High Density Lipoprotein Structure, Function and Metabolism: A New Thematic Series

Kerry-Anne Rye

Lipid Research Group, Centre for Vascular Research, Lowy Building,
University of New South Wales, Sydney, NSW, Australia, 2052

Corresponding author: Kerry-Anne Rye, Lipid Research Group, Centre for Vascular Research, Level 3, Lowy Building, University of New South Wales, Sydney, NSW, Australia 2052

Tel: +61 2 9385 1219; Fax: +61 2 9385 1797

e-mail: k.rye@unsw.edu.au or karye@ozemail.com.au
High density lipoproteins (HDL) were first identified in the late 1940’s and early 1950’s as the smallest and densest of all the lipoprotein classes (1). For many years, however, most of the attention of researchers in the lipoprotein field focused on the relationship between plasma low density lipoprotein cholesterol levels and the development of cardiovascular disease, with little consideration being given to HDL, which were regarded as innocent bystanders in the world of cardiovascular disease.

This point of view changed in 1975, with a publication that described an inverse relationship between HDL cholesterol levels and the development of ischemic heart disease (2). The authors of this report further hypothesized that strategies that increase HDL levels could potentially decrease the incidence of cardiovascular disease (2). Over the following four decades the association of high HDL cholesterol levels with a reduced incidence of cardiovascular disease was confirmed in multiple human population studies (3, 4). These findings were also reinforced in preclinical studies which showed that increasing HDL levels in mice by transgenic overexpression of human apolipoprotein A-I, the main HDL apolipoprotein, inhibited atherosclerotic lesion development (5) and that intravenous infusions of HDL into rabbits promoted lesion regression (6).

The positive outcomes of these studies supported the view that pharmacological interventions that increase HDL levels could potentially reduce the morbidity and mortality associated with cardiovascular disease in humans. They also provided an incentive for the development of a range of therapeutic agents designed specifically to increase HDL levels. Several approaches were employed in order to achieve this goal, including inhibition of the activity of cholesteryl ester transfer protein (CETP), infusion of reconstituted HDL preparations consisting of apoA-I complexed with phospholipids, and infusion of a small molecule agent that increases apoA-I synthesis. The CETP inhibitors, torcetrapib and dalcetrapib, were the first agents designed specifically to increase HDL levels to be
investigated in large scale, clinical cardiovascular outcome trials. Although both inhibitors increased HDL cholesterol and apoA-I levels as expected, the outcomes of these studies were disappointing. Neither torcetrapib nor dalcetrapib reduced cardiovascular events, and torcetrapib caused harm, possibly because of off-target effects (7, 8). Despite these setbacks, large-scale clinical outcome trials of two other CETP inhibitors are currently underway, and smaller studies of reconstituted HDL infusions and the small molecule activator of apoA-I synthesis are planned.

The reason why increasing HDL levels as a strategy for reducing cardiovascular events continues to be an option to a large extent reflects the strength of the aforementioned human population and preclinical animal studies. The disconnect that has emerged between the positive outcomes of these studies and the negative results of the CETP inhibitor clinical outcome trials serves to highlight the fact that there is still much that remains unknown about HDL structure, function and metabolism. The articles in this Thematic Review Series, which will be published over the next six issues of the Journal of Lipid Research, focus on what is currently understood, and what we still do not know, about these topics.

The first title in the series is by Michael Philips from the Children’s Hospital of Philadelphia Research Institute, who describes recent advances in understanding of HDL structure. This contribution summarizes what is known about the organization of apoA-I on the HDL surface and describes recently identified structural features of apoA-I that regulate its lipid binding capacity. The importance apoA-I flexibility in HDL biogenesis and the regulation of the subpopulation distribution of HDL in plasma is also discussed. The final section of this paper emphasizes the fact that apoA-I is a highly flexible molecule, and that this property is a key determinant of its capacity to be accommodated on the surface of HDL particles that vary widely in size.

The second contribution is from Sean Davidson and colleagues at the University of
Cincinnati, who further explore the theme of HDL-associated proteins. This manuscript is based on the recently reported observation that HDL transport a multitude of proteins that have the potential to impact function and metabolism (9). The authors describe recent developments in proteomics that have advanced understanding of how at least some of these proteins affect HDL function. The authors also point out that the protein cargo of HDL has the capacity to participate in protein-protein interactions that may further impact HDL functionality. When considered together, these findings raise an important question as to how various pathophysiological conditions affect the HDL proteome and the downstream functional consequences of these changes. These recent developments in the area of HDL proteomics further highlight the fact that an informed assessment of HDL function in terms of assessing cardiovascular risk has the potential to be more informative than a simple determination of HDL-cholesterol levels.

The focus of the next article in the series is the HDL lipidome, as discussed by Anatol Kontush, and colleagues from the INSERM Dyslipidemia, Inflammation and Atherosclerosis Research Unit in Paris. These authors systematically document what is currently understood about the HDL lipidome, with a specific focus on bioactive lipids. They go on to describe HDL lipids that are of structural importance, how the HDL lipidome is affected in a range of disease states, and what is known about the impact of HDL lipid composition on several of the known cardioprotective functions of HDL. The value of using lipidomics to identify HDL subpopulations that may be clinically relevant is also discussed. The final section of the review suggests that one of the main goals of future developments in the area of HDL lipidomic analyses should be the identification of biomarkers of HDL function.

The remaining articles in the series have a more physiological emphasis, starting with the contribution of Meliana Riwanto and Ulf Landmesser from the University of Zurich, who discuss what is known about the regulation of endothelial function by HDL. This review
highlights the fact that the beneficial effects of HDL on endothelial function are markedly attenuated in people with cardiovascular disease, and that this can be attributed to decreased activation of endothelial NO synthase, inhibition of endothelial inflammation and the prevention of endothelial cell apoptosis. They further summarize several studies that document the ability of HDL to promote endothelial repair and inhibit thrombosis, and point out that the beneficial effects of HDL on endothelial repair are impaired in people with cardiovascular disease and diabetes. These authors also highlight the fact that HDL from people with diabetes appear to have reduced anti-thrombotic functions.

The next review by Kasey Vickers (Vanderbilt University) and Alan Remaley (National Institutes of Health) focuses on some of the lesser known bioactive molecules associated with HDL, including fat-soluble vitamins, steroids, hormones, bile acids, and carotenoids. These molecules are transported by HDL and delivered to cells where they have multiple beneficial effects, including the improvement of endothelial function, the inhibition of apoptosis, and the inhibition of inflammation. The final section of this contribution focuses on the recently identified role of HDL as a carrier of microRNAs, the emerging evidence that HDL transfer microRNAs to a range of cell types where they subsequently regulate gene expression, and that the microRNA cargo of HDL is altered in people with cardiovascular disease.

The following contribution by Chieko Mineo and Philip Shaul from University of Texas, Southwestern Medical Centre, describes the role of HDL in the induction of signal transduction pathways in various cell types. This is an area that has not been investigated extensively, and is of particular interest as it has the potential to identify a role for HDL beyond cardiovascular disease. The review by Mineo and Shaul describes how the activation of endothelial cell eNOS by HDL initiates anti-apoptotic and anti-inflammatory signaling pathways and enhances endothelial cell and vascular smooth muscle cell migration. The
authors then describe what is known about the signaling pathways whereby HDL prevent leucocyte and platelet activation, enhance glucose uptake in skeletal muscle and adipocytes and improve insulin secretion from pancreatic beta cells. The final section of this review documents the role of HDL in a recently identified cholesterol sensing mechanism that regulates the efflux of cholesterol from multiple cell types.

The final article in the series by Philip Barter and Kerry-Anne Rye from the University of New South Wales in Sydney focuses on HDL function, as well as the properties of HDL that are thought to be instrumental in terms of cardioprotection. The authors summarize what is currently known about the cardioprotective functions of HDL: their ability to affect the export of cholesterol from macrophages, as well as their anti-inflammatory, antioxidant and anti-thrombotic effects. They then describe other, more recently identified and novel functions of HDL, such as their capacity to enhance endothelial repair, improve endothelial function, suppress leukocyte production in bone marrow and confer benefit in diabetes. They also summarize what is currently known about the contribution of specific HDL subpopulations and constituents to these functions, an effort that serves to highlight where there are large gaps in knowledge in this area.

In summary, this review series emphasizes the fact that strategies that target HDL should continue to be considered as a means of reducing cardiovascular risk and decreasing the morbidity and mortality associated with cardiovascular disease. When considered together, these review articles also serve as a timely reminder that, while knowledge of HDL biology has progressed significantly in recent years, there is likely still much to be learned before this information can be translated into effective therapeutic interventions.
REFERENCES


