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Expanding the Therapeutic Frontier in Atherosclerosis

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Cardiovascular disease (CVD), more specifically atherosclerosis, is the leading cause of death in the United States and other developing countries. Over the past three decades we have increased our knowledge of the pathological mechanisms and risk factors for atherosclerosis. Despite this, therapies designed to prevent or, more importantly, reverse the devastating outcomes of atherosclerosis remain limited. Through basic and clinical research we now know that atherosclerosis is a complex disease that involves both defects in lipid homeostasis as well as chronic inflammation. High circulating low density lipoprotein (LDL) coupled with decreased high density lipoprotein (HDL) have become the most common identifiable risk factors for the development of CVD.

It is clear that excess accumulation of LDL, often referred to as “bad cholesterol”, and oxidatively-modified LDL in the artery wall is one important trigger for the atherosclerotic process¹. This leads to migration of monocytes/macrophages to sites of LDL accumulation where they take up cholesterol and become foam cells that are unable to emigrate out of the artery wall. One mechanism that macrophages, and most cells, employ when faced with excess cholesterol stores is efflux to circulating acceptors such as lipid-poor HDL. HDL then serves to shuttle cholesterol back to the liver where it is removed from the circulation to maintain healthy cholesterol levels (reviewed in ^{2,3}), a process known as reverse cholesterol transport (RCT). When LDL and HDL levels are normal and RCT is functioning at capacity, there is balance in the system, with cells taking up enough cholesterol and other lipids to perform normal cellular functions without pathological effects. However, lack of exercise, poor diet and a myriad of other confounders (i.e. diabetes, obesity, high blood pressure, infection, chronic inflammation) can teeter the balance toward a pro-atherogenic state, leading to plaque development and rupture and often myocardial infarction and/or stroke.

Given that maintaining the balance between LDL and HDL is key to prevent the atherosclerosis, it seems logical that much of the pharmaceutical industry’s efforts and financial resources have been focused on the development of novel therapies that can lower LDL (bad cholesterol) and raise HDL (good cholesterol). To an extent, this approach has been effective. The development and wide use of statin therapy to decrease LDL levels and improve cardiovascular outcomes has been undoubtedly one of the greatest therapeutic advancements in CVD. Statins broadly work by inhibiting the rate-limiting enzyme in cholesterol synthesis, hydroxyl-methylglutaryl-coenzyme A (HMG-CoA) reductase. These drugs have proved largely successful in treating hyperlipidemia, reducing risk of heart attack and stroke and also providing some off-target benefits such as decreasing inflammation. Unfortunately, statins also carry a long list of unattractive side effects that many patients do not tolerate. In addition, there are certain individuals that do not seem to benefit from the protective attributes assigned to statin therapy. The reasons for this remain unknown but

genetic variation is a likely suspect and has given birth to a new outlook or approach to treatment of CVD based on pharmacogenetics and personalized medicine (reviewed in ^{4,5}). In addition, variation in cardiovascular outcomes in response to statins suggests that lowering LDL is not enough but perhaps needs to be paired with raising HDL.

In fact, the ability to raise HDL to therapeutic levels has become a bit of a “holy grail” in the search for effective CVD treatments. Basic research has shown that increasing HDL levels is one consistent method for plaque regression^{6–8}, an outcome that has remained elusive in patients. Several clinical trials have targeted key components in HDL metabolism in an attempt to raise HDL-cholesterol with less than satisfying results⁹. Therefore, it remains to be determined why efforts to raise HDL cholesterol have not worked and whether there are alternative approaches that may make this a viable strategy for treating atherosclerosis.

In this focused section on treating atherosclerosis in the *Journal of Cardiovascular Pharmacology*, Sorci-Thomas and Thomas address the conundrum of why strategies to raise HDL should work but have fallen short¹⁰. As the authors suggest, one potential issue with generally raising HDL is for patients with dysfunctional or pro-inflammatory HDL, as increasing levels of a lipoprotein that is ineffective or potentially pro-atherogenic would not be desirable. In addition, the authors propose the use of strategies that increase the circulating levels of lipid-poor apoA-I, the predominant protein component of HDL and one of the best cellular cholesterol acceptors, as potential future therapies for CVD. Offering additional alternatives to traditional LDL-lowering and HDL-raising strategies, Hennessy and Moore¹⁴ provide valuable insight into the advancement of microRNA and exploiting this technology for development of novel and innovative therapies ranging from familial hypercholesterolemia to “garden variety” atherosclerosis. Finally, Stojan and Petri¹⁸ discuss the problem of accelerated atherosclerosis in systemic lupus erythematosus (lupus) and highlight therapeutic strategies targeting these unique patients. Lupus subjects are unique and recent studies have demonstrated in both animal models and patients that statins, although providing the desired lipid-lowering effects, are not greatly cardio-protective^{15–17}. Therefore, for some patient populations, standard therapies, no matter how advanced or innovative, may not be enough and thinking outside the box will be required to effectively manage their CVD.

In closing, manipulating circulating cholesterol levels to treat atherosclerosis, although simple in theory, has proved to be a complex and often frustrating undertaking. Logical approaches, such as raising HDL, have been less than effective and often lowering LDL cholesterol is not enough. Only by understanding the complex mechanisms of atherosclerosis and how other diseases, such as autoimmunity, modulate this process will science begin to develop effective therapies. The frontier of treating atherosclerosis remains vast but recent discoveries continue to push back the boundaries and improve patient quality of life.

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