Making Things Stick in the Fight Against Atherosclerosis

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Commentaries on Cutting Edge Science

Prevention of atherosclerotic vascular disease through systemic risk factor management has had great success, but cardiovascular disease is still the leading cause of death. One approach to this treatment gap is complementary arterial wall–based therapy that inhibits either the trigger of atherosclerosis, lipoprotein retention, or its pathobiological consequences, nonresolving inflammation. A recent article by Kastrup et al describes a technical advance that brings this approach closer to reality. The investigators have developed and validated a drug-eluting adhesive biogel that has the durability and stability to provide chronic therapy directly to plaques in the setting of pulsatile arterial blood flow. This advance expands the opportunity to develop drugs that retard atherosclerotic plaque progression and promote plaque resolution and regression.

Currently available therapeutic strategies directed against atherosclerotic vascular disease focus primarily on reducing systemic risk factors, notably hyperlipidemia, diabetes mellitus, smoking, and hypertension. Lipid therapy, particularly with statins, is very effective, because it lowers the probability that apolipoprotein B100–containing lipoproteins (apoB LPs) will enter and be retained in susceptible regions of the arterial wall, which is the trigger for the pathobiological responses that initiate and promote atherogenesis. Indeed, if we could imagine a world where everyone’s plasma apoB LP level was maintained at a very low level starting in the early teenage years, which is the age at which atherosclerotic lesions usually first appear, the current leading cause of death would be close to nonexistent. However, although tremendous progress has been made in reducing heart disease, this ultimate goal is currently unachievable due to the difficulty of implementing effective lifestyle changes and limitations related to drug safety and compliance.

Therefore, translational biomedical researchers have turned their attention to complementary approaches that target atherogenic processes in the arterial wall. It is in this context that we can appreciate a technical advance recently reported by Kastrup et al., which describes a new method for applying drugs directly to clinically dangerous atherosclerotic lesions using an adhesive drug depot. However, before describing this report in more detail, it will be helpful to discuss the overall landscape of arterial wall–based therapy for atherosclerosis. For the reasons mentioned above, the most effective and disease-specific arterial wall approach would be to directly block processes involved in subendothelial apoB LP retention (eg, by using therapies that inhibit the interaction of apoB with subendothelial proteoglycans). Although innovative work is being done in this area, most effort has focused on trying to inhibit the primary pathobiological response to retained LPs, namely, maladaptive, nonresolving inflammation. This approach presents a fundamental challenge, however, because the inflammatory response defends us against pathological organisms and, through the process of inflammation resolution, promotes the return to tissue homeostasis. Thus, systemic anti-inflammatory therapy runs the risk of increasing susceptibility to infection and delaying tissue repair. In the case of systemic inflammatory diseases that affect multiple sites, such as systemic lupus erythematosus, the benefit/risk ratio of systemic anti-inflammatory therapy is usually high enough to rationalize its use. However, atherosclerotic lesions occur in a very small portion of the body. Indeed, because the majority of atherosclerotic lesions do not cause acute cardiovascular disease, the actual target area for therapeutic strategies designed to work on clinically significant atherosclerotic lesions is miniscule. Moreover, although systemic anti-inflammatory therapy would likely be most effective when started in the early stages of atherosclerosis, the time lag from early lesion formation to cardiovascular disease can be decades. Thus, the risks of systemic anti-inflammatory therapy for atherosclerosis may be too high, except perhaps for relatively short-term use in very high-risk individuals.

In this context, investigators have begun to conceive of strategies for lesion-targeted therapy. In one set of approaches, anti-inflammatory drugs can be incorporated into intravenously administered particles that have a predisposition to enter and perhaps be retained in atherosclerotic lesions. For example, recent work has tested the use of liposomal particles embedded with glucocorticoids in a mouse model of atherosclerosis. Drugs can also be incorporated into specially designed nanoparticles that enter areas of increased endothelial permeability, a feature of atherosclerotic lesions, and then be retained by chemical moieties that bind subendothelial matrix.

The potential advantage of this type of approach is that it is noninvasive and, by virtue of a relative increase in lesional versus systemic exposure, can lower the dose of drug compared with nontargeted strategies. However, systemic
exposure can still be substantial, and the strategy does not necessarily favor targeting of the minority of the most dangerous lesions. To enhance lesion-specific targeting, drugs can be applied directly to dangerous plaques during vascular catheterization. Indeed, this type of approach has been in practice for years in the form of drug-eluting stents, but the drugs in this case are used to inhibit smooth muscle proliferation as a means to prevent injury-induced stenosis, not to inhibit atherosclerosis. Investigators have also tried coating blood vessels with various types of biogels, but this approach has not been suitable for atherosclerosis, because the gels are too short-lived in the setting of arterial blood flow.\textsuperscript{14,15}

In this context, Kastrup et al\textsuperscript{8} describe the synthesis, validation, and preclinical testing of a type of drug-embedded biogel that is very durable, flow-resistant, and long-lasting. The gel is based on highly adhesive substances secreted by marine mussels and was initially validated using endothelial cell monolayers and endothelium-denuded carotid artery specimens in flow chambers under conditions that far exceeded in vivo arterial forces. For example, the gel retained its adherence to the denuded arteries even when subjected to shear stresses that were several orders of magnitude higher than physiological shear stress. The investigators then showed that the gel could be applied to arteries in vivo through a surgical incision in the carotid artery and abdominal aorta of mice. The gel could be applied up to lengths of several millimeters and lasted as long as 4 months after application, and the mice suffered no major adverse events, including those related to thrombosis or embolism. There was a low-level inflammatory response at the site of application, but this was resolved by the growth of new endothelialized fibrous cap. Most importantly, the concept was tested in vivo by using dexamethasone-loaded biogel applied directly to carotid plaques of fat-fed Apoe\textsuperscript{−/−} mice through arterial incision. Thirty days after gel application, the treated lesions were less inflammatory, as assessed by lower macrophage area and decreased plaque expression of VCAM-1 and decreased lesional mRNAs for Nfkbi and Mmp9. The treated lesions also had a thicker fibrous cap, which in humans is an indicator of plaque stabilization. Serum inflammatory markers of inflammation, for example tumor necrosis factor \textalpha, were also lower in the treated mice, which may have been a result of release of some of the dexamethasone into the systemic circulation. In that regard, assessment of dexamethasone exposure in other organs, such as lung, liver, and spleen, would have been informative, but one can confidently assume that the ratio of plaque:systemic exposure was very high using this technique.

The technical advance in this study will now enable the testing of various types of plaque-directed drugs in preclinical models of atherosclerosis. Immediate application to humans will be limited by several factors, including the inherent invasive nature of this approach, the challenges of identifying the types of vulnerable plaques that are the intended targets of the therapy, the choice of effective drugs, and the methods to assess efficacy. To the extent that patients with acute coronary syndromes undergo stenting of culprit lesions, drug-embedded biogel could be applied during catheterization. Indeed, culprit lesions themselves are at relatively high risk to cause recurrent disease,\textsuperscript{16} and so adhesive biogels containing drug combinations that block both injury-induced stenosis and then atherosclerosis progression could be embedded in the stents. Moreover, a recent study in humans characterized nonculprit lesions by intravascular ultrasound at the time of initial stenting to determine which plaque properties best correlated with future clinical events.\textsuperscript{16} The investigators found that high-volume plaques with thin fibrous caps and necrotic cores were the most likely to progress. Thus, this approach, as well as other imaging methods currently being developed,\textsuperscript{17} could be used to identify lesions for preventative adhesive biogel drug treatment.

In addition to these issues, the choice of drug to prevent lesion progression is far from obvious. The inflammatory cascade is highly complex, and the features of redundancy and compensation present major challenges for therapy.\textsuperscript{8} Moreover, as mentioned previously, blocking inflammation runs the risk of inhibiting inflammation resolution and thereby delaying or preventing tissue repair. In this regard, the findings of Kastrup et al showing that dexamethasone increased plaque fibrosis are encouraging, although its relevance to human plaques remains unknown. Perhaps a more promising approach is to take advantage of the nature’s own molecules for resolving inflammation. Evidence suggests that these molecules, if applied therapeutically, would not compromise host defense and would have the additional benefit of promoting tissue repair and the return to homeostasis.\textsuperscript{8} Indeed, some of these mediators of inflammation resolution, particularly small lipid mediators derived from omega-3 fatty acids such as resolvins, are in clinical trials for other inflammatory diseases (http://www.resolvyx.com/).\textsuperscript{18} Finally, the challenge of showing efficacy is substantial. Although clinical end point trials would be necessary before approval, such trials are time-consuming and expensive, and so intermediate markers of efficacy are critical. Ongoing noninvasive imaging efforts that attempt to monitor plaque inflammation, such as 18F-fluorodeoxyglucose positron emission tomography,\textsuperscript{19} may provide the means to achieve this goal.

In summary, arterial wall–based therapy for atherosclerosis may provide a strategy to fill the current treatment gap associated with systemic risk factor management, but the challenges are substantial. The ability to directly apply useful drugs to clinically dangerous plaques offers promise in terms of specificity and avoidance of systemic side effects. One important technical challenge, namely, that attributable to achieving stability and durability in the setting of pulsatile arterial flow, has now been addressed. The remaining challenges associated with choice of drug and assessment of efficacy will benefit from ongoing efforts to understand the molecular and cellular mechanisms of atherosclerosis progression and regression, particularly in the areas of inflammation and its resolution.

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References


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