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Invited critical review

Apolipoprotein M

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ABSTRACT

Apolipoprotein M (ApoM) is a novel apolipoprotein that was discovered in 1999 and is bound primarily to high-density lipoproteins (HDLs) in the plasma. Multiple factors may influence its expression at both the post-transcriptional and the transcriptional levels both in vivo and ex vivo as follows: hepatocyte nuclear factor-1α, 4α (HNF-1α, 4α), liver receptor homolog-1 (LRH-1), forkhead box A2 (Foxa2) and platelet activating factor (PAF) upregulate its expression; liver X receptor (LXR), retinoid X receptor (RXR), farnesoid X receptor (FXR), small heterodimer partner (SHP) and the majority of cytokines downregulate its expression. However, mechanisms underlying these processes remain unknown. Structurally, there exists a characterized hydrophobic binding pocket within the apoM protein, which enables it to bind functional lipids such as Sphingosine-1-Phosphate (S1P). Functionally, it facilitates the formation of preβ-HDL and enhances an avalanche of atheroprotective effects exerted by HDL. Moreover, in patients with diabetes, the levels of plasma apoM may decrease, whereas the augmentation of apoM decreases plasma glucose levels and magnifies the secretion of insulin. This article offers a panorama of the progress made in the research regarding the characteristics of apoM, particularly the regulation of its expression and its functions.

Contents

Abbreviations: apo, apolipoprotein; HDL, high-density lipoprotein; HNF-1α,4α, hepatocyte nuclear factor-1α,4α; LRH-1, liver receptor homolog-1; Foxa2, forkhead box A2; PAF, platelet activating factor; LXR, liver X receptor; RXR, retinoid X receptor; FXR, farnesoid X receptor; SHP, small heterodimer partner; S1P, Sphingosine-1-Phosphate; CVD, cardiovascular disease; HDL-C, HDL cholesterol; RCT, reverse cholesterol transport; MHC, major histocompatibility complex class III; TNF, tumor necrosis factor; HRP, haptoglobin-related protein; PON-I, paraoxonase-1; SNP, single nucleotide polymorphism; T1,2D, type 1,2 diabetes; RA, rheumatoid arthritis; ABCA1, ATP-binding cassette transporter A1; PPAR-γ, peroxisome proliferator-activated receptor γ; IL, interleukin; ABCG, ATP-binding cassette sub-family G; CETP, cholesteryl ester transfer protein; SR-B1, scavenger receptor class B member 1; MODY3, maturity-onset diabetes of the young type 3; MUP, major urinary protein; RBP, retinol binding protein; RAR, retinoic acid receptor; TR, thyroid hormone receptor; PI3K, phosphatidylinositol 3-kinase; DHC, dihydrocapsaicin; HRE, hormone response element; IGF-1, insulin-like growth factors; PAF-R, platelet activating factor receptor; TGF-α,β, transforming growth factor-α,β; EGF, epidermal growth factor; HGF, hepatic growth factor; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; ldlr, LDL receptor; $ldlr^{-/-}$, LDL-receptor deficient; LCAT, lecithin-cholesterol acyltransferase; CE, cholesteryl ester; TC, total cholesterol; LDL-C, LDL cholesterol; VLDL-C, VLDL cholesterol; CHD, coronary heart disease; Mets, metabolic syndrome; S1PR, S1P receptor; NF-κB, nuclear factor-κB; NO, nitrogen oxide; eNOS, endothelial nitric oxide synthase; apoM-Tg^N mice, mice overexpressing human apoM by approximately two-fold; apoM-Tg^H mice, mice overexpressing human apoM by approximately ten-fold; $apoM^{-/-}$ mice, apoM-null mice; $apoE^{-/-}$, apoE-null mice.

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1. Introduction

Cardiovascular disease (CVD) is among the leading causes of death worldwide. Innumerable studies have reported that plasma HDL cholesterol (HDL-C) levels correlate inversely with the escalated risk of CVD [1]. However, an increasing number of studies has determined that HDL function may best forecast its anti-atherogenic capacity, as opposed to its concentration [2,3]. HDL exerts atheroprotective effects by removing cholesterol from peripheral cells via the reverse cholesterol transport (RCT) system. Researchers have determined that HDL may exert anti-atherogenic effects via other means, including the reversal of endothelial dysfunction, spurring prostacyclin production, and hindering platelet aggregation [4]. HDLs contain many common apolipoproteins, including apoAI, apoAII and apoE [5]. ApoM is a comparatively new apolipoprotein and was identified by Xu et al. [6] in 1999; it is found primarily in HDL and is involved in both lipoprotein and lipid metabolism. The following is a brief review of the primary biological characteristics of apoM.

2. Genetic information

Almost all mammalian genomes contain the apoM gene. There exist significant similarities between human and murine apoM, as the resemblance between the two types is greater than 80%. The human apoM gene, the genomic sequence of which includes six exons and five introns situated on chromosome 6p21.3 within the major histocompatibility complex class III (MHC III) region, is approximately 2.3 kb [6]. There are many relevant genes in the vicinity whose biological functions remain unclear, such as the lymphotoxins α and β, BAT3 and BAT4, the open reading frame C6orf47, and the genes responsible for encoding tumor necrosis factor (TNF), indicating that apoM is associated with many inflammatory processes. The genetic frame of apoM is highly conserved among various types of living organisms such as the puffer fish, the African clawed frog and the zebra fish as well as porcine animals [7]. Based on a bioinformatics analysis, many binding sites for transcription factors as well as conventional TATA-box elements are located within the apoM proximal promoter region. Consequently, the existence of this genetic information among distantly related species serves as evidence that the apoM protein may contribute significantly to a wide range of biological processes.

3. Information regarding the apoM protein

Computer experiments have demonstrated that the human apoM protein is composed of 188 amino acid residues and has a molecular weight of approximate 21,253 Da; there exists no significant distinction between apoM and other proteins based on its primary structure. However, based on observations of its secondary structure, apoM is a member of the lipocalin superfamily and possesses the characteristic eight-stranded anti-parallel β-barrel [8,9]. Moreover, apoM has a hydrophobic binding pocket within the lipocalin fold [10] (Fig. 1). It is this pocket that enables apoM to bind small functional lipids, such as retinoid acid and S1P [11,12]. However, the sequence of the apoM protein lacks a peptidase cleavage site; therefore, plasma apoM retains its signal peptide. This feature is shared only with haptoglobin-related protein (HRP) and paraoxonase-1 (PON-I), each of which is associated with HDL [13,14]. Prior to the secretion of the mature protein, the peptide must be cut at by a signal peptidase [15]. Axler et al. [16] constructed a recombinant apoM(apoM^{Q22A}) molecule with a preserved signal peptidase cleavage site by replacing the amino acid glutamine with alanine and observed that apoM^{Q22A} could not bind lipoproteins. Christoffersen et al. [17] subsequently used this construct to generate a transgenic mouse model (apoM^{Q22A}-Tg mice) to prove that the absence of this signal peptide in human apoM caused faster elimination of apoM. They determined that compared with apoM-Tg mice (wild type human transgenic mice), plasma human apoM was barely detectable and was swiftly excreted from urine of the apoM^{Q22A}-Tg mice, whereas delegation of the kidney arteries caused a rapid increase in the levels of human apoM. These findings suggest that the signal peptide that mediates the binding of apoM to lipoproteins and prevents its elimination by the kidneys.

4. Distribution

As stated above, apoM is found primarily in HDL, although a small proportion is found in triglycerides, apoB-containing lipoproteins and chylomicrons [5,18]. In humans, plasma apoM concentrations are approximately 1 μM. Approximately 2% of LDL and 5% of HDL carry apoM molecules. Research has demonstrated that apoM is produced by specific tissues. Zhang et al. [19] examined the patterns of apoM expression during embryogenesis and determined that apoM mRNA was expressed between 7.5 and 18.5 days and was detected in both the kidneys and the liver on the 15th day in mouse embryos. In porcine embryos, apoM is expressed primarily in the liver and the kidneys [7]. Moreover, Faber et al. [20] confirmed that a high-proportion of apoM mRNA is expressed in the liver and kidneys and less so in other tissues in mice, which indicates that the liver and the kidneys are the tissues most for the expression of apoM. In the liver, hepatocytes produce apoM and secrete it into the plasma where it binds to HDL and may be involved in the metabolism of lipids and lipoproteins [21]. In the kidneys, apoM is taken up from the primary urine to the cells of proximal tubule by binding to the endocytic receptor megalin. As a result, mice with a constitutional renal knock-out of megalin excrete apoM in the urine [22]. Megalin mediates the tubular reabsorption of several small plasma proteins which convey small molecules and are filtered through the glomeruli [23,24], which prevents their loss in the urine, including apoM-S1P.

5. SNP

Several inquiries into the single nucleotide polymorphisms (SNPs) of apoM gene within its proximal promoter region have been undertaken, endeavors primarily focused on rs9404941 (T-855C), rs805296 (T-778C), and rs805297 (C-1065A), because of their links with CAD,