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Nanosized-drug delivery systems for treating inflammatory atherosclerosis

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Abstract
Atherosclerosis (AS) is a disease of the large and medium arteries that involves producing lipid-rich plaques in the intima and inner media, with inflammation playing a major role in the pathogenesis. Treatments for AS that are currently accessible are not always totally successful; adverse effects, primarily caused by immunodepression for anti-inflammatory chemicals, restrict their effectiveness. Given the enormous degree of freedom in nanoconstruct design, researchers have spent a lot of time in recent decades developing nanoparticles (NPs) formulations that are specially tailored for medication administration, visibility of atherosclerotic plaques, or a combination of these and other functions. We described the current state of knowledge in these fields, which is required to logically approach the use of NPs for the prevention, diagnosis, and treatment of AS. We reviewed the research that has been done on (1) understanding the role of the immune system and inflammation in cardiovascular diseases, (2) pathological and biochemical principles in atherosclerotic plaque formation, (3) the latest advances in the use of NPs for the detection and treatment of cardiovascular diseases, and (4) the cellular and animal models that can be used to study the interaction between the immune system and inflammation.

Keywords: atherosclerosis, inflammatory diseases, innovative nanomaterials, drug delivery, nanomedicine, imaging and theranostics, immune cells, cardiovascular diseases

Introduction

AS is a chronic inflammatory disease of the arterial wall. The aggregation of lipids, as well as the invasion of different immune cells, characterize atherosclerotic plaques. The accumulation of lipids, as well as the invasion of other immune cells, characterize atherosclerotic plaques. In atherosclerotic plaques, macrophages are the most common inflammatory cells [1]. Dyslipidemia and an imbalance in cellular cholesterol influx and efflux result in the accumulation and oxidation of LDL and LDL-like particles, stimulating endothelial cells (ECs) at atherosclerotic lesion-prone locations. Activated ECs then upregulate cell adhesion molecules and chemokines, allowing circulating monocytes to be recruited again [2]. Monocytes and resident macrophages in the arterial lumen pick up the oxidized particles, convert them into foam cells, and form early plaques. Pro-inflammatory cytokines (e.g., interleukins and tumor necrosis factor- (TNF-alpha) and chemokines (e.g., monocyte chemoattractant protein-1 (MCP-1)) are also secreted by foam cells. This amplifies the inflammatory response at the local level [3]. Despite attempts to reduce proatherogenic stimuli, immune cells like monocytes and macrophages continue to be pro-inflammatory within the plaque context [4]. Recent research suggests that pro-atherogenic stimuli like LDL cholesterol and oxidized low-density lipoprotein (Ox-LDL) may trigger long-term epigenetic reprogramming in innate immune cells. This causes them to remain activated even after the pro-atherogenic stimuli have been removed [5, 6].

AS is now recognized as an inflammatory condition defined by the infiltration of various immune cells (ICs) into the sub-endothelial region, mainly circulating monocytes (MCs), which eventually differentiate into macrophages (MΦs) and then foam cells (FCs), as well as plaque development and progression [5, 6]. The heterogeneity of the cells within and near to lesions during evolution [MCs, MΦs, and FCs, but also neutrophils, dendritic cells, T cells, and possibly others] complicates such a simplistic view [7, 8]. Although cells might have several functions and exhibit a continuum of markers of different subtypes, the markers of the various IC phenotypes are given special focus in the cited reviews [7]. MΦs, the AS's defining cells, is an excellent example of how distinct subtypes can play opposing roles. Evidence has led to the definition of more subtypes (e.g., Mox, M4, Mhem) and even "sub-sub types" (e.g., M2a, M2b, M2c); there could be a continuum of specializations, and MΦs could potentially transform into each other [7, 9].

The susceptible plaque is characterized by an autonomous state of inflammation (similar to chronic wound settings). The presence of active macrophages causes the secretion of matrix-component degrading enzymes (such as matrix metalloproteinases-MMPs), which limits SMC collagen formation and, as a result, helps vascular wall remodeling. These mechanisms are beneficial in early lesions, allowing for the resolution of disturbing endothelial layers and the avoidance of toxic species buildup, as well as the decrease of atherosclerotic plaques; nevertheless, they also cause fragility in late plaques, potentially leading to plaque rupture [10-12]. Inflammation influences the clinical outcomes of AS's

thrombotic complications and inhibiting it may slow progression, reduce the chance of plaque rupture, and even promote AS regression [13-16].

AS treatment

Current AS treatments attempt to reduce promoting factors such as hypertension, smoking, and dyslipidemias; considered medications (e.g., cholesterol hepatic synthesis inhibitors like statins) have a specific effect on cholesterol (or other lipids) production and transport to artery walls [17-19]. Several ways have been studied, including inhibiting cholesterol absorption in the intestine (e.g., with ezetimibe), limiting cholesterol reverse transport in ICs (e.g., with an agonist for the liver X receptor (LXR) like GW3965), and delivering synthetic forms of high-density lipoproteins [18-22]. Inflammation control is another promising technique; the interleukin-1 pathway, in particular, has been identified as a potential therapeutic target. In the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), a monoclonal antibody targeting interleukin-1 was evaluated [23]. While AI medicines have a good therapeutic index, systemic administration is generally limited by significant side effects such as bone marrow suppression, neutropenia, and immunodepression.

It would be ideal to find a successful method for all of the AS phases; for example, Resolvin E1 is mentioned in [10] Libby *et al*. as a mediator that reverses all of the advanced lesions associated processes contributing to plaque resolution in early phases. Controlling the release or activation of chemicals used to treat or cure AS symptoms/consequences is another potential option. Using medicines modified with glutamyl to take advantage of the elevated concentration of GT in AS lesions is one possibility [24]; devising strategies that take advantage of high cholesterol concentrations; addressing routes that go from monocyte to pro-inflammatory MΦs, and then to foam cells [25]. Macrophages have been the primary targets in the fight against AS because of their dual role in producing inflammation and controlling tissue regeneration. Vannella and Wynn gave an informative overview of macrophage behavior in various tissues, the mediators of the many mechanisms involved, and lastly, numerous potential approaches to modify them [26]. It would be ideal for forcing them out of AS lesions while they are transforming into foam cells; to this end, activating or releasing a "macrophage migration-enhancement factor" [27-29], or interfering with cell surface adhesion molecule only in overabundance of cholesterol or other AS markers [30].

Targeted NPs for AS

As previously stated, spatial and temporal management of drug activity can limit collateral short and long-term effects, as well as make delivery more convenient. These principles strongly suggest that efficient, targeted delivery systems for AI compounds, similar to those based on their encapsulation into NPs, be developed [31]. Several types of NP have been studied for drug delivery; Allen *et al*. [32], Ulbrich *et al*. [33], Cheraghi *et al*. [34], and Matoba *et al*. [35] describe the properties and production techniques for several of these. Many NPs still have limitations and drawbacks for clinical use; these can stem from a lack of perfect control over the final fate of many formulations since they frequently accumulate in the reticuloendothelial system (RES), from polydispersion and/or poor reproducibility in their preparation, or from the sometimes-difficult scale-up and high cost of their production, especially in the RES [33, 36]. The physicochemical properties of NPs, on the other hand, can be finely tailored during synthesis, allowing for NP target specificity and drug loading optimization [32].

Allijn *et al*., Duivenvoorden *et al*., Gomes *et al*., used a "biomimetic" strategy to achieve active targeting: NPs can stem from, or have features similar to, aggregates like LDL or HDL, which naturally accumulate in AS plaques [18, 37, 38]. More specific tissue or cell targeting can be identified by examining nanoparticle libraries *in vitro* or *in vivo* [16, 39]. Still, the mechanisms of the found specificity must be understood to ensure that it is preserved downhill of nanoconstruct alterations or in other biological conditions. Libraries are frequently tested in cell cultures first, but in-vivo experiments are required at the very least to assess the impact of various biological media. Indeed, when NPs enter an organism, they are typically destroyed. Their biological properties are altered when they are coated with a protein corona (PC); individuality PC creation (also known as "opsonization") is a common first step. The RES has taken a step toward NP sequestration. To avoid such an occurrence, various measures have been developed. Controlling nano constructs has become a popular strategy in recent years. Since it was discovered that deformable particles are stiff, Off-target RES is less likely to be taken up by macrophages. a few tissues [40, 41].

NPs mediated Treatment and Diagnosis of AS

Zhang *et al*. (2017) neatly reviewed the use of NPs for AS treatment and plaque visualization; we picked more recent works not covered there (Table 1) [6]. We'll go through some of these and other related works in this session. Often, inherent features of NPs lead to the employment of drug delivery systems in conjunction with photothermal and radiofrequency-mediated triggering effects; for example, Johnston proposed the use of photothermal death of macrophages utilizing iron oxide NPs with thin gold and dextran coatings, excited by a 755nm laser pulse. The particles were being used for MRI and *in vitro* photothermolysis in this paper. In the NANOM-FIM study [42, 43], NPs made up of silica shells holding gold and eventually magnetic nanoparticles were administered on AS plaques via a bioengineered on-artery patch or a magnetic navigation system; detonation of NPs using a NIR laser resulted in a substantial reduction in overall atheroma volume.

A novel and intriguing technique are to intervene early in the recruitment of monocytes from the progenitors of pro-inflammatory macrophages M1 [35, 44]. The researchers proposed polymeric NPs containing Pioglitazone; a PPAR agonist demonstrated to impact macrophage polarization. The formulation was tested in ApoE $^{-/-}$ mice fed a high-fat diet (HFD) and injected with angiotensin II, which promoted monocyte/macrophage-driven inflammation.

Conclusion

We briefly reviewed the background information required to comprehend the use of NPs for anti-inflammatory medication

delivery and activation. We tried to concentrate on how fundamental research, in conjunction with translational and clinical factors, may address various parts of this to provide a better answer for the underlying mechanisms of NPs intra-plaque internalization, as well as the molecular and cellular processes at the foundations of various treatments. We emphasized that a better knowledge of these would allow for the prediction of potential adverse effects, including long-term ones, and the application of similar methodologies and (nano) tools to other disorders. While single studies can be carried out in specialized groups, a deeper understanding of concepts, mechanisms, and applicability of developed (nano)tools necessitates a highly interdisciplinary environment involving, for example, cardiologists, biologists, physicists, chemists, and engineers; professionals who can communicate with one another; and fostering the development of multi-faceted scientists.

Table 1: Selected recent original works on detection and treatment of AS using NPs

Molecular/Functional target	NPs	Imaging platforms	Animal model/ patients, dose, and administration route	Results
Macrophages, TNF-alpha, MMP9	LDE, Lipid core NPs resembling the lipid structure of low-density lipoprotein, carrying PTX or MTX	*Ex-vivo* optical imaging	Model: 38 New Zealand white rabbit, 1% cholesterol diet for 8 weeks, -Treatment: I.V injections 4 mg/ kg 1/w	Increased regression of plaque area as (59%) and of intima area (-48%) by LDE-PTX, -43% by LDE-PTX+ LDE-MTX. Reduced expression of MMP-9 (-74% LDE-PTX, 78% LDE-PTX+LDE-MTX) and TNF-alpha (-65% by LDE-PTX, 79% by LDE-PTX+LDE-MTX).
Macrophages, foam cells	Lipid coated polymeric NPs loaded with MTX	Fluorescence imaging, PET/CT.	Model: Apo-/- male mice on HFD Treatment: retro-orbital NPs injection with 20 µg equivalent of MTX, 2/w 30 days	50% less plaque coverage (athero-protective effect) in the aortic arch as compared to the control groups of saline and free MTX injection ($p<0.05$)

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