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Review

The ABC transporters in lipid flux and atherosclerosis

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ABSTRACT

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality in the United States and in many other countries. Dysfunctional lipid homeostasis plays a central role in the initiation and progression of atherosclerotic lesions. The ATP-binding cassette (ABC) transporters are transmembrane proteins that hydrolyze ATP and use the energy to drive the transport of various molecules across cell membranes. Several ABC transporters play a pivotal role in lipid trafficking. They are critically involved in cholesterol and phospholipid efflux and reverse cholesterol transport (RCT), processes that maintain cellular cholesterol homeostasis and protect arteries from atherosclerosis. In this article we provide a review of the current literature on the biogenesis of ABC transporters and highlight their proposed functions in atheroprotection.

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1. Introduction

Atherosclerotic cardiovascular disease is the leading causes of morbidity and mortality in the United States and in many other countries [1,2]. Dysfunctional lipid homeostasis plays a central role in the initiation and progression of atherosclerotic lesions. Modified or oxidized low-density lipoprotein (LDL) cholesterol induces endothelial dysfunction with focal inflammation which in turn causes increased expression of atherogenic signaling molecules that promote the adhesion of monocytes and T lymphocytes to the arterial

Abbreviations: ABC transporters, ATP-binding cassette transporters; APP, amyloid precursor protein; ApoA-I, apolipoprotein A-I; ApoE, apolipoprotein E; AMPK, adenosine monophosphate activated protein kinase; ASCVD, atherosclerotic cardiovascular disease; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; IFN-γ, interferon-γ; LDL, low-density lipoprotein; LDLr, low-density lipoprotein receptor; LXR, liver X receptor; PPAR-γ, peroxisome proliferator-activated receptor-γ; RCT, reverse cholesterol transport; RXR, retinoid X receptor; VLDL, very low density lipoprotein.

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Table 1
ABC transporters of known relevance to atherosclerosis.

Symbol	Expression	Known functions	Relevance to atherogenesis
ABCA1	Macrophages	Regulation of the efflux of cellular cholesterol and phospholipids to apoA-I	HDL formation
	Endothelial cells Hepatocytes Adipocytes	ApoE-mediated cholesterol efflux	Prevent lipid accumulation in macrophages Attenuate risk of coronary artery disease Deficiency leads to Tangier Disease
ABCA2	Macrophages Fibroblasts	Trafficking of LDL-derived free cholesterol	Possible impact on atherosclerotic lesion formation
ABCA5	Cardiomyocytes Oligodendrocytes astrocytes Kupffer cells Macrophages	Regulation of cholesterol efflux to HDL3 Possible regulation of ABCA1 expression	Prevents lipid accumulation in macrophages
ABCA7	Brain Lungs Macrophages Platelets Kidney Adipose tissue	Regulation of cellular efflux of phospholipids, but not cholesterol, to apo A-I *in vitro*	Possible prevention of lipid accumulation in macrophages
ABCB4	Hepatocytes	Regulation of phosphatidylcholine secretion into bile and its translocation across the plasma membrane	Prevents the accumulation of phospholipids in hepatocytes Exports phosphatidylcholine into bile Possible impact on atherosclerotic lesion formation Deficiency leads to progressive familial intrahepatic cholestasis (PFIC3)
ABCG1	Arterial endothelial cells Macrophages Hepatocytes	Promotes cholesterol efflux to the mature forms of HDL (HDL2 and HDL3)	Prevents excessive accumulation of lipids in hepatocytes and macrophages Protects arteries from atheroma development Required for anti-apoptotic effect of HDL against oxidized LDL-induced apoptosis in macrophages
ABCG4	Macrophages	Promotes cholesterol efflux to the mature forms of HDL (HDL2 and HDL3)	Prevents excessive accumulation of lipids in hepatocytes and macrophages Can work cooperatively with ABCA1 to move cholesterol into HDL particles
ABCG5/ ABCG8 dimer	Enterocytes Hepatocytes	Main transporters of biliary cholesterol	Biliary excretion of dietary sterols Prevent premature coronary atherosclerosis Deficiency leads to Sitosterolemia

endothelium and their penetration into the intima. Monocytes accumulate in the subendothelial space and undergo transformation into macrophages which express scavenger receptors that allow them to take up modified lipoproteins. Ultimately, when net influx of cholesterol exceeds efflux, these macrophages become lipid-overloaded foam cells [3,4]. Foam cell accumulation leads to fatty streaks. Eventually engorged foam cells undergo secondary necrosis and form the lipid core of advanced atherosclerotic plaques [5].

Several ATP-binding cassette (ABC) transporters play a pivotal role in lipid trafficking [6]. ABC transporters are integral membrane proteins that carry diverse solutes across lipid bilayers, often against a concentration gradient. They are critically involved in cholesterol and phospholipid efflux and reverse cholesterol transport (RCT), processes that maintain cellular cholesterol homeostasis and protect arteries from atherosclerosis. RCT, the removal of cholesterol from peripheral cells (including vascular macrophages) for transport to the liver, is of particular significance for atheroprotection. ABC transporters also participate in the regulation of intestinal cholesterol absorption and excretion, which influences plasma cholesterol. The intent of this review is to discuss current knowledge about the role of ABC transporters in multiple aspects of cholesterol disposition and the impact of these proteins on atherogenesis (Table 1).

2. The ABC transporters

2.1. Overview

ABC proteins transport a varied array of substrates across extra- and intracellular membranes against a concentration gradient. Unidirectional (inward or outward) transport by ABC proteins requires energy which is provided at the cost of ATP hydrolysis [7]. Substrates of the ABC transporters include lipids, bile acids, xenobiotics, heavy metal ions, inorganic acids, glutathione conjugates, sugars and peptides for antigen presentation [8]. As they transport exogenous and endogenous compounds across lipid bilayers, they reduce the body load of potentially harmful substances. Mutations of ABC transporters are medically relevant [9,10] and can result in multidrug resistance in cancer cells [11,12] and in a number of human diseases such as Tangier disease [13,14], Stargardt disease [15,16], cystic fibrosis [17,18], sitosterolemia [19], cholesterol and bile transport defects [20], and hyperinsulinemia [21].

2.2. Structure–function relationships

The ABC transporters constitute one of the largest families of proteins in living organisms. The human genome carries 49 ABC genes. They are grouped into seven structural classes, or subfamilies: ABCA to ABCG, on the basis of amino acid sequence and domain organization [9]. The presence of a strongly conserved ATP-binding motif defines membership in the family and the basic functional organization of an ABC transporter in the membrane is the same from bacteria to humans, and in all subclasses [7]. ABC transporters are characterized by two well conserved hydrophilic cytoplasmic nucleotide binding domains (NBD) and two hydrophobic transmembrane domains (TMD) containing 6–12 membrane-spanning alpha-helices (Fig. 1). The TMD provide the specificity for the substrate [22,23]. The NBD or ATP site, a 200- to 250-amino acid globular protein unit, consists of the highly conserved Walker type A