REVIEW

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Cyclodextrin related drug delivery system to promote atherosclerosis regression

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As one of the biggest threats to human life and health, atherosclerosis (AS) can cause heart disease, stroke and peripheral vascular changes. Low-density lipoprotein (LDL) cholesterol is an identified risk for AS. In the presence of oxidative stress, LDL particles can be oxidized to form lipoproteins, which are particularly atherosclerotic. The pathogenesis of AS and traditional treatment for AS are reviewed. Since cyclodextrin (CD) is a widely used cyclic oligosaccharide functioned as a solubilizer and hydrophobic drug inclusion compound, it can promote cholesterol dissolution, increase cholesterol efflux and LXR-dependent cellular reprogramming, and activate the anti-inflammatory mechanism. The rapid development of nanotechnology may provide broad prospects for the development of new nanomaterials, especially amphiphilic micelles and polymosomes, thus combining with CD to promote AS degeneration, reduce inflammation, and enhance the reverse transport of cholesterol. Therefore, to build a drug delivery system based on CD which can achieve an efficient entrapment of anti-atherosclerotic drugs is a new promising strategy in future.

1. Introduction

As chronic inflammatory injury of arterial wall, atherosclerosis (AS) may lead to cardiovascular and cerebrovascular ischemic events, such as cerebral and myocardial infarction. LDL cholesterol is an intense independent risk factor for AS. The disorders of lipid metabolism cause the increase of LDL. Nowadays, the current treatment for AS is to significantly reduce LDL. However, current treatment for AS is not effective for all patients. Therefore, looking for other methods of reducing cholesterol levels to treat AS has become an urgent need. Since cyclodextrins (CDs) have the ability to promote cholesterol dissolution and increase cholesterol efflux, increase Liver X receptor (LXR)-dependent cellular reprogramming, it is hoped that this publication cannot only provide a synopsis of pathogenesis and current traditional treatments for AS, but can also offer practical insights for future development of CD-based drug delivery system for AS regression.

2. Pathogenesis of atherosclerosis

Pathogenesis of AS is caused by various factors. Lipid metabolism disorder, oxidative stress, inflammatory cytokine mediated vascular smooth muscle cell (VSMC) injury and fibrinolysis, blood coagulation in the vascular wall and renin angiotensin system internal stability can regulate the development of AS (Viola and Soehnlein 2015). The lipid is trapped in the subendothelial layer of the arterial wall, then bioactive substances, including oxidized low-density lipoprotein (ox-LDL), are produced to stimulate vascular cells to generate inflammatory molecules and recruit monocytes and T cells to the arterial wall. The blood mononuclear cells recruited to the blood vessel wall are precursors of lipid rich macrophages that form fat stripes (Libby et al. 2009), which finally result in AS.

2.1. Atherogenic modified LDL leads to the formation of foam cells

Lipid metabolism disorder and oxidative stress can form LDL which can cause AS, leading to lipid accumulation and foam cell formation (Orekhov 2018; Orekhov and Sobenin 2018). It is worth noting that macrophages are not the only source to form foam cells. Smooth muscle cells and pericyte like cells can also ingest LDL particles and transform into foam cells (Orekhov 2018). The release of pro-inflammatory cytokines, such as IL-8, IL-1 and IFN-γ, helps to recruit more and more monocytes and macrophages, thus triggering the plaque growth on vascular wall (Mclaren et al. 2011). After foam cells are formed, they accumulate and form fatty plaques in endarterium. This process is the initial state of the development of atherosclerotic plaques (Tertov et al. 1992). Further plaque formation contributes to the release of extracellular matrix degrading protease. Collagen and elastin derived from this cleavage are responsible for the formation of fibrous caps that block the necrotic core. The cells in the necrotic core die and release the intracellular inclusions, leading to the formation of a lipid rich necrotic core. In this phase, intermediate plaque is formed. Further development of the intermediate plaque helps to enhance the growth of these processes and necrotic environment (Mclaren et al. 2011).

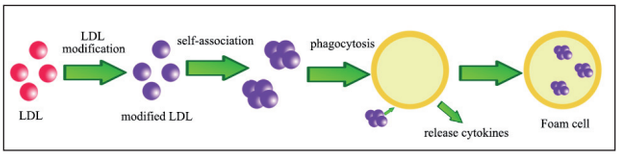

Fig. 1: The sequence of the formation of foam cells.

2.1.1. Lipid metabolism

Cholesterol is one of the most abundant sterol molecules in mammals. It is one of the basic components to form cell membranes. It can regulate membrane rigidity with neighboring lipid molecules, fluidity and permeability, and combine with transmembrane proteins to maintain or change membrane conformation. Cholesterol is also an important precursor for the synthesis of oxidized

sterols. The abundance of cellular cholesterol is highly regulated and depends on the balance between cholesterol synthesis, cholesterol efflux and cholesterol absorption from LDL (Goldstein and Brown 1990; Goldstein et al. 2006).

Cholesterol is mainly synthesized in the liver. Acetyl coenzyme A is converted into cholesterol through about 30 steps of enzymatic reaction. Cholesterol and triglycerides are then assembled into very low-density lipoprotein (VLDLs), which are then secreted into the blood or stored in cells to form lipid droplets. Cholesterol in diet can be internalized by NPC1L1 on the surface of small intestinal cells (Zhang et al. 2018). It is then assembled with esterified cholesterol to form chylomicrons for secretion. VLDL can be transformed into LDL in the blood and bind to LDL receptors on the surface of surrounding tissues and is internalized. LDL is then divided into lysosomes and hydrolyzed to release the free cholesterol. The cholesterol is transported to other organelles or plasma membranes continuously through the help of peroxisome membrane and other mechanisms to perform their biological functions (Chu et al. 2015; Luo et al. 2019).

In most tissues and cells, excess cholesterol can enter the blood through ATP binding cassette (ABC) transporter family proteins, ATP binding cassette transporter A1 (ABCA1) and ATP binding cassette transporter G1 (ABCG1). The high density lipoprotein can be formed by binding apolipoprotein AI (apoA-I) with them. ABCA1 is composed of six transmembrane fragments and a large glycosylated extracellular domain. It is widely expressed throughout the body and plays an important role in macrophages. It can help to remove excess cholesterol, excrete them to lipid-poor ApoA-I and prevent macrophages to transform into foam cells, so the ABC transporter family plays an important role in protecting AS. ApoA-I receives cholesterol from ABCA1 and produces new high density lipoprotein. These lipoprotein granules mature under the action of lecithin: cholesterol acyltransferase, and then receive cholesterol released by ABCG1. ABCA1 can transport phospholipids directly or through lipid bilayer inversion. In liver and intestinal cells, cholesterol can be excreted into bile or intestine through ABCG5 and ABCG8, and then recovered or excreted. Other cholesterol can also be transformed into cholesterol esters under the help of cholesterol esterase and then stored in lipid droplets, or encapsulated in the center of the lipoprotein particles, then released into the blood. These all processes are strictly regulated at multiple levels. Cells have various mechanisms, which can sense and respond to metabolic state to maintain the stable state of cholesterol metabolism.

2.1.2. Chemically modified LDL

Since the 1980s, the role of lipid metabolism in the pathogenesis of AS has been elaborated. Disorders in lipid metabolism play an important role in promoting the development of AS (Libby et al. 2011). The formation of foam cells is inseparable from the accumulation of lipids in the cells and then evoking a complex process of chronic inflammation (Chrysohoou 2018). It is considered to be the main pathological progression leading to early AS (Maguire et al. 2019; Moore and Tabas 2011; Pryma et al. 2019).

There is almost no doubt that chemically modified LDL is the main source to accumulate lipids and finally result in foam cells. So far, the chemical modifications of LDL include acetylation, desialylation, maleylation, succinylation, oxidation of valence metal ions, treatment of formaldehyde, malondialdehyde, phospholipase A2, C and D (Arnold et al. 1989; Fogelman et al. 1980; Orekhov and Sobenin 2019). Chemically modified LDL is absorbed by arterial cells (such as macrophages, pericytes and smooth muscle cells) in an uncontrolled manner to bypass the LDL receptor (Doodnauth et al. 2019; Orekhov 2018).

2.1.3. Oxidative stress lead to oxidized LDL

Some presumes consider oxidative stress is the major cause of AS (Libby 2002). Once LDL precipitates enter the subendothelial space, they are converted into ox-LDL by reactive oxygen species produced by normal metabolism (Suciu et al. 2018). There are many factors affecting the sensitivity of LDL to oxidation, including the size and composition of LDL, and the presence or absence of endogenous antioxidants (such as α-tocopherol). Ox-LDL is one of the initiators of fat stripe formation. It also induces chemokines, adhesion molecules including IL-1, TNF-α, CC motif, and CCL2 (Garciagonzalez et al. 2015). Certainly, ox-LDL can promote the development of inflammation, it can cause losing of normal function of endothelial cells, and easy enter and accumulate in the arterial wall. In addition, when ox-LDL binds to lectin like oxidized LDL receptor 1, which is the main receptor of ox-LDL, this process can improve the level of adhesion molecules (such as intracellular adhesion molecules), which play a role in the adhesion of monocytes to endothelial cells (Li et al. 2013; Libby et al. 2010; Mango et al. 2011). Once the monocytes enter the vascular endothelial cells, they migrate to the inner layer of the artery wall under the help of the monocyte chemoattractant protein-1 (MCP-1) (Dunn et al. 2008).

In addition, the interaction of ox-LDL and its receptor can lead to the increase of reactive oxygen species. The matrix metalloproteinase activity can also be increased (Szmitko et al. 2003). Under the influence of ox-LDL, overexpression of matrix metalloproteinases plays a role in some chronic diseases such as inflammation and AS (Hossain et al. 2013). All of these factors add up to cause instability and rupture of plaques in blood vessels, which eventually lead to thrombosis (Szmitko et al. 2003). In the long run, smooth muscle cells and endothelial cells will apoptosis under the influence of ox-LDL (Gonzalez and Trigatti 2017).

2.2. Inflammatory cytokines mediated VSMC injuries and fibrinolysis

AS shows a series of typical pathological features of inflammatory reaction, including VSMC fibrosis, monocyte/lymphocyte exudation and tissue necrosis/degeneration. In addition, it also exhibits exclusive performance, and ordinary chronic inflammation, including endothelial destruction, lipid accumulation, monocyte migration, calcification and thrombosis, all of which are related to the formation of AS (Ross 1999). The source of these pathological changes is due to the complex response of vascular endothelial cells and arterial wall VSMC to multiple injuries, involving a large number of inflammatory cytokines (Manduteanu and Simionescu 2012; Ross et al. 2010). Ross (1999) described an inflammation hypothesis in which the development process of AS was usually accompanied by the characteristics of chronic inflammation, interacting with each other and not limited to AS lesions, in which inflammatory cytokines play different functions. C-reactive protein can accelerate the inflammatory response of AS through a variety of mechanisms and is a specific marker of inflammation. (Demmer et al. 2013). MCP-1, which is produced at the site of AS injury but not in the normal vessel wall, is an effective pro-inflammatory chemokine for monocytes (Rundle et al. 2013). Transforming growth factor-β, also one of the anti-inflammatory cytokines, can play an anti-AS effect and is widely expressed in atherosclerotic plaques and inflammatory cells in humans and rats (Li et al. 2013). In addition, the nuclear factor κB (NF-κB) is a key protein complex in the inflammatory response. This transcription factor is activated by a series of inflammatory molecules (such as tumor necrosis factor-α, IL-6 and IL-8). NF-κB initiates the expression of apoptosis regulators and inflammatory cytokines. The NF-κB pathway includes NF-κB, inhibitor κB and IκB kinase. By improving the activity of pro-inflammatory genes, Ox-LDL in AS is linked to NF-κB signaling in a dose-dependent approach (Dąbek et al. 2010). Activation of endothelial cells and pathogenic proteins can lead to the accumulation and proliferation of VSMCs, and can also be regulated by the NF-κB pathway in AS.

Generally, the balance between pro-inflammatory and anti-inflammatory cytokines is a key factor to determine the occurrence of AS. Therefore'it is of great significance to study the inflammatory related molecules for the treatment of AS (Kang et al. 2013; Loland et al. 2013; Zahradka et al. 2013).

2.3. The renin-angiotensin system (RAS)

RAS plays an important role in controlling blood pressure, blood flow, body fluid volume and electrolyte balance. The pathogenesis of many clinical diseases is related to the abnormal function of RAS,

including the whole pathogenesis of AS (Ferrario and Strawn 2006; Oparil and Haber 1974a, b). The precursor of angiotensin I is a kind of angiotensinogen produced in the liver. Angiotensin I is an inactive decapeptide that can be converted into angiotensin II, which is the main action substance of RAS. In the past, it was believed that angiotensin II affected AS by changing hemodynamic effects. But in the past 20 years, the direct cellular effects produced by angiotensin II can play a role in the structural changes of the blood vessel wall in AS (Sata and Fukuda 2010). The main functional factor in RAS is angiotensin II. The function of angiotensin II is mainly mediated by two transmembrane domain receptors, called angiotensin II type 1 receptor (AT1R) and angiotensin Type II receptor (AT2R), which exhibit a complex regulation and function model (De Gasparo et al. 2000). Both AT1R and AT2R can be identified accurately on the vessel wall. Most of the atherosclerotic effects of angiotensin II are mediated by AT1R (Nouet and Nahmias 2000; Sayeski and Bernstein 2001). Previous studies have shown that in the animal model of high cholesterol AS, the number of AT1 receptors in the diseased vascular medium increased by 5 times compared with healthy controls (Yang et al. 1998). A high AT1R binding rate was also found in the neointima of the diseased artery. The highest receptor density was found on VSMC. But the significant response mediated by AT1R in endothelial cells and macrophages was determined by cell culture studies, while AT2R accounted for only 10 % of the total angiotensin receptor in the blood vessels of healthy controls (Wang et al. 1998; Yang et al. 1998). These results indicate that the angiotensin II-AT1R pathway not only plays a role in promoting the occurrence and development of AS, but also participates in the occurrence and development of AS through local pathways.

3. Current treatment options for atherosclerosis

3.1. Cholesterol metabolism related approaches

The disorder of lipid metabolism, which results in the formation of macrophage-derived foam cells, is an important one in the discussion of pathogenesis of AS. Therefore, the approaches against cholesterol metabolism attract attentions from fundamental science researchers.

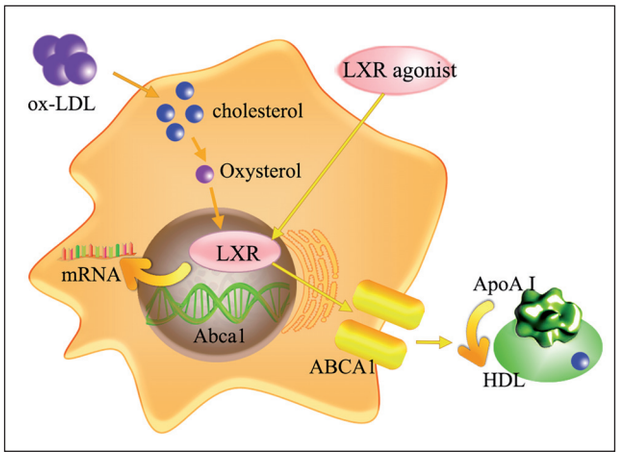

Fig. 2: Schematic diagram of LXR-mediated cholesterol clearance mechanism. ABCA1 protein mediates RCT mainly in two steps. In the first step, ABCA1 on the normal peripheral cell membrane firstly mediates the outflow of phospholipids in the cell, and combines with apoA-I outside the cell to form a disc-shaped phospholipid-apoA-I complex. In the second step, cholesterol in the cell flows out through the membrane through diffusion and is captured by this complex to form pre-HDL. Under the action of lecithin-cholesterol acyltransferase, it transforms into mature HDL rich in cholesterol lipid globules, then the RCT process can be triggered.

The formation of foam cells is due to the increase in ox-LDL uptake and/or the decrease in cholesterol efflux, which leads to the accumulation of cholesterol in the cytoplasm of macrophages. The reverse cholesterol transport (RCT) process is the concentrated transport of cholesterol from surrounding tissues (including atherosclerotic plaques) to the liver, so as to circulate or excrete in bile, including cholesterol removal from liver and cholesterol outflow from surrounding tissues. In peripheral tissues, the expression of cholesterol efflux transporter in macrophages and subsequent activation of cholesterol efflux in macrophages is the first step of RCT. The accumulation of cholesterol in the blood vessel wall can be reduced through the RCT process, so as to achieve the purpose of preventing the occurrence of AS. The efflux capacity of cholesterol can quantify the total efflux mediated by related pathways of cholesterol efflux by macrophages (such as ABCA1, ABCG1 and scavenger receptor B1). Macrophages mainly respond to lipid efflux mediated by ABC transporters (ABCA1 and ABCG1) and scavenger receptor B1 (Westerterp et al. 2014). LXR directly regulates ABC transporters genes. It is generally believed that increasing the cholesterol efflux of macrophages by upregulating ABCA1 and ABCG1 genes can produce the protective effect of synthetic LXR agonists against AS (Calkin and Tontonoz 2010). Guo et al. (2017) researched that activating the expression of LXR target genes in the atherosclerotic plaques can significantly increase the expression of ABCA1 and ABCG1 in the aorta, which results from the increased RCT effect.

In addition, statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) inhibitors, which play a role in reducing serum cholesterol and LDL concentrations. HMG-CoA reductase can be competitively inhibited by statins, thereby reducing LDL cholesterol and triglyceride levels (Maron 2000). Recent studies have found that these compounds not only had the ability to lower blood lipids, but also reduced the production of reactive oxygen species and increased the antioxidant capacity of LDL. This may be the ability of statins to reduce LDL oxidation, thereby increasing the effectiveness of preventing atherosclerotic diseases (Rosenson 2004).

3.2. Anti-inflammatory therapeutics for atherosclerosis

AS is considered to be an inflammatory disease, in which pathogen-related molecular patterns cause the inflammatory response of atherosclerotic injury, and mononuclear phagocytes play an important role in the inflammatory response of AS injury (Ammirati et al. 2015). In the presence of ox-LDL and inflammatory cytokines, the expression of vascular cell adhesion molecule-1 and P-selectin in endothelial cells increases; this increase is related to E-selectin (found only on endothelial cells and is caused by P-selectin). The increase in the expression of selectin stimulates the recruitment of leukocyte cells in blood (Dong et al. 1998; Leeuwenberg et al. 1992; Poole and Florey 1958). NF-κB is activated by the oxidized lipoproteins and pro-inflammatory factors such as IL-1β and TNF-α, followed by transcription of the vascular cell adhesion molecule-1 gene. The production of chemokines such as MCP-1 and IL-8 contribute to the recruitment of monocytes to endothelial cells through the regulation of NF-κB (Collins and Cybulsky 2001).

Vinpocetine, which is an alkaloid extracted from the periwinkle plant, can inhibit the progression of AS. For several years, it has played an important role in enhancing cerebral circulation and cognitive function. It is currently used as a dietary supplement to prevent cerebrovascular diseases and aging-related symptoms in many countries (Jeon et al. 2010). Vinpocetine inhibits the transcription of adhesion molecules, selectins and pro-inflammatory factors by targeting the NF-κB pathway, thereby inhibiting the adhesion of human umbilical vein endothelial cells to monocytes (Berdeaux et al. 1988). MCP-1 helps monocytes transformed to macrophages and through the NF-κB pathway, vinpocetine can indirectly affect the above transform process. Vinpocetine can also inhibit inflammatory cytokines through NF-κB, such as the release of IL-6, TNF-α, MCP-1, matrix metallopeptidase 9 and reactive oxygen species by macrophages that phagocytose ox-LDL to achieve the purpose of reducing abnormal migration and proliferation of vascular smooth muscle cells. In addition, vinpocetine has a significant inhibitory effect on the intracellular reactive oxygen generation induced by platelet-derived growth factor (Cai et al. 2012). In addition, vinpocetine can increase the collagen content-

which contributes to increase the thickness of the fiber cap, thus atherosclerotic plaque can be stabilized. The above studies show that vinpocetine can inhibit many steps in the development of AS.

4. Cyclodextrins promote atherosclerosis

In general, the disorders of lipid metabolism cause an increase in LDL, which moves into an inflammatory pathway for the development of AS. Thus, the current treatment for AS is to significantly reduce LDL. However, current traditional treatment for AS is not effective for all patients in reducing LDL (Montalescot et al. 2013; Sabatine et al. 2015). Therefore, looking for other methods of reducing cholesterol levels to treat AS has become an urgent need. Cyclodextrins (CD) are cyclic oligosaccharides made up of different numbers of glucose molecules connected by α-1,4 bonds. CDs are divided into α-, β-, and γ-CDs according to the number of D(+)-glucose units connected by α-1,4-bonds which are 6, 7, and 8, respectively,. In addition, the FDA generally considers CDs as safe substances. Among CDs, β-CD has an effective and ideal molecular size, so it is a common host molecule for many water-soluble molecules. This makes β-CD the most popular and widely studied member of this class of compounds (Cho et al. 2014). β-CD has a hydrophilic outer layer and a hydrophobic central cavity. Through hydrophobic interaction, the central cavity which is lipophilic in nature can contain many hydrophobic guest molecules (Szejtli 2005).

Because the complex inflammatory response can be triggered by the accumulation of cholesterol and the deposition of cholesterol crystals, improving the solubility of cholesterol by CD is a promising way to promote AS regression.

4.1. CD promotes cholesterol dissolution and increases cholesterol efflux

The atherosclerotic process involves the accumulation of lipid-rich foam cells in the arteries, where oxidized and unoxidized sterols and their esters accumulate in these foam cells. Ox-LDLs are cytotoxic and can hinder the removal of cholesterol from cells. To remove them may be a key to AS treatment. Recent reports indicated that ApoA-I is the main initial receptor for cholesterol in macrophages loaded with ox-LDL *in vitro*, and it had insufficient induction of cholesterol efflux. In these cells and human atherosclerotic lesions, the release of 7-ketocholesterol (a major oxidized sterol) is more significantly impaired (Atger et al. 1997). The research showed that hydroxypropyl-beta-CD can efflux of 7-ketocholesterol in a selective manner. The efflux of 7-keto-cholesterol was found to be time and concentration dependent. The removal rate of hydroxypropyl-β-CD was 50 times higher than that of ApoA-I. In the prescribed concentration range (0-5 mg/ml), the efflux rate of 7-keto-cholesterol was higher than that of cholesterol with no cytotoxicity. The efflux of free 7-keto-cholesterol was related to the decrease of intracellular free and esterified 7-keto-cholesterol. The efflux of other oxysterols was also enhanced by hydroxypropyl-β-CD. According to its different effects on efflux, the physical dissolution of 7-keto-cholesterol by cyclodextrin was much greater than that of cholesterol. These data indicated the importance of extracellular sterol lysis in the efflux of cellular oxysterols and the mobilization of intracellular free and esterified oxysterols in macrophages loaded with ox-LDL. Therefore, the synthesis of sterol solubilizers such as hydroxypropyl-β-CD may further increase the solubility of cholesterol, resulting in the occurrence of AS regression (Atger et al. 1997).

4.2. CD increases cholesterol metabolism and LXR-dependent cellular reprogramming, resulted in more efficient RCT

AS is characterized by remodeling of the arterial wall, which is caused by the retention and accumulation of different types of lipids in the subendothelial layer. Inflammation in the blood vessel wall is related to lipid deposition and the appearance of cholesterol crystals, and inflammation is one of the causes of the disease. Cholesterol crystals may be the result of excessive cholesterol deposition in atherosclerotic lesions, and are one of the pro-inflammatory factors that lead to the inflammatory reaction in the process of AS formation (Warnatsch et al. 2015). Complement activation, the formation of a neutrophil network and the induction of innate immune pathways can be triggered by cholesterol crystals. Therefore, treatments focusing on preventing cholesterol phase transition or removing cholesterol crystals can inhibit tissue inflammation and disease development (Nymo et al. 2014).

Studies have found that subcutaneous injection of CD can significantly reduce the occurrence of AS and induce the regression of AS. This is mainly induced by increasing LXR-dependent cellular reprogramming and enhancing the metabolism of cholesterol crystals. These effects result in a decrease of cholesterol crystals in lesions. In addition, cholesterol metabolism and LXR-dependent cell reprogramming induced by CD lead to more effective RCT and reduced expression of pro-inflammatory genes. The anti-atherosclerotic effect of CD depends on the expression of LXR in bone marrow cells of LDL receptor-deficient mice. These studies indicated that CD mediated the protective effect of AS by increasing the metabolism of cholesterol crystals and LXR-dependent cell reprogramming (Zimmer et al. 2016).

Thus, CD can normalize cholesterol and immune homeostasis in the vascular system by promoting cholesterol dissolution, enhancing LXR activity and evoking cholesterol efflux.

5. CD-modified polymers may be a promising approach for AS regression

Nanomaterials are microstructure materials with characteristic length scales in the nanometer range, and have been extensively studied in the fields of biology and medicine. The rapid development of nanotechnology may provide broad prospects for the development of new nanomaterials, especially amphiphilic micelles and polymosomes, combined with CD to promote AS degeneration, reduce inflammation, and enhance the reverse transport of cholesterol.

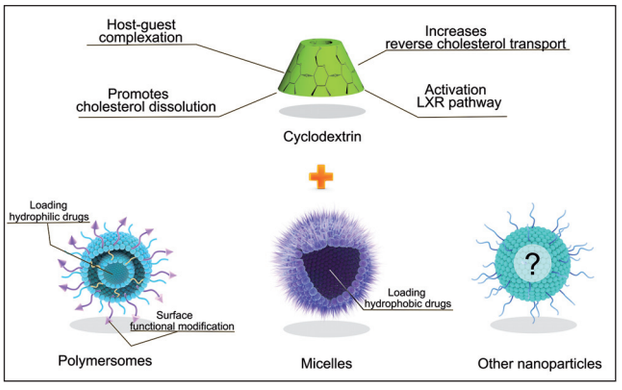

Fig. 3: Cyclodextrin combined with various functional nanoparticles may be a promising approach for AS regression.

5.1. Multifunctional micelles for targeting AS

Amphiphilic block copolymers can self-assemble in solution to become various forms, including micelles, spherical nanoparticles, cylindrical nanoparticles, and vesicles, showing unique properties and numerous potential applications. In addition, convenient surface functionalization methods build a multifunctional system for micelles (Letchford and Burt 2007).

Functional micelles can neutralize charged nucleic acids to form cores, while protecting nucleic acids from non-specific interactions and enzymatic degradation, so they have great potential as gene delivery vehicles. In addition, in order to enhance specificity and transfection efficiency, micelles can be modified to include targeting ability. The design of targeting micelles, such as micelles

containing inhibitors of dys-regulated miRNAs, can thus inhibiting AS. Suppression of dys regulated miRNAs has produced therapeutic effects in diseased cells associated with AS and has been proposed for the treatment of human diseases (Kuo et al. 2014). However, systemic administration of miRNA inhibitors is characterized by non-specific targeting, which has always been a problem that may cause adverse side effects. A study reported the addition of two different peptide sequences to miRNA inhibitors containing micelles. The first micelle used a peptide (arginine-glutamic acid-lysine-alanine), and this micellar system showed lesion-specific targeting in a mouse model of AS. Another peptide micellar system (valine-histidine-proline-lysine-glutamine-histidine-arginine) was identified by phage and passed vascular cell adhesion molecule-1, thereby targeting vascular endothelial cells (Kuo et al. 2014). This targeted micelle was successfully used as a delivery system for new type of therapeutic nucleotide, and its effectiveness in inhibiting macrophages and endothelial cells to promote atherosclerotic mirna was verified in *in vitro* experiments. Therefore, it may provide a new complementary strategy for dysfunctional macrophages and inflammatory endothelial cells in diseased arteries.

The micelles can also be developed for imaging of AS. AS is the main cause of sudden death and myocardial infarction. It is caused by unstable plaques that rupture and block blood vessels without warning. Current imaging methods cannot distinguish between stable or unstable plaque ruptures. Amphiphilic micelles can overcome this shortcoming because they can be modified by various targeting moieties, which can specifically bind to diseased tissues. It has been proven that monocytes are an early marker of AS, and the easy rupture of plaques is related to the accumulation of monocytes. Therefore, micelles targeted to monocytes can be used to distinguish different stages of AS. A study reported an amphiphilic micelle of monocyte chemoattractant protein-1 peptide, which can self-assemble under mild conditions to form nanoparticles with a diameter of 15 nm and a surface charge close to neutral. This amphiphilic micelle has good biocompatibility and high affinity for monocytes, and is expected to be widely used in AS imaging (Poon et al. 2017). In addition, the fine coagulation that occurs on the surface of the atherosclerotic plaque lumen constructed a new target for diagnosis and treatment of micelles-based drug delivery system. A modular multifunctional micelle is reported, which contains targeting elements, fluorophores and pharmaceutical ingredients in the same particle (Peters et al. 2009). The rupture of atherosclerotic plaque exposes collagen and other plaque components to the blood. This rupture can cause the activation of thrombin and lead to hemostasis in the blood vessel, thereby forming a thrombus at the rupture site. The pentapeptide cysteine-arginine-glutamic acid-lysine-alanine was used to achieve the atherosclerotic plaque targeting effect in ApoE-negative mice fed a high-fat diet. The entire surface of the plaque is bound by the fluorescent micelles, especially concentrated on the shoulder of the plaque, which is an easily ruptured location. Compared with non-targeted micelles, targeted micelles can deliver higher concentrations of anticoagulant hirudin to plaques (Peters et al. 2009).

5.2. Biological mimicking poly(DL-lactide-co-glycolide) (PLGA) nanoparticles

Platelets have inherent affinity for plaques and play an important role in the occurrence and development of atherosclerosis, especially in the late stage of thrombosis after erosion or rupture of vulnerable plaques (Lindemann et al. 2007; Von Hundelshausen and Schmitt 2014; Wu et al. 2017). Rapamycin has an effective anti-atherosclerotic effect, but its clinical application is limited by low concentration of atherosclerotic site and severe systemic toxicity (Martinet et al. 2014).

PLGA nanoparticles with excellent biocompatibility, stability, non-toxic and nonimmunogenicity have been proved to be promising drug delivery carriers. By using PLGA nanoparticles coated with platelet membrane as a drug delivery platform, atherosclerosis is treated by mimicking the inherent targeted plaque of platelets (Song et al. 2019). In atherosclerotic arterial tree, the radiation efficiency of PLGA nanoparticles coated with platelet membrane was 4.98 times higher than that of control nanoparticles, indicating that PLGA nanoparticles could target to atherosclerotic plaques *in vivo*. In the atherosclerotic model established in ApoE deficient mice, the PNP coated with rapamycin significantly attenuated the progression of atherosclerosis and stabilized the atherosclerotic plaque. These results demonstrate the perfect efficacy and decomposing potential of PLGA nanoparticles coated with platelet membrane as a therapeutic method for atherosclerosis.

In addition, macrophage apoptosis is the main factor leading to the vulnerable atherosclerotic lesions. To identify instable plaques before thrombosis is crucial for the treatment. Due to the function of HDL in the RCT pathway, HDLs has become an interesting possibility for the development of image-guided therapy. With apoE promoting cholesterol efflux in foam cells, apoA-I containing HDL promoted the transport of cholesterol in the lesion. Targeting HDL nanoparticles to develop contrast agents for early detection of vulnerable plaques and start preventive treatment with vascular protective effects by using HDL can reduce incidence rate and mortality of thromboembolism (Song et al. 2019; Study 2000).

Thus, the development of apoptosis targeted HDL-mimicking PLGA nanoparticles to carry contrast agents for early detection of instable plaques, and the use of vascular protection of HDL for preventive treatment is attractive for image-guided atherosclerosis therapy. HDL-mimicking PLGA nanoparticles were developed to detect vulnerable plaques by targeting the collapse of mitochondrial membrane potential during apoptosis (Marrache and Dhar 2013). The HDL-mimicking PLGA nanoparticle modified with cholesterol oleate and phospholipid bilayers, and the core contains diagnostic quantum dots for optical imaging. *In vitro* uptake, apoptosis detection and cholesterol binding studies showed that PLGA nanoparticles mimicking HDL have broad detection ability and therapeutic potential. *In vitro* studies have shown that these PLGA nanoparticles have potential in RCT. Biodistribution and pharmacokinetic studies *in vivo* showed favorable tissue distribution, controllable pharmacokinetic parameters and a significant reduction in triglycerides.

5.3. Polymersomes for inflammation targeting

The accumulation of inflammatory cells and their products induces atherosclerosis or plaque maturation, which eventually leads to plaque rupture, leading to ischemic stroke or myocardial infarction (Benjamin et al. 2017). Atherosclerotic lesions contain a complex mixture of multiple immune cell populations, such as dendritic cells (Getz et al. 2011; Paulson et al. 2010). Dendritic cells are present at all stages of atherosclerotic lesion development and have been found to have both atherogenic and protective effects, although their accumulation is associated with the level of plaque instability (Gautier et al. 2009; Weber et al. 2011). The targeting of dendritic cells by polymersomes, which is a vesicular structure with central aqueous chamber surrounded by hydrophobic membrane, has attracted wide attention in AS.

By using near-infrared fluorescence imaging and flow cytometry as multi-mode methods, the biological distribution of micelles and polymers assembled from poly (ethylene glycol)-bl-poly (propylene sulfide) block copolymers with chemically identical surface properties were compared at the organ and cell levels (Yi et al. 2016). The results showed that the targeting effect of the polymers on splenic dendritic cells was very effective. In the mouse model of AS, the polymers showed superior specificity for dendritic cells in atherosclerotic lesions. In addition, there were significant differences in the distribution of polysomes in atherosclerotic mice compared to control group.

5.4. CD-based drug delivery system

5.4.1. Delivery of hydrophobic and hydrophilic drugs

Cyclodextrins are cyclic oligosaccharides with a hydrophilic shell and a lipophilic center cavity. The lipophilic center cavity provides a microenvironment for the encapsulation and solubilization of hydrophobic “guest” molecules. Due to these characteristics, CD

can form clathrates in which part all of the guest molecules are surrounded by the hydrophobic environment of the CD cavity. With the characteristics of this host-guest complex, CD can improve the encapsulation of drugs, which has aroused research interest in drug delivery systems. For example, an amphiphilic copolymer composed of polyethylene glycol and lactide (PEG-PLA) and β-cyclodextrin (β-CD) in an orderly connection can self-assemble into a stable nanoparticle. The use of this kind of nanoparticles for drug delivery has made considerable progress in recent years (Hu et al. 2016; Shen et al. 2016; Zhang et al. 2017). CD-based amphiphilic polymer nanoparticles have the advantages of improving drug loading stability and encapsulation, increasing intracellular drug concentration, and controlling the release of payload, etc., and can be used as a carrier for hydrophobic and hydrophilic drugs. A three-arm star polymer PEG-PLA-CD centered on β-CD is reported (Hu et al. 2016). According to the PEG block volume fraction in the range of 20-42%, amphiphilic polymers tend to self-assemble into polymersomes in the central water chamber (Zhu et al. 2015). The hydrophilic model drug was successfully delivered by CD-based polymersomes with a central aqueous chamber. In addition, when the volume fractions of the PEG block out of the range of 20-42%, the β-CD based PEG-PLA can self-assemble into micelles. The hydrophobic model drug was orally delivered with a favorable bioavailability (Zhang et al. 2017).

5.4.2. Delivery of biomacromolecules

Nowadays, CD are still dominant in forming inclusion compounds with small hydrophobic molecules, but their ability of delivering biomacromolecules was also studied. In the past ten years, progress in this field has led to the emergence of more and more complex CD derivatives, which provide a simple way to further expand the original and a better CD-based gene delivery system. Various methods have been used to generate and improve the efficiency of gene delivery in cells, and the CD-based gene transfer system is one of the most promising methods (Loftsson 2002). The commercial availability of CD, the simplicity and relative cheapness of large-scale synthesis of suitable derivatives, robustness, biocompatibility and the lack of immunogenicity are in line with important standards for the future development of CD-based gene delivery systems. In addition, CDs also have the ability to form clathrates with chemical drugs, used for drug/gene co-delivery, may act as absorption enhancers in therapeutic transfer, and can regulate the cytotoxicity of other polymers. Therefore, there is no doubt that CD-based delivery systems will play an important role in promoting non-viral gene delivery against diseases.

6. Conclusions

Disorders of lipid metabolism cause an increase in LDL, which results in an inflammatory pathway for the development of AS. Thus, the current treatment for AS is based on a significant reduction of LDL levels. However, this is not effective in all patients. Therefore, looking for other methods of reducing cholesterol levels to treat AS has become an urgent need.

CD have been approved by the FDA for use in human drug delivery systems. They function solubilizers and hydrophobic drug inclusion compounds, which can increase the solubility of cholesterol, accelerate the efflux of cholesterol in *in vitro* foam cell experiments, and activate the anti-inflammatory mechanism. It is worth noting that CD nanoparticles can also be used as carriers for hydrophobic/hydrophilic drugs and biomacromolecules. Recently, the research on CD-based nanoparticles for AS regression is limited. How to build a drug delivery system based on CD which can achieve an efficient entrapment of anti-atherosclerotic drugs, promote AS regression, reduce inflammation and augment reverse cholesterol transport is a new strategy in future.

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