Review

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**Anti-inflammatory mediators for molecular imaging of atherosclerosis**

**Abstract:** Nanomedicine, a young and innovative field, offers interesting approaches for diagnosis and treatment in personalized medicine. Myocardial infarction and stroke belong to the most important challenges in this context because an improved early diagnosis of individuals well before fatal clinical endpoints occur is urgently needed. The underlying cause of myocardial infarction and stroke is atherosclerosis, a chronic immune-mediated inflammation of the vascular wall involving monocytes, macrophages, T-lymphocytes, and arterial wall cells. Hence, an immense number of pro-inflammatory mediators have been investigated in the context of nanomedicine and atherosclerosis but, interestingly, only few anti-inflammatory biomarkers. Nevertheless, the anti-inflammatory axis is always present as a negative feedback if a critical inflammatory perpetuation destabilizes atherosclerotic lesions. Hence, we could show that the immune-modulating, anti-inflammatory molecules, adiponectin and interleukin-10, are useful for molecular imaging of AS plaques. Based on recent publications in animal models of atherosclerosis, we strongly assume that the inflammatory “brake” mechanisms may represent an interesting new tool to specifically target the scenario of culprit AS-lesions. In this review article we discuss the potential of adiponectin, interleukin-10 and other anti-inflammatory active molecules like targeted liposomes and high dense lipoproteins towards this.

**Keywords:** atherosclerosis; inflammatory brake; nanomedicine.

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**Introduction**

Despite considerable therapeutic advances over the past 50 years, cardiovascular events are the leading causes of death worldwide. This is primarily due to the increasing prevalence of atherosclerosis (AS) which is associated with a sedentary and obesogenic life style increasingly present in the so-called Western, industrialized world. Atherosclerosis is a sub-acute inflammatory condition of the vascular wall, characterized by the infiltration of macrophages and T-cells which interact with one another and with the arterial wall cells (1). The chronic inflammatory process leads to the formation, progression and rupture of vascular lesions, called AS-plaques (2).

The early identification and the ability to follow the development of AS-plaques are still unsolved challenges for medical imaging, which is limited not only by the performance of present imaging techniques, but also by the availability of specific molecules for targeted recognition (3). Unfortunately, so far AS is only diagnosed at the advanced stages of the disease: either by directly measuring the degree of stenosis, or by evaluating the effect of arterial stenosis on organ perfusion (4). Nevertheless, over the past few years, advances have been made in imaging techniques that enable the visualization and monitoring of AS-lesions’ progression or regression (5). However, a reliable, non-invasive technique to detect different stages of AS for an applicable, clinical characterization of AS-plaques is still missing (6). With time, an immense number of mediators involved in the inflammatory scenario of AS progression have been suggested, and tested to recognize AS-lesions (7, 8). Interestingly, the great majority of all studies focused on pro-inflammatory molecules, practically none on anti-inflammatory ones (3).

To close this gap, we review herein the potential of anti-inflammatory candidate molecules for an improved molecular imaging of AS lesions. The majority of the data
is based on recent observations in animal models of AS by which anti-inflammatory molecules uncoupled, or coupled with nanoparticles (NPs) have turned out to be promising for an improved diagnosis of vulnerable AS lesions (9–12). Vulnerable AS plaques are characterized by a thin fibrous cap, a large, necrotic lipid core, an increased number of activated macrophages, and less collagen and smooth muscle cells content (13). Referring to the utmost importance of inflammatory activation for the generation of vulnerability, the diagnostic use of anti-inflammatory molecules implicates also potential theranostic effects.

**Liposomes – “nanofat” carriers for anti-inflammatory action**

Nanoparticles offer new possibilities as homing devices for various drugs or contrast agents. Although cancer therapy and cancer diagnostics are still dominating the field, the detection of AS plaques is an equally attractive endeavor in the prevention of cardiovascular diseases (CVD) (4, 7, 14). Liposomes belong to the most widely studied class of NPs in use. They are composed of biologically degradable phospholipid molecules and in aqueous solution they typically assemble to closed bilayer structures (15). They are easy to handle and offer a unique variety of possible combinations concerning their overall size and charge. The surface of liposomes is often coated with polyethylene glycol (PEG-) molecules to yield “stealth” particles which can elude the reticulo-endothelial system (RES), and thus, can have prolonged circulation times ranging from hours to days (16). Such liposomes are easily modifiable with signal-emitting groups to be detected by different imaging modalities. For magnetic resonance imaging (MRI) iron oxide nanoparticles or lipid conjugated gadolinium (Gd3+) ion chelates are widely used. Gadolinium-based products, however, should be used with caution, since free Gd3+ is highly toxic and intracellular gadolinium is known to induce cell apoptosis. Especially in patients with renal insufficiency the risk for inducing nephrogenic systemic fibrosis is significantly increased after exposure to gadolinium based contrast agents (17). Using liposomes for MRI requires a balance between blood circulation time, time required for accumulation and retention of nanoparticles in the plaque and blood clearance rates. The latter is important to reduce background signal for imaging (18). As gadolinium complexes have relaxivities between 3 and 15 mM·s⁻¹ at 3 Tesla and a tissue relaxation rate of 1 s⁻¹ a very high concentration of about 50 nmol Gd³⁺ per gram of tissue is required for detectable signal alterations.

In contrast, iron oxide nanoparticle loaded liposomes produce local magnetic susceptibility, which results in a distance dependent dephasing of hydrogen nuclei. Such superparamagnetic liposomal contrast agents have a thousand times higher magnetic moments compared to paramagnetic gadolinium containing ones, therefore improving sensitivity tremendously (19). For nuclear medicine, liposomes are radiolabeled with ⁶⁷Cu, ⁶⁸Ga or ¹⁸F for positron emission tomography (PET), while ⁶⁷Ga and ⁴⁴⁶In are frequently used radiolabels for single photon emission computed tomography (SPECT) (19).

Besides incorporation or labeling with diagnostic markers, functionalized groups can be attached to the distal end of the PEG-chains for coupling of molecules enabling recognition of specific biologic targets (20–22). The targeting moiety, such as an antibody, biomarker or specific ligand must ideally have a high affinity for the desired target molecule. Targeted probes tested for cardiovascular imaging typically consist of a targeting sequence linked to the NP which is fused to a contrast agent appropriate to the particular imaging technique applied (23). By choosing the proper ligand, liposomes can be specifically directed to inflammatory sites, for instance to monocyte derived inflammatory macrophages in advanced AS lesions.

Alternatively, stealth liposomes can be loaded with therapeutic substances with anti-inflammatory properties. In this context, a very promising setup was recently published by Lobatto et al. (24). First, they induced AS in a rabbit model by balloon angioplasty of the aorta. Then, they prepared long-circulating anti-inflammatory PEGylated liposomes by encapsulating the corticosteroid prednisolone in the aqueous interior of the liposomes. Large scale good manufacturing practice (GMP) production was achieved by using high-shear homogenization for liposome preparation instead of extrusion membranes. Shelf life stability studies with the liposomal corticosteroid product indicated that it remains stable for at least 2 years when stored between 2 and 8°C. The liposomes were injected into the animals, and a ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) showed an anti-inflammatory effect which persisted over one week after a single dose. The positive effect was also proved by MR imaging compared to no changes with the free corticosteroid (24). Thus, liposomes can be used to achieve strong anti-inflammatory effects – a strategy promising for the future treatment of AS in humans.

Disadvantages of liposomes for in vivo studies are that their performance strongly depends on the formulation, the targeting sequence, the applied imaging technique,
and unfortunately also on the animal models, creating atherosclerotic lesions different to those in humans. This is one of the major limitations that hamper the translation from promising pre-clinical findings with diagnostic liposomes in animal models of atherosclerosis to clinical studies (25). Hence, no liposomal imaging agent for targeted imaging of AS is approved or in clinical trials. However, the capability to include high payloads of contrast generating materials into liposomes makes them highly attractive for diagnosis. Especially, ligand targeted liposomes show great promise to identify different components of the plaque scenario with high specificity. This can be especially valuable in the early phase of clinical trials to detect inflammatory changes before morphological changes occur (25, 26).

**HDL – native anti-inflammatory nanoparticles**

High density lipoprotein (HDL) particles are the smallest and most dense lipoprotein entities with diameters in a range from 8 to 10 nm. They contain paraoxonase, a potent antioxidant enzyme, and are rich on different amounts of exchangeable apolipoprotein species, of which the most prominent candidate is apolipoprotein AI (apo-AI) (27). Physiologically, HDL plays a significant role in reverse cholesterol transport and mediates antioxidant effects as well as anti-inflammatory and antithrombotic functions. In contrast to low density lipoprotein (LDL), where the entire particle is taken up, only the core lipids of HDL are shuttled into the cells. This uptake process is referred to as selective cholesterol uptake mediated by the scavenger receptor class B type I (SR-BI) (28). Cholesterol is off-loaded and either converted into a bile salt by hepatocytes or is directly excreted into the bile. A significant fraction of HDL cholesterol is also delivered to the liver by way of the LDL-receptor, after first being transferred from HDL to LDL by cholesterol ester transfer protein (CETP). As an inverse correlation exists between blood HDL levels and the risk to develop CVD, elevated serum concentrations of HDL are regarded as advantageous (29, 30).

Hence, the use of artificial HDL as a transport vehicle may be attractive for therapeutic and diagnostic applications. More recent papers underline this potential of HDL-like NPs, so far most promising in cancer research (31). The small size of artificial HDL (<30 nm) allows it to maneuver deeply into target organs, e.g., tumors (32), a characteristic which is probably also useful for the management of AS lesions.

**Reconstituted HDL**

Besides the application in cancer, studies concentrate on the intrinsic anti-atherogenic and cardioprotective properties of HDL, and deal with the use of reconstituted (r)HDL as therapeutic agent (33). Repeated treatment with rHDL was shown to reduce inflammatory and atherogenic processes in different animal studies. Such preclinical studies have been refined to human clinical trials revealing that rHDL is well tolerated by patients. It was found that intravenous injections of rHDL significantly raises the plasma levels of HDL (34). Recently, Ibanez et al. (35) compared the anti-inflammatory and plaque stabilizing properties of wild type HDL and rHDL. They found that the infusion of rHDL(Milano) exerts superior positive effects than wild type HDL (35). rHDL can further be applied for the targeted delivery of lipophilic and poorly water soluble drugs, as well as for cholesterol modified siRNA (36–38). Modified rHDL has also been studied as contrast agent for AS imaging. Macrophage infiltration is positively correlated with lesion progression, plaque size and intimal thickness (39). Hence, HDL particles penetrate the plaque due to their small size and target macrophages. Based on this, HDL seems to be excellently suited for the recognition of atherosclerotic plaques. Regarding antioxidant and anti-inflammatory properties, HDL particles may also mediate disease-stabilizing effects. In a very recent paper Duivenvoorden et al. have developed statin-loaded rHDL NPs, which were identified as potent modulators of plaque inflammation. The statin-loaded rHDLs accumulated in atherosclerotic plaques where they were taken up by macrophages. For a long-term, low dose treatment with statin-loaded rHDLs, an inhibition of plaque inflammation progression was achieved, while a short-term, high dose treatment was able to markedly decrease inflammation in advanced atherosclerotic plaques (40).

**Synthetic HDL**

Over the last decade, the method for lipoprotein inspired imaging of AS by producing fully synthetic HDL-particles containing a spherical nanocrystalline core was established (41, 42). In synthetic HDLs the inner lipophilic core is surrounded by a monolayer of phospholipids with apo-AI molecules associated to the surface. The nanocrystalline core can be composed of either Gold-nanoparticles for computed tomography (CT) imaging, quantum dots (QD) for optical imaging (41) or ironoxide-nanoparticles for magnet resonance imaging (MRI) (42). Additionally, fluorescent dyes or phospholipid anchored Gadolinium
(Gd)-chelates can be incorporated into the outer phospholipid monolayer of synthetic HDLs to construct a multimodal signal-emitting particle for molecular imaging. The synthetic HDL particles are spherical and highly homogeneous, having a diameter and lipid to protein content similar to natural HDL. In vivo experiments in the atherosclerotic apoe deficient mouse model revealed an accumulation of nanocrystalline HDL particles in the vessel wall and macrophages of atherosclerotic lesions (41).

In summary, artificial HDL assemblies may represent a flexible nanoplatform with future potential for molecular diagnostics and therapeutics, concurrently possessing intrinsic antiatherosclerotic and anti-inflammatory activities. Nevertheless, there are also substantial obstacles. HDL is strongly internalized into cells of the liver. If labeled with Gd the recirculation of GdHDL particles will make nuclear imaging impossible due to the ever present background signal relative to the half-life of the isotope. Additionally, studies using GDTPA-lipids show that the Gd label is liable and can transfer to other lipoproteins in the vascular phase (43). This fact limits clinical translation of the rHDL platform for MR diagnostic imaging. The use of iron oxides may be an alternative but changes in the charge and size of the synthetic HDL following incorporation of iron may again cause significant problems.

**Interleukin-10 – the anti-inflammatory “master” cytokine**

A broad spectrum of proinflammatory cytokines has been reported to be involved and to stimulate the progression of AS (11, 44–52), whereas, more recently, few were found to potentially aid in AS regression (53–55). Not the least, this may be caused by the fact that the investigation of the role of regulatory T cells (Tregs) dominated the discussion how to achieve a sufficient atheroprotective immune response (53, 56). Apart from this, Pinderski Oslund et al. found that activated T-lymphocytes overexpress the anti-inflammatory cytokine interleukin-10 (IL-10), and that this event is capable of blocking AS actions in vitro and in vivo (57, 58). Xie et al. showed in a cross-sectional study that decreased serum IL-10 concentrations were significantly associated with an increased likelihood of ischemic stroke (59). Further, IL-10 expression was found elevated in advanced and unstable AS-plaques (60), and it appears to contribute to the regulation of the local inflammatory response, and is involved in the control of cell death within plaques (60–63). This is underlined by the recent observation where IL-10 mediated the immunoregulatory response in conjugated linoleic acid-induced regression of AS (64). One of the most important facet of this immunological “brake” is represented by inhibition of pro-inflammatory cytokines and mediators from macrophages and dendritic cells (65–67). Hence, IL-10 is believed to be the most prominent anti-inflammatory cytokine. Albeit, this cytokine is neglected in the recent AS research.

Many cells produce IL-10. Major sources are T-helper cells (68) like CD8 positive T-cells (69), monocytes, macrophages (65), subsets of dendritic cells (66), human B lymphocytes (70) and mast cells (71). The spectrum of non-immune cells comprises keratinocytes, epithelial cells, and tumor cells (72, 73). IL-10 signals mainly through a two-receptor complex: IL-10 receptor 1 (IL-10R1) and IL-10 receptor 2 (IL-10R2) (74). Nevertheless, the IL-10-binding receptor complex is one of only a few regulating factors known so far.

As summarized, many characteristics suggest IL-10 as an interesting biomarker for AS. Hence, we investigated the potency of IL-10 as targeting molecule for molecular imaging of AS plaques. This was based on the assumption that where inflammatory fire is strongly present (in vulnerable AS lesions) there is increased need for “fire water” – i.e., an upregulated anti-inflammatory cascade most likely mediated by the anti-inflammatory “master” cytokine IL-10. Indeed, we could show that recombinant IL-10 preferentially accumulates in AS-plaque areas. Nanoconstructs of IL-10 and PEGylated liposomes (Figure 1) increased IL-10’s stability in vivo and the specificity of target recognition (12). Notably, no significant immune reactions were observed so far when the nanoconstruct was injected into wild type mice (12). To conclude, IL-10 combined with multifunctionalized liposomes is a promising candidate for multi-modal AS-plaque imaging (12). Further investigations are needed to clarify if this holds also true in the human system. Potential drawbacks may be given by the fact that IL-10, as an abundant molecule, may reduce the sensitivity of the imaging modality. This should be clarified in future investigations.

**Adiponectin – an anti-inflammatory molecule of unconventional origin**

It is well established now that adipose tissue is a highly active endocrine organ, also centrally involved in the regulation of inflammation (75–77). The most important anti-inflammatory adipokine is adiponectin (78), predominantly
synthesized by adipocytes (79). The basic structure of the full-length form of adiponectin (fAd) is a 247 amino acid protein with four domains (80). In the bloodstream, adiponectin circulates at concentrations of 2–30 μg/mL (81) and in different molecular weight forms; high molecular weight (oligomer); medium molecular weight (hexamer); and low molecular weight (trimer) adiponectin (82, 83). These subfractions exert different biological functions (82–84). Adiponectin is thought to protect against diabetes and AS (11, 82, 83, 85–88). Li et al. showed that local treatment with adiponectin reduces atherosclerotic plaque size in rabbits by decreasing the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) in the vascular walls (89). Recently, Waki et al. showed that leukocyte elastase secreted from activated monocytes and/or neutrophils can cleave fAd (95). This cleavage might be the reason for the generation of the 17 kDa globular fragment of adiponectin (gAd), which is found at lower levels (about 1% of total adiponectin) in the circulation (96). Globular Adiponectin was shown to increase insulin-stimulated glucose uptake and to boost β-oxidation of fatty acids (97, 98), while other functions remain controversial (99, 100). Apart from the anti-atherosclerotic and anti-diabetic properties, adiponectin has potent anti-inflammatory effects (101). The latter are associated with the ability to stimulate the production of nitric oxide (NO) (102) which protects endothelial cells (103, 104). Endothelial damage plays a crucial role in the formation of AS leading to adhesion and penetration of monocytes followed by macrophage-to-foam cell transformation (105). Adya et al. found that gAd decreased glucose and C-reactive protein-induced angiogenesis with a concomitant reduction in matrixmetalloproteinase-2 (MMP-2), MMP-9, and vascular endothelial growth factor in human microvascular endothelial cells (106). Thus, gAd may support the regeneration of AS damaged vascular tissue. Two main receptors are known to bind adiponectin, namely adipoR1 and adipoR2 (107). AdipoR1 is expressed mainly on vascular smooth muscle cells and endothelial cells, predominantly binding gAd. AdipoR2 binds both gAd and fAd and is highly expressed on hepatocytes, and in smaller amounts in the hypothalamus and on brain endothelial cells (108). Further, fAd was shown to bind to T-cadherin (109) and to the multifunctional protein, calreticulin (110). With respect to AS, adiponectin has been shown to accumulate in the subendothelial space of vascular walls after injury of the endothelial barrier where it binds to different types of collagen of the vascular intima (111). In contrast, adiponectin was not detected in the subendothelial space of human atherosclerotic lesions covered by an intact endothelium (112).

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We investigated i) the role of adiponectin and subfractions in obesity associated preatherosclerosis of humans (82, 83, 87, 88, 113), and ii) the potential of fluorescence-labeled gAd and fAd subfractions (fAd-SFs) to bind to atherosclerotic lesions in apoE-deficient mice (9–11). By the animal studies, we found a low binding efficiency of fAd but a, probable inflammation-mediated, strong accumulation of gAd in the fibrous cap of atherosclerotic plaques (9, 10). Thus, gAd may be an appropriate targeting sequence for the molecular imaging of AS lesions (9). We developed also nanoconstructs between gAd and PEGylated stealth liposomes (10) (Figure 1). By means of the NPs, a higher payload of signal emitting molecules could be transported.
to the atherosclerotic plaques (10). Moreover, we investigated constructs between gAd and protamine-oligonucleotide NPs, called proticles. Proticles are biodegradable NPs, which have been previously developed for the delivery of various active compounds like antisense oligonucleotides or small peptides (114–117). They show a certain affinity to monocytes and macrophages which may be of additional interest for sequential AS plaque targeting. Limitations may be given by clinical unfavorable effects of gAd alone or in combination with NPs. The fact that Ad is an abundant molecule of the physiologic scenario argues against this. Nevertheless, this physiologic abundance can also reduce the sensitivity of the imaging modality. Further investigations are underway by our group to clarify this.

Taken together, our results indicate an interesting potential of gAd-targeted NPs for the imaging of atherosclerotic vascular lesions. Combinations of targeted NPs may be useful for the discrimination between stable and vulnerable plaques (10).

Conclusion

In the foregoing we have summarized evidence that anti-inflammatory mediators constitute a new innovative scope of application for diagnosis and therapeutic modification of atherosclerotic lesions. Early diagnosis and identification of individuals at risk by molecular imaging well before fatal clinical endpoints occur is warranted for an improved personalized medicine of AS. Interestingly, to the best of our knowledge, only few anti-inflammatory biomarkers have been investigated in the context of nanomedicine and AS. This is astonishing because anti-inflammatory activation is always present as a negative feedback mechanism, if inflammatory perpetuation of AS lesions towards clinical endpoints occurs. Thus, this inflammatory “brake” may probably more specifically target the scenario of vulnerable, culprit AS-lesions than the more unspecific systemic and local inflammation. Novel molecules with the ability to balance the inflammatory force, and safe as well as specific delivery are warranted. The implementation of multi-functional probes (theranostic particles for concomitant imaging and therapy) combined with the advantages of differential imaging (e.g., high spatial resolution, soft tissue contrast MRI, high sensitivity PET) will improve the diagnostic performance. The immune-modulating, anti-inflammatory characteristics of adiponectin and IL-10 are useful in this context, and will be further investigated by our group for their usability in humans.

Thus far, there is no robust blood test ready for clinical use to identify patients with active perpetuation of AS towards vulnerability.

In addition to the Framingham risk score, a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual, we must find distinct cardiovascular phenotypes and biomarker signatures that complement the clinical decision-making for an early preventive treatment of AS. It must be noted that relevant studies so far largely dealt with single adipokines, cytokines, chemokines and their receptors measured in limited numbers of patients. Proteomics for improved diagnostics can extend the portfolio of techniques and introduce new avenues. For example, potentially “druggable” microRNAs are of high interest (118, 119). Further, the relationships between oxidation-specific epitopes (OSE), apolipoprotein-A (apoA), progredient AS, and plaque vulnerability may be promising (120). Human atherosclerotic lesions showed a differential expression of OSEs and apoA as they progress, rupture, and become clinically symptomatic. These findings may provide a rationale for targeting OSE for biotheranostic applications in humans (120).

Taken together, the recognition of individual inflammatory/metabolic signatures by approaches of personalized medicine may give important and new insights towards early diagnosis and monitoring of AS, and may finally provide the basis of new therapeutic strategies. Anti-inflammatory feedback cascades will be an interesting part for completion of this mission.

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References


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