory M2 macrophage within plaques [104].

In order to suppress the uptake of oxLDL by macrophage and further inhibit formation of foam cell, Dr. Moghe's laboratory designed a library of sugar-based amphiphilic core-shell layered

nanoparticles (AM NPs), and demonstrated those AM NPs had high binding to scavenger receptor A (SR-A) and CD36 on macrophage and down-regulation of both scavenger receptors, thus preventing oxidized lipid uptake in macrophages and switching them to an atheroprotective phenotype (Fig. 8). When intravenously administered to a mouse model of cardiovascular disease, these AM NPs showed a pronounced increase in lesion association compared with the control nanoparticles, causing a significant reduction in neointimal hyperplasia, lipid burden, cholesterol clefts, and overall plaque occlusion. Thus, synthetic macromolecules configured as NPs are not only effectively mobilized to lipid-rich lesions but can also be deployed to counteract atheroinflammatory vascular diseases, highlighting the promise of nanomedicines for hyperlipidemia and metabolic syndromes[105]. Zhang et al. used 1-(palmitoyl)-2-(5-keto-6-octene-diyl) phosphatidylcholine as a CD36-targeted ligand to improve the macrophage targeting property and antiatherogenic bioactivities of epigallocatechin-3-gallate (EGCG) containing nanoparticle, and the results showed CD36-targeted nanoparticle delivered more EGCG to macrophage cytosol and decrease cholesterol accumulation and inflammatory responses in macrophages, which may in turn prevent atherosclerosis formation and development[161]. To more effectively treat atherosclerosis, the combinations of some therapeutic targets had been attempted as better options to have synergistic action, such as combination of reducing lipid accumulation and minimizing inflammation. Dr. Moghe' laboratory incorporated the antioxidant α -tocopherol into the core based on sugar-derived amphiphilic polymers that suppress activity of scavenger receptor for internalizing oxLDL. These composite nanoparticles inhibited key features of atherosclerosis (modified lipid uptake and the formation of foam cells), while minimizing inflammation in the most advanced *ex vivo* models available today[162].

The underlying essence of atherosclerosis is characterized by the deposition of cholesteryl ester (CE) rich macrophage foam cells in the artery wall. Although significant advances have been made to reduce circulating chole

sterol levels, either by inhibiting *de novo* synthesis (by statins) or reducing cholesterol absorption (by Ezetimibe), no therapy is currently available to efficiently enhance the removal of CE from existing atherosclerotic plaques to facilitate plaque regression [163, 164]. Therefore, the burden of existing plaques in the arteries and associated pathological consequences still remain after these conventional interventions, and CE abundant in macrophage within plaques will be a novel target against atherosclerosis. Since only unesterified or free cholesterol (FC) can be effluxed from the cells to extracellular cholesterol acceptors, hydrolysis of CE is the obligatory first step in CE mobilization from macrophages. This reaction, catalyzed by neutral cholesteryl ester hydrolase (CEH), is increasingly being recognized as the rate-limiting step in FC efflux, which regulates the process of reverse cholesterol transport and ultimate elimination of cholesterol from the body [157]. Hence, our lab developed mannose-functionalized dendrimer nanoparticles (DNP) for the specific delivery of LXR ligand (TO901317) [165], which could increase the CEH expression, to plaque-associated macrophage in order to enhance the removal of cholesteryl esters (CE) from existing atherosclerotic plaques and facilitate plaque regression. Results showed mannose functionalized DNP could specifically deliver to macrophages and increase CEH expression *in vitro* as well as *in vivo*, thus reducing the progression of atherosclerosis.

3.2.3 HDL as a drug carrier to target dysfunctional macrophage in atherosclerosis

Additionally, various physiological functions of HDL, such as RCT, anti-oxidation and anti-inflammation etc., have always been utilized as cardiovascular drugs carrier to exert synergistic action against atherosclerosis. In addition, natural macrophage-targeted property of high-density lipoprotein (HDL) via scavenger receptor was widely utilized in treatment of atherosclerosis [166-169]. Tang et al. demonstrated that inhibiting macrophage proliferation or selective depletion of macrophages reduce plaque inflammation and produce long-term therapeutic benefits. He proved that statin-loaded HDL

nanoparticles(S-HDL)accumulated four-fold higher S-HDL in aortic arch from atherosclerotic Apoe^{-/-} mice compared to healthy mice and reduced macrophage accumulation in aortic roots by 45%, thus effectively attenuating inflammation in atherosclerosis. She et al. developed a cyclic peptide, LyP-1 (CGNKRTRGC), which specifically targets atherosclerotic plaques,penetrates into plaque interior, and accumulates in plaque macrophages.The results showed that systemic treatment with LyP-1triggered apoptosis of plaque macrophages, reduced plaque inadvanced hypoxic plaques using Apoe^{-/-}mice atherosclerosis models, and did not increasethe necrotic core of plaques or lead to detectableside effects.With those evidences, peptide LyP-1 could be served as a targeted ligand for the development of newnanomedicines targeting macrophage within atherosclerotic plaques[106].

Duivenvoorden et al. developed reconstituted HDL (rHDL) nanoparticles that delivered statins to atherosclerotic plaques. rHDL labelled with Cy5.5 (lipid monolayer) and DiR (hydrophobic core) was intravenously injected into apoE^{-/-} mice. NIRF shows that Cy5.5 and DiR preferentially accumulate in the areas rich in atherosclerotic lesions. Finally 3-month low-dose statin-rHDL treatment inhibited plaque inflammation progression, while one-week high-dose regimen markedly decreases inflammation in advanced atherosclerotic plaques in an apoE^{-/-} mouse model [154]. Zhang et al. constructed recombinant HDL loaded with cardiovascular drug tanshinone IIA (TA) and demonstrated that rHDL containing TA could strongly accumulated in atherosclerotic plaques and had much potent efficacy against advancement of atherosclerosis compared with other conventional nanoparticle-based formulations[170]. However, HDL' nascent receptor SR-B1 is overexpressed not only in the atherosclerotic lesion's macrophage but also in the hepatic hepatocytes, inevitably resulting in the uptake of rHDL by liver [167]. Hence in order to decrease the unintended drug encapsulated in rHDL uptake by liver and actively increase the drug accumulation in atherosclerotic lesions, Liu et al decorated rHDL with macrophage-targeted moiety hyaluronic acid (HA) to decrease the non-targeted uptake by liver and

deliver a large amount of drug into atherosclerotic lesions so as to efficiently suppress the advancement of atherosclerosis (Fig. 9). Compared with rHDL without HA, HA decoration endowed rHDL with better atherosclerotic plaques targeting property and lower liver accumulation, proved by results from *ex vivo* imaging and tissue distribution. Furthermore, atheroprotective efficacy in model animal showed that HA-modified rHDL (HA-rHDL) containing Lovastatin (LT) had the best potent efficacy than other LT preparations, which was further demonstrated by the fewest atherosclerotic lesions sizes, the most minimum mean intima-media thickness, the lowest macrophage infiltration and expression of matrix metalloproteinase-9, respectively. Above results demonstrated that the newly designed HA-rHDL could decrease the non-targeted uptake by liver and actively deliver a large amount of drug into atherosclerotic lesions so as to efficiently suppress the advancement of atherosclerosis[171].

3.2.4 Dysfunctional macrophage as a target for imaging of atherosclerosis

Atherosclerotic plaques that develop within the arterial wall are hardly observed by conventional angiography and thus it provides few information regarding underlying processes that may lead to plaque rupture. Efficiently plaque-targeted imaging of atherosclerosis is crucial to reveal underlying disease timely. Hence macrophage-targeted strategy was also successfully applied into the imaging of atherosclerosis[146, 172, 173]. Tarin et al. prepared a targeted probe based on gold-coated iron oxide nanoparticles modified with an anti-CD163 antibody, which highly bound to membrane receptor CD163 over-expressed by macrophage at inflammatory sites such as atherosclerosis. The specificity of the targeted probe was validated *in vitro* by incubation of the probe with CD163(+) or (–) macrophages. Subsequently, the targeted probe was injected to 16 weeks old ApoE-deficient atherosclerotic mice and the abdominal aorta was imaged by magnetic resonance imaging(MRI). The accumulation of probe in the site of plaques increased over time and the signal intensity decreased significantly 48 hours after the injection. It was also reported that CD44 was present in rupture-prone macrophage-rich regions of

human atherosclerotic plaques at a level over 10 times higher than that in healthy vascular tissues[174]. El-Dakdouki et al. prepared magnetic glyconanoparticles with hyaluronan immobilized on the surface, which could selectively bind CD44. In T2⁺ weighted MRI, significant contrast changes in aorta walls were observed only with a very low dose of the magnetic nanoparticles, allowing the effective detection of atherosclerotic plaques[175]. As a ligand for SR-A overexpressed by activated macrophages within atherosclerotic plaques, dextran sulfate (DS) was employed by You et al. to coat superparamagnetic iron oxide nanoparticles (DS-SPIONs) to prepare MRI contrast agent of atherosclerosis[176]. Similar macrophage-targeted strategies for imaging of atherosclerosis were also reported based on HDL[169, 177, 178], CD36[161, 179, 180] and CD44[171, 175] as macrophage targeted moieties.

3.3 Dysfunctional macrophages in rheumatoid arthritis (RA)

RA, as an autoimmune disease with unknown initiator, is highly characterized by chronic systemic inflammation that predominantly affects articular tissue. It is well acknowledged that macrophage could act as amplifiers of local and systemic inflammation, with a direct contribution to matrix degradation[11, 12]. At a systemic level, monocytes are first attracted to the RA joint, where they differentiate into macrophages and become activated. Active macrophage then secrete TNF- α and IL-1, which induce synovial fibroblasts to express cytokines (such as IL-6 and IL-8), growth factors (such as granulocyte-macrophage colony-stimulating factor) and matrix metalloproteinases (MMPs) that contribute to cartilage and bone destruction. TNF- α also increases the expression of adhesion molecules on endothelial cells, which could recruit more monocytes to the joint and enhance macrophage activation and differentiation (Fig. 10)[181, 182]. The augment of sublining macrophages in the synovium is a prominent feature of inflammatory lesions and an early symbol of active rheumatic disease. The degree of synovial macrophage infiltration positively correlates with the degree of joint erosion, and depletion of these macrophages from inflamed tissue could produce a profound therapeutic

benefit[183-185]. Hence, the central role of activated macrophages in inflammation and bone homeostasis as well as modulating the cytokine environment in systemic arthritis make them suitable for a strong target in the treatment of RA[14]. Currently the antimacrophage therapy counteracting activation of macrophage mainly focuses on: 1) down-regulate the production of pro-inflammatory cytokines produced by active macrophage; 2) eliminate dysfunctional macrophage physically from the inflammatory foci or systemic loci and 3) upregulate the anti-inflammatory cytokines.

The inflamed regions of RA display excessively infiltrated pro-inflammatory cytokines including tumor necrosis factor- α , IL-1, IL-6 and IL-8 that proactively contribute to hyperplasia of synovial membrane, bone erosion, and cartilage destructions in joints. Hence suppression of those pro-inflammatory cytokines produced by active macrophage in synovial tissues has become a novel therapeutic target in RA therapy[186-188]. For instance Notch1, a signaling receptor, plays important roles in the regulation of inflammatory responses in many diseases like rheumatoid arthritis. Suppression of Notch signaling with γ -secretase inhibitor has shown to reduce the severity of inflammatory arthritis[189, 190]. Kim et al. fabricated Notch1 targeting siRNA delivery nanoparticles (siRNA-NPs) via self-assembled poly-siRNA and thiolated-glycol chitosan nanoparticles (Fig 11)[191]. The results showed that siRNA-NPs enhanced target ability of active macrophage in synovial joints via the enhanced permeation and retention (EPR) effect and thus prevented the undesired therapeutic outcome induced by non-specific inhibition of Notch1 pathway in normal tissues. *In vivo* studies demonstrated that siRNA-NPs significantly inhibited Notch1 pathway, thus retarding progression of inflammation, bone erosion, and cartilage damage in CIA mice without undesirable severe toxicity. In order to quench the inflammation produced by active macrophage in RA sites, Hayder et al. demonstrated intravenous injection of azabiphosphonate (ABP)-capped dendrimer targeted inflammatory macrophage within RA,

directed them toward anti-inflammatory activation and thus inhibited the development of inflammatory arthritis in two animal models[192].

Severity of rheumatoid arthritis has been directly linked to the number of macrophages present in the arthritic synovium. Such pro-inflammatory macrophage activation in the diseased state has been termed as M1-macrophage phenotype. Alternatively, macrophages involved with anti-inflammatory processes are considered to be M2-like phenotype. Therefore, strategies that can effectively switch macrophage from predominant M1 in the synovium to M2 state may be potential to the treatment of rheumatoid arthritis. Depletion of systemic and joint macrophages with clodronate loaded liposomes is not a viable strategy given the key role of macrophage in immuno-surveillance[183]. Jain et al. selectively modified the macrophage phenotype by delivering an anti-inflammatory cytokine (Interleukin 10) encoding plasmid DNA encapsulated into a nanoparticle system modified with tuftsin peptide to achieve active macrophage targeting. Enhanced localization of tuftsin-modified alginate nanoparticles was observed in the inflamed paws of arthritic rats upon intraperitoneal administration. Importantly, targeted nanoparticle treatment was successful in reprogramming macrophage phenotype balance as ~66% of total synovial macrophages from arthritic rats treated with the IL-10 plasmid DNA loaded tuftsin-alginate nanoparticles were in the M2 state compared to ~9% of macrophages in the M2 state from untreated arthritic rats. Treatment significantly reduced systemic and joint tissue pro-inflammatory cytokines (TNF- α , IL-1b, and IL-6) expression and prevented the progression of inflammation and joint damage as revealed by magnetic resonance imaging and histology[96].

Among the key molecules involved in inflammation and the family of phospholipase A2 (PLA2) enzymes, cPLA2 α is one of the most expressed one in active monocytes/macrophages and regulates normal and pathologic processes through arachidonic acid release from phospholipid membranes, used as substrates for the synthesis of lipid mediators, including prostaglandins and leukotrienes, that play

critical roles in the development and maintenance of inflammation[13]. Courties et al. applied siRNA technology combined with use of cationic liposome that was able to efficiently transfect monocytic cells *in vivo*, thus specifically silencing the expression of cPLA2 α in functionally relevant cell types in an experimental model of RA. Results indicated that systemic siRNA-mediated cPLA2 α gene silencing was effective for the treatment of collagen-induced arthritis[94].

3.4 Dysfunctional macrophages in inflammatory bowel disease (IBD)

Macrophages are an integral part of the normal intestinal tissues and well located in lamina propria and Peyer's patch, where they play as an immune effector cells against any pathogenic attack. In the healthy intestine, macrophages in lamina propria do not induce strong pro-inflammatory responses against either microbial ligands or host cytokines/chemokines. While under stimulation from an inflammatory signal, inflammatory monocytes are recruited from blood and then transformed into inflammatory macrophages in the lamina propria, and unlike resident macrophages inflammatory macrophages would greatly produce severe intestinal inflammatory reaction and tissue damage by over-expressing triggering receptor expressed on the surface of myeloid cells, nod-like receptors (NLRs), toll-like receptors (TLRs) and TNF- α [15, 16, 193, 194]. Recent studies have also demonstrated that depletion of macrophages in the IL10^{-/-} mouse prevents development of colitis[195]. Therefore inflammatory macrophages within intestine present as attractive targeting strategy for treating inflammatory bowel disease.

Accumulating evidences have shown that macrophage contribute to IBD progression by producing pro-inflammatory cytokines such as TNF- α . Therapeutic strategies against TNF- α have been shown to effectively treat IBD in multiple clinical trials using the monoclonal antibody infliximab[195-197]. However, serious infections and side effects have been associated, including immunodeficiency-related infections and formation of antibody against TNF- α . Therefore anti-TNF- α therapeutic agents

need to be targeted delivery to inflammatory sites. With the advance of nanotechnology and gene therapy, gene silencing via siRNA represents a promising treatment strategy for intestinal inflammation[99, 198]. Zhang et al. developed galactosylated trimethyl chitosan–cysteine (GTC) nanoparticles (NPs) to orally deliver a mitogen-activated protein kinase-kinase-kinase-kinase 4 (Map4k4) siRNA (siMap4k4), a key upstream mediator of TNF- α action, to the activated macrophages for treatment of dextran sulfate sodium (DSS)-induced ulcerative colitis (UC). The *in vitro* and *in vivo* gene knockdown tests showed that siMap4k4 loaded NPs effectively inhibited TNF- α production accompanied with significant histological improvements from H&E-stained colonic sections[101]. Laroui et al. also proved that biodegradable, non-cytotoxic polylactide nanoparticles (NPs) containing TNF α siRNA/polyethyleneimine (PEI) complex were efficiently taken up by inflamed macrophages and thus significantly inhibit TNF- α secretion by the macrophages. *In vivo* studies showed that TNF α siRNA/PEI-loaded NPs were efficiently delivered to the colonic tissue and that TNF- α siRNA released from NPs efficiently inhibited LPS-induced synthesis/secretion of colonic TNF- α [99]. In order to improve the macrophage targeting properties, Xiao et al. synthesized a macrophage-targeted bioreducible cationic polymer conjugate with sodium triphosphate (TPP) as gene delivery for TNF- α siRNA (Fig. 12). These NPs were efficiently taken up by macrophages and conferred high-level RNAi, which remarkably decreased TNF- α expression and had potent anti-inflammatory effects both *in vitro* and *ex vivo*[100].

In order to obtain the criterion of both colonic sustained release of TNF- α siRNA and macrophages targeting delivery at the same time, Huang et al. developed an orally administrated nanoparticle that could actively target the colonic macrophages and suppressed the local expression of TNF- α for IBD. This vehicle was constructed by cationic konjac glucomannan composed of mannose and β -glucan (cKGM), phytagel and an antisense oligonucleotide (ASO) against TNF- α . It was given to

dextran sodium sulfate (DSS) colitic mice via gastric perfusion. The distinctive swelling properties of cKGM allowed for the spontaneous release of cKGM&/ASO nanocomplex from the phytagel matrix into the colon lumen, where the ASO was efficiently internalized into colonic macrophages via mannose receptor-mediated endocytosis. The administration of this nanoformulation significantly decreased the expression level of TNF- α and alleviated the symptoms of colitis in the dextran sodium sulfate-induced colitic mice. [98].

3.5 Dysfunctional macrophages in obesity and ensuing insulin resistance for type 2 diabetes

Macrophages only constitute 10-15 % of the cell population in the lean adipose tissue, where they predominantly exhibit an anti-inflammatory phenotype, classically termed as M2-like state. However, in obese humans and rodents, macrophages make up 40-50 % of the interstitial cell population in the adipose tissue, dubbed as adipose tissue macrophages (ATMs), and switch phenotype to a more pro-inflammatory M1-like state, which are a major source of pro-inflammatory cytokines such as tumor necrosis factor α (TNF α) that can function in a paracrine and potentially an endocrine fashion to cause insulin resistance. The causal relationship between obesity and type 2 diabetes has recently been generally identified as chronic low-grade systemic inflammation induced by pro-inflammatory M1-like macrophages in those obese adipose tissues. Pharmacological or genetic inhibition of pathways had proved that attenuating inflammatory responses could protect experimental animals and human subjects from obesity-induced insulin resistance [21, 23, 199].

Most clinical therapies to inflammation involved in obesity-related complications focus on anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and glucocorticoids (like dexamethasone), which have been widely used in the clinic by obese and/or diabetic patients for few decades [200-202]. However, high doses and long term administration are always accompanied with serious adverse effects, including bleeding, gastrointestinal irritation and Cushing-like syndrome etc.

More clinical evidences suggest that those side effects result from the drugs' off-target effect, particularly liver hepatocytes, muscle cells and enterocytes. Hence specifically targeting ATM via nanomedicines could substantially resolve those limitations and improve the therapeutic outcomes [21, 179].

Ma et al reported that nanoscale polysaccharides based on biocompatible glucose polymers can efficiently target adipose macrophages in obese mice (Fig. 13). The results suggested that nanocarriers with size in 70-500 nm efficiently distributed to visceral adipose tissue and selectively bond with macrophages after regional peritoneal administration. Up to 63% of the injected dose remained in visceral adipose tissue 24 h after administration, leading to more than 2-fold higher local accumulation in comparison to liver, which is the dominant site of uptake for most nanomedicines. Furthermore, a single-dose administration significantly reduced pro-inflammatory markers in adipose tissue of obese mice [111].

PPAR γ nuclear receptor agonists have been shown to attenuate macrophage inflammatory responses implicated in the obesity [203, 204]. However, current PPAR γ agonists in clinic, such as rosiglitazone (RSG), are often associated with severe adverse effects that greatly limit their therapeutic effect. Mascolo et al. synthesized polymeric NPs with a diameter of around 200 nm as RSG delivery vehicle (RSG-NPs), which could be preferentially taken up by circulating monocytes, residing in the liver (Kupffer cells) and in the white adipose tissue (WAT). In *ldlr*^{-/-} mice fed high fat diet, treatment with RSG-NPs alleviated inflammatory reaction in white adipose tissue and liver. In addition unlike treatment with free RSG, RSG-NPs did not alter genes related to normal lipid metabolism or cardiac function, suggesting an obvious reduction of free RSG-related side effects [110].

Obesity and its related metabolic syndromes like diabetes are also closely related with the microenvironment within adipose tissue [205, 206]. A major reason of obesity is that the over-eating of

energy-rich food accumulates in the parenchymal adipocytes of adipose tissue, particularly in liver and muscles. This process is termed as adipogenesis that highly needs the simultaneous development of angiogenesis[207]. Therefore, it would be anticipated that efficiently suppressing angiogenesis could inhibit adipocyte hyperplasia and thus palliate insulin resistance by reducing the infiltration of inflammatory macrophages into adipose tissue. To target angiogenic vessels in obese fat tissues, Hossen et al. designed prohibitin (an adipose vascular marker)-targeted nanoparticle (PTNP) encapsulating cell death-inducing peptide [D(KLAKLAK)₂] via modification by a linear peptide containing a white fat vessels targeting motif (KGGRAKD). Treatment with PTNP caused a potential antiobesity effect on dysfunctional adipose cells, including adipocytes and macrophages, suggesting that vascular-targeted nanomedicine may be effective for the control of the adipose function and peripheral fat deposition in the body. In addition, drug delivery via the PTNP system, that was actively accumulated in obese fat mediated by its multivalent active targeting, resulted in a subsequent enhancement in drug delivery to adipose endothelial cells[112].

Some innovative anti-obesity therapies also realize with the extension of understanding for progression of obesity[208]. Recent evidences showed obesity is highly related to an expansion and proliferation of white adipose tissue (WAT) in the body. The primary function of WAT is to store energy, whereas brown adipose tissue (BAT) generates heat through energy expenditure. Transforming WAT into BAT is of great interest for obesity treatment. Xue et al. engineered a targeted nanoparticle through self-assembly of a biodegradable triblock polymer PLGA-b-PEG and an endothelial-targeted iRGD peptide, which can actively bind to angiogenic vessels through integrin $\alpha_v\beta_3/\alpha_v\beta_5$ receptors and WAT vasculature through the membrane protein prohibitin. Here they used this functionalized nanoparticle to deliver either Peroxisome Proliferator-Activated Receptor gamma activator rosiglitazone or prostaglandin E₂ analog to adipose tissue vasculature, each of which

could induce adipose tissue transformation and angiogenesis, thus facilitating the transformation of WAT into BAT. The *in vivo* results showed that i.v. administration of these NPs actively targeted WAT vasculature stimulated the angiogenesis that is required for the transformation of adipose tissue, and transformed WAT into BAT, by the up-regulation of angiogenesis and brown adipose tissue markers. In a diet-induced obese mouse model, these angiogenesis-targeted NPs inhibited body weight gain and modulated several serological markers including cholesterol, triglyceride, and insulin, compared with the control group. These findings suggest that angiogenesis-targeting moieties-modified NPs containing angiogenic stimulator could be an effective therapeutic regimens for clinical treatment of obesity and other metabolic diseases[113].

Type2-diabetes is also characterized by microvascular changes and monocyte recruitment and macrophage activation. A major limitation to better understanding, preventing, and curing diabetes has been the inability to “monitor” the disease initiation, progression, or regression, especially during the latent phase. Hence early diagnosis and monitoring of disease progression for patients with diabetes could benefit a lot to both patients and caregivers[209-211]. In a pilot clinical study, non-diabetic healthy volunteers and patients with onset diabetes were administrated with a clinically approved MRI contrast-imaging agent, based on the dextran-coated iron oxide nanoparticle that is readily taken up by macrophages owing to its size and surface properties, allows for the effective visualization of the pancreas and distinction of onset diabetes patients from nondiabetic controls[20].

3.6 Dysfunctional macrophages in human immunodeficiency virus type I (HIV-1)

HIV infection is still a severe global life-threatening concern accounting for more than 25 million deaths in last three decades. More than 34 million people are living with HIV infection. As one of cell types easily infected by HIV-1, macrophage, that has to be mentioned, plays a crucial role in the different phases of HIV-1 infection, including HIV-1 transmission through the whole body, the acute

and chronic phases of HIV-1 infection, the development of acquired immunodeficiency syndrome (AIDS) and HIV-associated diseases, including neurocognitive disorders[25]. Macrophage, similar to CD4⁺ T helper cells, also expresses high levels of the HIV-1 receptor CD4 on their surface and is highly permissive for HIV-1 infection. First step of HIV-1 infects host cells via virus ligand (surface glycoprotein gp120), which interacts with HIV-1 receptor CD4 receptor present in both T cells and macrophages. Second step involves the fusion of viral envelope with host cell membrane mediated by the engagement of the co-receptors (CCR5). At the first phase, macrophages are critically involved in the initiation and the orchestration of the adaptive cellular and humoral immune response that helps to diminish viral infection; while with the advancement of HIV-1 infection, highly migratory infected-perivascular macrophages will be served as a reservoir to hijack and disseminate the virus throughout the body. [6, 212-214]. Besides, HIV-infected macrophages in lymph nodes express the viral protein Nef, which will be shuttled to B cells. After reaching B lymphocytes, Nef affects cellular functions and interrupt the B cell function (Fig.14). In addition, Nef-activated and HIV-1 infected macrophages might also be critically related to the apoptosis of CD4⁺ and CD8⁺ T cells[215].

The current foundation of HIV-1 therapy is still based on antiretroviral therapy (ART). However, long term treatment of ART cannot eliminate all infected cells from the patients, and virus levels rapidly rebound once ART treatment is stopped. The main reasons for recurrence are due to 1) the plenty persistence of long-lived HIV-1 reservoirs like macrophage; 2) eradication of HIV-1 from those reservoirs is difficultly feasible, because HIV-1 produced by tissue-associated macrophages might be targeted insufficiently by antiviral drugs due to the low bioavailability of the drugs in certain tissues; 3) multidrug pumps on macrophage render HIV-1 resistant toward HIV-1 protease inhibitors though reduction of the concentration of inhibitors within the macrophage, thus decreasing concentrations of the anti-HIV drugs and possibly promoting the emergence of escape mutants[25, 26,

117, 216]. Therefore, it is crucial to develop novel therapeutic options to target HIV-1 reservoirs to potentially reduce the required drug dosage, shorten the duration of treatment, mitigate dose-dependent toxicity, and reduce the emergence of drug resistance. Macrophages, one of the most important HIV-1 reservoirs, are responsible for transmitting HIV-1. Failure to eliminate HIV-1 reservoir underpins the limitations of current ARV therapies. Thus eradicating HIV-1 infected macrophage has emerged as a promising solution for effective anti-HIV-1 [217, 218]. In order to targeted delivery of ARV to HIV-1 infected macrophage, Kutscher et al employed 1,3- β -glucan (GLU) as macrophage-targeting ligand to functionalize chitosan (CS) shell and (PLGA) core nanoparticles loaded with the ARV nevirapine (GLU-CS-PLGA). Specific GLU interaction with recognition receptor dectin-1 on the surface of macrophages enhanced the intracellular ARV delivery. *Ex vivo* imaging showed that these functionalized nanoparticles actively targeted macrophages in the liver and kidney [117]. Ghosh et al. also achieved enhanced macrophage-specific delivery of anti-AIDS drug stavudine and improved *in vivo* behaviors through optimized PLGA nanoparticles as drug carriers [219].

Based on the advancement of molecular probing, more and more essential elements, such as proteins, enzymes and receptors, intimately involved in the infection and transmission of HIV-1 have been recognized. Those elements could be served as potential target for discovery of anti-HIV-1 regimen. Galectin-1, an adhesion molecule, is expressed in macrophages and implicated in HIV-1 viral adsorption to the host cell. Reynolds et al. demonstrated that galectin-1 siRNA delivered by gold nanorod efficiently inhibited galectin-1 gene expression on the macrophage, which could potentially reduce the galectin-1-mediated HIV-1 infection [220]. The CCR5 protein belongs to the beta chemokine receptors family of integral membrane proteins and is predominantly expressed on HIV-1 host cells, including T cells, macrophages and dendritic cells etc. CCR5 also plays very essential roles for the entry of HIV-1 to target immunological cells like macrophage and later transmission during the acute infection. HIV-1

viral entry to host cells is collaboratively accomplished by the first binding of viral gp120 to host HIV-1 receptor CD4 and subsequent binding to a cellular co-receptor CCR5. Following co-receptor binding, HIV-1 stably anchors to the host cell membrane, thus leading to viral-cell membrane fusion and insertion of the viral nucleotides into the host cell. Hence, the co-receptor CCR5 could be a possible target for design of viral-infected host cell-targeted anti-retroviral agent delivery system. Bronshtein et al. used cytoplasmic membranes from cells expressing CCR5 to decorate liposomes containing toxin EDTA to target the HIV-infected cells (Fig. 15). These results demonstrated the CCR5-expressing cell membrane-derived liposomes specifically targeted towards gp120-expressing HIV model cells, and led to 60% reduction in the viability of gp120-expressing cells compared to no effect on control cells that do not express gp120, which suggesting the targeted-binding between CCR5 and gp120 [221].

Macrophage also serves as targets for AIDS relevant pathogens, e.g. *Mycobacterium tuberculosis* (TB), thereby fueling the establishment of opportunistic infections associated with the progression of AIDS. It is estimated that one third of HIV infected individuals are co-infected with TB. In addition, TB infection in HIV-1 positive patients appears to amplify the HIV-1 production, resulting in increased HIV-1 viremia and hastening the progression of HIV-1 disease. Furthermore, HIV-1 infection in itself also impairs appropriate immune response to the infection from TB, enhancing the progression and severity of TB. Therefore, establishing effective regimen for co-infection of HIV-mycobacterium could provide some promising clinical outcomes for late phase HIV patients.

Narayanasamy et al. developed a kind of Gallium (Ga) nanoparticles which could reside inside the macrophages for a longer time. Ga is a metal highly similar to iron (Fe) that is crucial to the metabolism and growth of most microbes, including HIV. While unlike Fe^{+3} , Ga^{+3} cannot be reduced and thus once bound to Fe binding sites in an enzyme, the enzyme will be inactivated. Thus, all Fe-dependent pathways both in bacteria and virus would be potentially blocked by the presence of Ga, leading to growth

inhibition and ensuing death. Ga is also not susceptible to classical drug efflux pumps and therefore less vulnerable to generally encountered antibiotic resistance mechanisms. Results clearly showed that the Ga nanoparticle was highly internalized by macrophage and was maintained sustained-release for up to 15 days, and significantly inhibited growth of both HIV and mycobacterium in the macrophage for up to 15 days following single drug loading[222].

4 Concluding remarks and future perspectives

Dysfunctional macrophages play critical roles in the evolution of various diseases such as cancer, inflammatory and autoimmune disorders. Due to their plasticity, macrophages undergo phenotypical and functional switches with the advancement of many diseases. Identification of distinct disease-promoting macrophage subsets would lay a solid foundation for development of macrophage-targeting strategies to eliminate or correct those macrophages. Macrophage subtype populations are not limited to pro-inflammatory M1-like macrophages and anti-inflammatory M2-like macrophages. For instance, M2-like macrophages are also considered tumor-associated macrophages promoting the progression of the tumor tissue and helping tumor cells escape from the immune system. Therefore, blockade of dysfunctional macrophage accumulation, restoration of biological function and conversion of macrophage in diseases' focus from the pathogenic one back to therapeutic one will become important therapeutic strategies in future.

While much advances have already been made, there is room for improving the efficacy of targeting dysfunctional macrophages in diseases' site. Questions as to how to correctly modulate functions of specific macrophage phenotype to reach therapeutic intervention, how to monitor therapeutic response accurately and timely, and how to avoid the compromised immune-protective functions of macrophage caused by therapeutic intervention, and many others remain yet to be fully addressed. To translate macrophage targeting nanomedicines from bench to bedside, some

directions may be taken into account: 1) relationships between macrophages and nanoparticles shall be fully elucidated and utilized to better achieve macrophage-specific targeting; 2) It is desirable to develop theranostic nanomedicines that incorporate both diagnostic probe (or imaging) and therapeutic agents in a single system, enabling visualizing and monitoring the progression of diseases timely during treatments; 3) Thorough *in vivo* investigations shall be conducted, such as PK/PD, metabolism and long-term toxicity studies. We are optimistic that nanoparticle-based nanomedicines will help target specific macrophages to better treat dysfunctional macrophages-associated diseases by combining the in-depth understandings of complex relationships between macrophages and diseases' progression and advances in nanotechnology.

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Fig. 1.Protective and pathogenic functions of macrophage subsets. Adapted with permission from [2].

Fig. 2. Graphical illustration of different types of nanoparticles.

Fig. 3. Multifunctional nanomedicines targeting dysfunctional macrophages-associated diseases.

Fig 4. Pro-tumorigenic functions of tumor-associated macrophages. Adapted with permission from [121].

Fig. 5. Multifunctionality of Man-HA-MnO₂ NPs: MnO₂ particles (~15 nm) are entrapped in hyaluronic acid (HA) with mannan molecules attached. When Man-HA-MnO₂ NPs are recognized and uptaken by mannose receptor of TAMs, hyaluronic acid (HA) reprograms anti-inflammatory, pro-tumoral M2 TAMs to pro-inflammatory, antitumor M1 macrophages, which might be via a TLR2-MyD88-IRAK1-TRAF6-PKCζ-NK-κB-dependent pathway. The reprogrammed M1 macrophages secrete high level of IL-12, IFN-γ and H₂O₂. The high reactivity of MnO₂ NPs toward H₂O₂ allows for the simultaneous production of O₂ and Mn²⁺ ions and regulation of pH of tumor hypoxia. Once MnO₂ NPs are reduced into Mn²⁺ ions, they exhibit strong enhancement in both T1- and T2-weighted MRI. Adapted with permission from [131].

Fig 6.Left panel: Macrophage-membrane-coated emtansine liposome was fabricated by coating an emtansine liposome with an isolated macrophage membrane to confer the biomimetic functions of the macrophage, thereby facilitating the specific targeting to metastatic sites and enhancing the therapeutic efficacy on cancer metastasis. Adapted with permission from [89].

Fig. 7. Potential molecular imaging targets in atherosclerosis. White boxes show putative targets for molecular imaging of atherosclerosis. Atherogenesis involves recruitment of inflammatory cells from blood, represented by the monocyte in the upper-left-hand corner of this diagram. Monocytes are the most numerous leukocytes in atherosclerotic plaque. Recruitment depends on expression of adhesion molecules on macrovascular endothelium, as shown, and on plaque microvessels. Once resident in the arterial intima, activated macrophages become phagocytically active, a process that provides another potential target for plaque imaging. Oxidatively modified low-density lipoprotein (mLDL)–associated epitopes that accumulate in plaques may also serve as targets for molecular imaging. Foam cells may exhibit increased metabolic activity, augmenting their uptake of glucose, a process already measurable in the clinic by ^{18}F -FDG uptake. Activated phagocytes can also elaborate protein-degrading enzymes that can catabolize collagen in the plaque's fibrous cap, weakening it, and rendering it susceptible to rupture and hence thrombosis. Mononuclear phagocytes dying by apoptosis in plaques display augmented levels of phosphatidylserine on their surface. Probes for apoptosis such as annexin V may also visualize complicated atheromata. Microvessels themselves can express not only leukocyte adhesion molecules (shown in green) but also integrins such as $\alpha\text{V}\beta3$. Proof-of-principle experiments in animals support each process or molecule in white boxes as target for molecular imaging agents. Adapted with permission from [146].

Fig. 8. The envisioned paradigm to counteract atherosclerotic plaque development aims to repress lipid-scavenging receptors at the level of lesion-based macrophages. Sugar-based AMs were designed to competitively block oxLDL uptake via binding and regulation of SRs on human macrophages. A library of AMs, with systematic variations in charge, stereochemistry, and sugar backbones, was synthesized and kinetically fabricated into serum-stable, core/shell NPs and screened *in vitro* to identify shell architectures that exhibited maximal atheroprotective potency. To demonstrate lesion-level intervention, the lead NP was administered in an atherosclerosis animal model to challenge lesion development during coronary artery disease. Adapted with permission from [105].

Fig. 9. Schematic diagram on preparation methods and atherosclerotic lesion targeting property of HA-LT-rHDL. Adapted with permission from [171].

Fig. 10. Overview of the pathogenesis of rheumatoid arthritis. Monocytes are attracted to the rheumatoid arthritis (RA) joint, where they differentiate into macrophages and become activated. They secrete tumour-necrosis factor (TNF) and interleukin-1 (IL-1). TNF increases the expression of adhesion molecules on endothelial cells, which recruit more cells to the joint. Chemokines, such as monocyte chemotactic protein 1 (MCP1) and IL-8, are also secreted by macrophages and attract more cells into the joint. IL-1 and TNF induce synovial fibroblasts to express cytokines (such as IL-6), chemokines (such as IL-8), growth factors (such as granulocyte-macrophage colony-stimulating factor; GM-CSF) and matrix metalloproteinases (MMPs), which contribute to cartilage and bone destruction. TNF contributes to osteoclast activation and differentiation. In addition, IL-1 mediates cartilage degradation directly by inducing the expression of MMPs by chondrocytes. Adapted with permission from [181].

Fig. 11. Schematic diagram of Notch1 targeting siRNA delivery nanoparticles (siRNA-NPs). (A) The siRNA-NPs are prepared by encapsulating poly-siRNA into tGC nanoparticles. (B) The siRNA-NPs are taken by activated macrophage and the nanoparticles can deliver therapeutic Notch1-specific siRNA in RA treatment. Adapted with permission from [191].

Fig. 12. Schematic illustration of TPP-PPM/siRNA nanoparticle (NP) formation, macrophage-targeting delivery and the release of siRNAs to the cytoplasm. Adapted with permission from [100].

Fig. 13. Proposed mechanism of dextran–dexamethasone conjugate accumulation in obese VAT, macrophage uptake, and uncoupling of the paracrine loop between M1 macrophages and adipocytes: (a) dextran conjugates (green color) accumulate in the left perirenal adipose tissue (AT) and left gonadal AT after intraperitoneal left-side injection in obese mouse. The anatomical depiction shows mice, which have one mesenteric, two perirenal, and two gonadal AT depots. (b) Transverse cross section of mouse abdomen showing green dextran solution location after administration to the peritoneal cavity. (c) Rapid association of dextran conjugate with M1 macrophages in inflamed AT is enabled by transport across the peritoneum to directly access interstitial cells. (d) Simplified summary of inhibition of paracrine loop between M1 macrophages and adipocytes with dextran–dexamethasone conjugates. In the obese state, hypertrophied adipocytes produce MCP-1, which recruits monocytes, and local release of pro-inflammatory cytokines TNF α and IL-6 induces an M1 macrophage phenotype. M1 macrophages further release pro-inflammatory cytokines and chemokines including MCP-1, TNF α , and IL-6, which further enhance the pro-inflammatory gene expression of adipocytes through NF- κ B and further enhance adipocyte inflammation. Dextran conjugates are taken up by M1 macrophages through receptor-mediated endocytosis, and free dexamethasone is released within the cells after esterase hydrolysis. Dexamethasone then binds to the glucocorticoid receptor that inhibits the transcription of pro-inflammatory genes. Additional implicated cells (e.g., T cells) and altered metabolic pathways are not depicted. Adapted with permission from [111].

Fig. 14. HIV-1-infected macrophages shuttle Nef to B cells to impair follicular IgG2 and IgA responses. Adapted with permission from [215].

Fig. 15. The concept and rationale of targeting HIV-infected cells by CCR5-conjugated cell derived liposomes. (a) Cell-derived liposomes are prepared by homogenization and extrusion of ghost cells, which membranally express the HIV co-receptor CCR5. The source of the cells can be any autologous lineages that express CCR5 (naturally or exogenously). (b) Cell derived liposomes, which will be targeted against gp120-expressing cells using CCR5 as a targeting ligand, can interfere with all extracellular steps of viral pathogenesis; Such as, syncytium formation between infected cells and uninfected susceptible cells, viral budding from infected cells, viral maturation and attachment to susceptible cells. (c) The cell derived liposomes (when administered along with soluble CD4) are primarily intended to target, fuse with and deliver their cytotoxic content into gp120-expressing/HIV-infected cells. Accordingly, the same mechanism of gp120 binding may also prove efficient in preventing syncytium formation and inactivation of roaming virions by clustering. Adapted with permission from [221].