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The potential of apolipoprotein mimetic peptides in the treatment of atherosclerosis

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Medical landscape

There is a clear medical need for new approaches to treat cardiovascular disease. Especially useful would be treatments that are complementary to, but function through a different mechanism than, current low-density lipoprotein (LDL)-lowering agents. Despite the widespread use of statins to control LDL cholesterol levels and lessen the burden of cardiovascular disease, atherosclerosis remains a leading cause of death worldwide, and mortality from cardiovascular disease is expected to increase dramatically in developing countries over the coming decades. Fortunately, some help is on the way through new agents that are under clinical investigation, especially the widely recognized PCSK9 inhibitors, although these compounds function through the same basic LDL-lowering approach as currently prescribed drugs.

In this context, improving or augmenting the function of high-density lipoprotein (HDL) represents an attractive strategy for combating atherosclerosis. HDLs facilitate the process of reverse cholesterol transport (RCT) and exhibit other atheroprotective properties. The relation of HDL to atherosclerosis is extremely complex, and questions remain about how best to harness the potential of HDL for medical applications. Even so, HDLs appear to confer cardiovascular protection even among patients treated with statins who have achieved very low (<50 mg/dL) LDL cholesterol levels [1]. Importantly, HDL-mediated therapeutics would offer a mechanistically distinct approach from the LDL-lowering agents to combat cardiovascular disease.

Apolipoprotein mimetic peptides

Short synthetic peptides with sequences that mimic those found in natural apolipoproteins have been studied since the 1980's for their potential to generate HDL-like nanoparticles and

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improve the function of endogenous HDLs [2]. As their name implies, apolipoprotein mimetic peptides are designed to recapitulate the behavior of apolipoproteins, most often apolipoprotein A-I (apoA-I) or apolipoprotein E, in promoting the formation and functions of endogenous lipoproteins, especially HDLs. Among the reported properties of apolipoprotein mimetic peptides are lipid-associating ability, activation of enzymes involved in HDL maturation and remodeling, promotion of cholesterol efflux, binding of oxidized lipids, anti-inflammatory and anti-oxidant effects, and inhibition of atherosclerosis progression in a variety of animal models. To date, several small human clinical trials involving apolipoprotein mimetic peptides have been reported [2].

Among the most important recent developments in the field of apolipoprotein mimetic peptides are:

- Some apolipoprotein mimetic peptides have been shown to target the intestine as the site of action, rather than acting generally by their presence in the plasma [3]. This surprising finding could explain why the apoA-I mimetic peptide **D4F** exerted some positive effects when administered orally to humans, whereas **L4F** was essentially inactive when administered intravenously or subcutaneously [4,5]. Building on the hypothesis that the intestine is the key site of action, tomatoes were genetically engineered to express an apolipoprotein mimetic peptide, and those tomatoes were fed to mice, resulted in impressive reductions in atherosclerotic lesions and related biomarkers [6]. Additional work is needed to identify the specific molecular targets and mechanisms of action in the intestine.
- The therapeutic scope of apolipoprotein mimetic peptides has been greatly expanded in recent years to include numerous afflictions besides atherosclerosis. The disease models in which apolipoprotein mimetic peptides have shown benefit include cancer, colitis, asthma, sickle cell disease, insulin resistance, endotoxemia, and cognitive function and Alzheimer's disease [7,8]. Although it is unknown at present if a single mechanism of action accounts for the efficacy in these various diseases, the anti-inflammatory properties of the peptides could certainly contribute to their effectiveness in some of these models [8,9].
- The field has recently begun to explore more vigorously anti-atherogenic mechanisms that are potentially independent of the RCT pathway. Historically, the characterization of apolipoprotein mimetics understandably focused on RCT-centric mechanisms, such as the capacity of the peptide to promote cholesterol efflux and increase the level of lipid-free or pre-β HDL in the plasma through HDL remodeling. More recently, however, other functions have been studied that are not necessarily linked to RCT, and in certain cases may even be independent of HDL. These functions include selective binding of oxidized lipids [10], modulation of the expression of certain enzymes and cytokines [11,12], and reduction of the levels of certain oxidized metabolites [13,14], much of which are associated with anti-inflammatory effects. Spurred by an increasing catalog of diseases for which the peptides exert benefits, and the possibility that apolipoprotein mimetics act in compartments other than the plasma, it seems likely that other RCT-independent functions of these peptides will be identified in the future.

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Current challenges and future potential

A critical bottleneck in the future clinical development of apolipoprotein mimetic peptides is the lack of an efficient, reliable method for selecting the best candidates from a development program. A wide range of peptide sequences has shown efficacy as apolipoprotein mimetics [2], including those with no direct sequence homology to natural apolipoproteins, peptides composed of unnatural D-amino acids, and even constructs having exotic branched peptide architectures [15–17]; the potential sequence space is therefore very large. Moreover, although there are numerous assays commonly used to characterize apolipoprotein mimetics, none of these assays has been proven to reliably predict in vivo efficacy against the development of atherosclerosis. With so many different peptide sequences exhibiting various degrees of activity in different aspects of vascular biology, it is currently not possible to select lead sequences for further development with confidence. In vivo atherosclerosis studies require multiple weeks of duration and relatively large group sizes, so the development of a process to efficiently identify peptide candidates that will be efficacious in vivo is of paramount importance.

The most obvious path for developing improved apolipoprotein mimetic peptides is through a more detailed understanding of their molecular mechanism of action. One unexplored area with great potential to shed light on mechanism is how the peptides affect the complex proteome/metabolome of HDL particles. Also, to identify which properties are most important for anti-atherogenic acitivity, one possibility would be to design and comparatively test a series of peptides that are each functional in only one mechanistic aspect of interest (i.e., active in promoting RCT but have no anti-inflammatory properties, etc.). Such efforts would allow the subsequent design of functionally targeted peptides and would facilitate the development of an improved peptide screening/selection process. Of course, it is possible that multiple mechanisms of action combine to give rise to the observed efficacy. Without a deeper mechanistic understanding of these peptides, their design and selection will continue to involve a process of trial and error.

Despite the unresolved issues that must be overcome to realize the full potential of apolipoprotein mimetic peptides, there are great prospects for these peptides in the treatment of atherosclerosis. Basically, a huge untapped sequence space for the design of improved compounds exists. For instance, there are almost no examples of mimetic peptides incorporating non-proteinogenic amino acids, which could confer a variety of beneficial functions. Peptides are in general easy to synthesize and combinatorialize, so the potential exists for large libraries to be generated and screened for improved compounds. Going beyond the basic α-helical structure that characterizes most apolipoprotein mimetic peptides, there is even greater potential to design molecules with improved functionality. Indeed, a few studies have explored dual-domain peptides created by combining an apolipoprotein mimetic peptide with another motif chosen to confer a particular function to the molecule. [18–20].

Given the huge burden of cardiovascular disease, and the abundance of positive results for apolipoprotein mimetic peptides in atherosclerosis and other disease models, vigorous

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further development of these compounds is warranted. Such studies may well lead to clinical benefits for patients.

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