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Overexpressed PLTP in macrophage may promote cholesterol accumulation by prolonged endoplasmic reticulum stress

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ABSTRACT

It is well known that phospholipid transfer protein (PLTP) is involved in the lipid metabolism and development of atherosclerosis (AS). Abundant PLTP is considered to be expressed on the foam cells derived from monocyte/macrophages in atherosclerotic plaques, suggesting that high level of active PLTP may promote the formation of foam cells. However, the exact role of PLTP on the process of macrophage derived foam cell formation remains unclear. The accumulation of free cholesterol (FC) in the cytoplasm may lead to the prolonged endoplasmic reticulum stress (ERs) and the imbalance of intracellular cholesterol homeostasis. Different PLTP level definitely alternates the phospholipids (PL) and cholesterol level in plasma, strongly suggesting that active PLTP may change the level of FC and PL intracellularly, which subsequently induced the ERs in macrophage. Thus, we hypothesize that high level of PLTP may promote the accumulation of cholesterol in macrophage via the alteration ratio of FC to PL. Therefore, validating this hypothesis may clarify the role of PLTP in macrophage ERs in AS and also raise a novel strategy in the regression of AS plaques via restoring intracellular membrane lipid homeostasis and attenuating ERs.

Introduction

Atherosclerosis (AS) has been regarded as mainly the pathology basis of coronary heart disease (CHD), which is one of the major cause of people death [1]. The one of key risk factors of AS was dyslipidemia [2,3]. Of note, high level of apolipoprotein B-containing lipoprotein and oxidized low-density lipoprotein (oxLDL) were easily uptaked by monocyte/macrophage and eventually cause the formation of the foam cells [4]. In addition, lipid accumulation in advanced AS lesions may lead to the impairment of the fibrous cap and enlargement of necrotic core [1]. Although prolonged endoplasmic reticulum stress (ERs) response was mainly responsible for the apoptosis of lipid-laden macrophages in the end-stage of AS [5,6], it remains unclear which multi-steps of ERs are operating and interconnecting with each other.

Unfolded protein response (UPR) considered as ER-adaptive response includes three distinct ER-associated signaling pathways: PKR-like eukaryotic initiation factor 2α kinase (PERK), inositol-requiring transmembrane kinase/endonuclease 1 (IRE1) and activating transcription factor-6 (ATF6). However, prolonged ERs caused by excess improperly folded proteins can lead to cell apoptosis [7]. For example, hyperlipidemia could result in turbulence of cellular homeostasis and prolonged ERs in the liver and small intestine, which is associated with HDL dysfunction [8]. Feng and colleagues reported that free cholesterol (FC) loading could activate PERK-ATF4-CHOP (C/EBP homologous protein) and X-box binding protein-1 (XBP-1) signal pathways caused by perturbation of calcium homeostasis in endoplasmic reticulum [5]. As cellular messenger, the increased ratio of FC to PL (phospholipids) in the cytoplasm possibly induces ERs associated cell death [9]. Thus, it can be seen that both cholesterol trafficking and homeostasis of ER are participated in the process of AS.

Phospholipid transfer protein (PLTP) plays a critical role in plasma lipid metabolism [10–12]. Most of cell types expressed PLTP for the participation of the phospholipids exchange intracellularly [10]. Besides, PLTP can convert the spherical HDL into lipid-poor preβ-HDL, an acceptor of cellular cholesterol efflux [11,12], and increase cholesterol efflux from cell by interacting and stabilizing ATP-binding cassette transporter A1 (ABCA1) prevailingly mediated for removal of cholesterol and phospholipid [13]. PLTP can also modulate the lipoprotein susceptibility to oxidative damage due to altering the distribution of vitamin E in vivo [14]. Recently, human epidemiological study reported high

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PLTP activity is associated with depressed LV systolic function [15]. Similarly, destabilization of AS plaques in the mice model of PLTP overexpression may be caused by increasing the accumulation of cellular reactive oxygen species and the expression of inflammatory factors [16]. Moreover, PLTP is found to be secreted and expressed in cultured macrophages with cholesterol loading, and abundant PLTP is also detected in macrophage foam cells of human plaques, which are associated with intracellular lipid droplets [17,18]. Thus, PLTP may play a significant role in mediating the intracellular homeostasis of macrophage via trafficking of lipids. During AS progress, over expressed PLTP may result in impairment of homeostasis caused by accumulation of abnormal lipid and activation of ERs-apoptosis signal pathways on macrophage and elucidate the roles of PLTP on the conversion of macrophages developing into foam cells in each period of AS.

Hypothesis

We hypothesize that with the stimulation of oxLDL, high level of PLTP may promote process of transport lipid and then result in the increasing FC and decreasing PL in macrophage cytoplasm. The higher ratio of FC to PL in PLTP-overexpressed macrophage will induce the prolonged ERs, such as the activation of PERK-ATF4, IRE1-XBP1, ATF6-ATF6 (N). Besides, the increasing of stress in ER will in turn lead to the upregulation of macrophage scavenger receptors (CD36, SR-A1, LOX-1) and the accumulation of cholesterol in macrophage eventually (Fig. 1).

Theoretical evidences for the hypothesis

Accumulation of cholesterol in foam cells derived from macrophages

OxLDL-cholesterol has been trafficked by the scavenger receptors of macrophage such as CD36, scavenger receptors-A1 (SR-A1), lectin-like oxLDL receptor (LOX-1) to the ER in the cytoplasm [19], where the cholesterol can be esterified to the cholesteryl fatty acyl esters (CEs) co-interacting with membrane developing lipid droplets by acyl-CoA-cholesterol acyl transferase (ACAT) and neutral cholesteryl ester hydrolase (nCEH) [20]. Nevertheless, accumulation of toxic lipids in macrophages can lead to a prolonged ERs and induces cell death. Yao and colleagues reported that minimally modified low-density lipoprotein (mm-LDL) could induce both the activation of IRE1-XBP1 and ATF6 pathways caused by accumulation of free cholesterol in the macrophage cytoplasm [21]. Suppression of ERs promotes the shifting of M2 macrophage toward CCR7^{+} M1 macrophages and inhibits the formation of foam cells, suggesting that ERs may play a critical role in regulating phenotype differentiation and macrophage cholesterol deposition [22]. Both intracellular protein transport and secretion are mainly regulated in ER and Golgi. However, ApoE transport and secretion have been proved to be perturbed by increase of cholesterol level in the cytoplasm. Interestingly, apoE secretion can be still restored via removal of excess cholesterol, suggesting that strategies for normalization of ER cholesterol content may rebuild cellular balance of lipid metabolism [23]. Taking together, the accumulation of cholesterol in the cytoplasm may be regarded as a warning signal for macrophage, which can lead to prolonged ERs. Thus, further studies should be concentrated on how to remove superabundant cholesterol from the macrophage cytoplasm to relieve the ERs and inhibit cell apoptosis in AS.

Atherogenic role of PLTP in AS

PLTP is involved in the metabolism of triglyceride-rich lipoproteins and the remodeling of high-density lipoproteins (HDL), meaning that it plays an important role in development of AS. The deficiency of systemic PLTP in mice is associated with decreased susceptibility to AS [24], whereas increasing expression of PLTP in mice aggravates the development of AS [25]. It is worth mentioning that macrophage-derived PLTP is regarded as a primary contributor of plasma PLTP activity. However, deficiency of PLTP in macrophage leads to increased apoA-I and decreased the VLDL/LDL levels, retarding the atherosclerotic lesion development in LDLr$^{-/-}$ mice fed on western-type diet [24]. Consist with the atherogenic role of PLTP, Samyn et al. reported that macrophage cholesterol efflux and RCT to faeces are impaired by elevation of

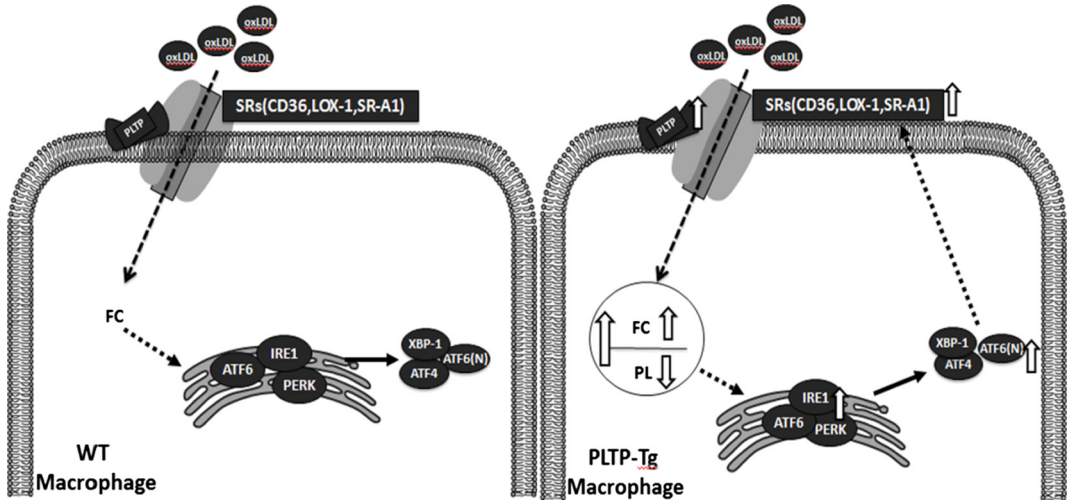

Fig. 1. Overexpressed PLTP in macrophage promote the accumulation of cholesterol. After the intervention of oxLDL, overexpression of PLTP in macrophage can increase the ratio of FC and PL in the cytoplasm than WT macrophage. The increasing FC and decreasing PL in the ER can continuously activate the UPR, such as PERK-ATF4/IRE1-XBP1/ATF6-ATF6 (N) and then upregulate the expression of scavenger receptors including CD36, SR-A1 and LOX-1, which result in the higher level of cholesterol eventually in the PLTP-Tg macrophage. PLTP-Tg macrophage, bone marrow derived macrophages of PLTP-overexpressed mice; WT macrophage, bone marrow derived macrophages of wild type mice; FC, free cholesterol; PL, phospholipids; PERK, double-stranded RNA-activated protein kinase (PKR)–like ER kinase; IRE1, inositol requiring enzyme 1; ATF4/6, activating transcription factor 4/6; ATF6 (N), activated N-terminal cytosolic fragment of ATF6; XBP1, X-box binding protein 1; CD36, C luster of Differentiation 36; SR-A1, scavenger receptor A1; LOX-1, lectin-like oxLDL receptor-1. ⋯⋯▸, multistep stimulation; ⟶, direct stimulation; ⇧, increase; ⇩, decrease.