The HDL Handbook

Biological Functions and Clinical Implications

Tsugikazu Komoda

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Preface

When I started to write this book "The HDL Handbook: Biological Functions and Clinical Applications", Professor Takashi Miida of Juntendo University in Tokyo strongly supported my plan. Of course, he is also an excellent contributor to this book. In addition, Professor David Alpers, Professor Emeritus of Washington University, School of Medicine, well revised the present HDL book. Therefore, I want to thank him for his revision of this book. Unfortunately, since planning to publish this HDL book, two and half years have passed. Some contributors immediately accepted my planning, however, half of the contributors have not been able to complete the publication of "The HDL Handbook: Biological Functions and Clinical Applications".

However, the contents of this HDL book include up-to-date progress on HDL research. The contents of this book are a crystallization of the work from all the contributors, because, despite being busy, all the contributors carefully revised their chapters under the suitable comments from eight reviewers. Therefore, if you read this book, you will be fascinated by the renewal of development of HDL researches and the present book is a very useful tool not only for basic researchers in institutes or pharmaceutical companies but also practical physicians. In addition, this book will be evaluated as an HDL Bible for medical and co-medical graduate students by their counselors.

Furthermore, since this book is small, it is portable. However, the contents of this HDL book contain the latest news of HDL molecules.

Finally, I believe that this book should be read to give an excellent impression of the HDL fields.

Tsugikazu Komoda, MD

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Chapter 1

Role of Phospholipid Transfer Protein in HDL Remodeling and Atherosclerosis

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INTRODUCTION

Phospholipid transfer protein (PLTP) plays an important role in the regulation of high density lipoprotein (HDL) metabolism. The regulatory role of PLTP is achieved via its two main functions, phospholipid transfer activity (Tall et al., 1983; Rao et al., 1997) and the ability to modulate HDL size and composition in a process called HDL remodeling (Rye and Barter, 1986; Tu et al., 1993; Jauhiainen et al., 1993). The regulation of HDL metabolism is achieved by the concerted action of a number of plasma and cellular factors. These include the cellular receptors, scavenger receptor class B type 1 (SR-B1) and ATP-binding cassette transporter A1 (ABC-A1), as well as plasma proteins such as cholesteryl ester transfer protein (CETP), lecithin-cholesterol acyltransferase (LCAT), and the endothelial-bound enzymes, lipoprotein lipase (LPL) and triglyceride (TG) hydrolase hepatic lipase (HL). As indicated by the inverse relationship between HDL cholesterol and incidence of coronary heart disease in many epidemiological studies (Gordon and Rifkind, 1989), the plasma HDL level has a major impact on the progression of atherosclerosis. Although the exact mechanism behind the athero-protective role of HDL is still not fully understood, the reverse cholesterol transport (RCT) hypothesis has been widely accepted (Curtiss et al., 2006). Reverse cholesterol transport is the process by which cholesterol is transported from peripheral cells to the liver for elimination (Eisenberg, 1984). Preβ-HDL particles, a subpopulation of HDL, act as efficient acceptors in the efflux process of cholesterol at the plasma membrane of peripheral cells (Eisenberg, 1984). PLTP is able to generate preβ-HDL particles through HDL remodeling, and has a major role also in maintaining

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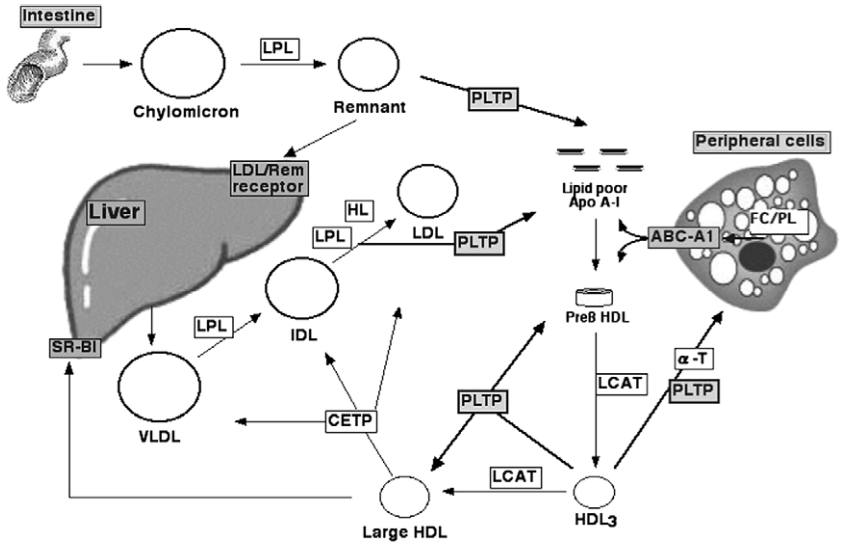

FIGURE 1.1 The physiological role of PLTP in HDL metabolism. Participation of PLTP is illustrated by bold arrows. The functions of PLTP are: (i) transfer of surface remnants (phospholipids and cholesterol) upon lipolysis of triglyceride-rich lipoproteins; (ii) generation of preβ-HDL during remodeling of HDL; and (iii) transfer of α-tocopherol from HDL particles to cell membranes. Abbreviations used: VLDL, very low density lipoprotein; LDL, low density lipoprotein; IDL, intermediate density lipoprotein; HDL, high density lipoprotein; Rem, remnant; PLTP, phospholipid transfer protein; CETP, cholesteryl ester transfer protein; LCAT, lecithin-cholesterol acyltransferase; HL, hepatic lipase; LPL, lipoprotein lipase; SR-BI, scavenger receptor class B type I; ABC-A1, ATP-binding cassette transporter A1; a-T, α-tocopherol.

plasma HDL levels owing to its ability to transport surface remnants produced by lipolysis of triglyceride-rich lipoproteins (Figure 1.1). Thus, PLTP can be envisioned to play an important role in the prevention of atherosclerosis (Castro and Fielding, 1988; von Eckardstein et al., 1996; van Haperen et al., 2000; Tall and Lalanne, 2003). In spite of these effects on HDL, studies in genetically modified mouse models have suggested that systemic PLTP deficiency is athero-protective *in vivo*, and that PLTP overexpression is pro-atherogenic. Recent studies have focused on this apparent inconsistency, and have examined the effects of local PLTP on atherogenesis, using transplanted macrophages.

MOLECULAR BIOLOGY AND STRUCTURE OF PHOSPHOLIPID TRANSFER PROTEIN

The PLTP gene is located on chromosome 20 (20q12-q13.1), and has a length of 13.3 kilobases, including 15 introns. PLTP cDNA is 1750 bp in length, and encodes a 17 amino acid hydrophobic signal peptide and a 476 amino acid mature protein (Day et al., 1994). Most tissues show expression of PLTP

mRNA, but liver and adipose tissue are probably the major contributors to plasma PLTP (Dusserre et al., 2000). Although the predicted molecular weight mass of the mature protein is 55 kDa, plasma PLTP appears as an 80-kDa protein by sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE) under reducing and non-reducing conditions (Oka et al., 2000a). The discrepancy between the calculated molecular weight mass and the mass estimated by SDS-PAGE may be explained by the fact that PLTP has six potential *N*-glycosylation sites and numerous *O*-glycosylation sites (Day et al., 1994). As the protein additionally contains four cysteine residues, it also has the potential to form two intra-chain disulfide bonds. In contrast to apolipoproteins that are primarily hydrophilic, PLTP has a high content of hydrophobic residues scattered throughout, with over 40% of the amino acids being hydrophobic. Three other hydrophobic proteins of the lipid transfer/lipopolysaccharide binding protein family, namely lipopolysaccharide-binding protein (LBP), neutrophil bactericidal permeability-increasing protein (BPI), and CETP share structural homology with PLTP. However, these proteins also exhibit significant structural differences (Albers et al., 1996). For example, the carboxyl terminal portion of CETP is the most hydrophobic of these four proteins, and its main function is to bind and transfer neutral lipids (Tall et al., 1983; Albers et al., 1984). Although the carboxyl terminal portion of PLTP is somewhat hydrophobic, it does not have the functional capacity to transfer neutral lipids (Tollefson et al., 1988). Unlike PLTP, BPI has a very basic amino-terminal domain, which is responsible for its cytotoxic activity, whereas the hydrophobic carboxyl-terminal domain is believed to anchor the protein in the granule membrane (Gray et al., 1989). LBP and BPI share 44% amino acid sequence identity to bind lipopolysaccharide (Schumann et al., 1990). Furthermore, both proteins have similar amino-terminal amino acids (Tobias et al., 1988). Secondary structure predictions suggest that PLTP has two potential transmembrane regions spanning from residues 169 through 181, and residues 288 through 304 (Albers et al., 1996). Two potential disulfide bonds exist between cysteine residues 5 and 129, and between cysteine residues 168 and 318. The cysteine residues 146 and 185 form a disulfide bridge that is essential for the correct folding and secretion of PLTP (Huuskonen et al., 1998, 1999; Qu et al., 1999).

We have shown that two forms of PLTP exist in human plasma, one with high activity (HA-PLTP) and another with low activity (LA-PLTP) (Oka et al., 2000b; Kärkkäinen et al., 2002). The LA-PLTP is associated with apoA-I, and the HA-PLTP co-purifies with apoE (Murdoch et al., 2002). LA-PLTP is located between LDL and HDL on size-exclusion chromatography, having an apparent molecular mass of 520 kDa and a Stokes diameter of 12−17 nm (Oka et al., 2000a; Murdoch et al., 2002). In contrast, HA-PLTP is associated with an average molecular mass of 160 kDa and a Stokes diameter between 7.6 and 12.0 nm. HA-PLTP but not LA-PLTP is able to remodel HDL, resulting in the formation of two types of particles, preβ-HDL and large fused HDL (Vikstedt