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Cholesterol in the retina: The best is yet to come

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ABSTRACT

Historically understudied, cholesterol in the retina is receiving more attention now because of genetic studies showing that several cholesterol-related genes are risk factors for age-related macular degeneration (AMD) and because of eye pathology studies showing high cholesterol content of drusen, aging Bruch's membrane, and newly found subretinal lesions. The challenge before us is determining how the cholesterol-AMD link is realized. Meeting this challenge will require an excellent understanding these genes' roles in retinal physiology and how chorioretinal cholesterol is maintained. In the first half of this review, we will succinctly summarize physico-chemical properties of cholesterol, its distribution in the human body, general principles of maintenance and metabolism, and differences in cholesterol handling in human and mouse that impact on experimental approaches. This information will provide a backdrop to the second part of the review focusing on unique aspects of chorioretinal cholesterol homeostasis, aging in Bruch's membrane, cholesterol in AMD lesions, a model for lesion biogenesis, a model for macular vulnerability based on vascular biology, and alignment of AMD-related genes and pathobiology using cholesterol and an atherosclerosis-like progression as unifying features. We conclude with recommendations for the most important research steps we can take towards delineating the cholesterol-AMD link.

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Abbreviations

ABCA1	ATP-binding cassette transporter A1
ACAT	acyl-CoA: cholesterol acyl-transferase
AMD	age-related macular degeneration
apoA-1	apolipoprotein A1
apoE	apolipoprotein E
apoB-48	apolipoprotein B-48
apoB-100	apolipoprotein B-100
BLamD	basal laminar deposit
BLinD	basal linear deposits
BrM	Bruch's membrane
CETP	cholesteryl ester transfer protein
CM	chylomicrons
CTX	cerebrotendinous xanthomatosis
CVD	cardiovascular disease
CYP	cytochrome P450
EC	esterified cholesterol
FFA	free fatty acids
GCL	ganglion cell layer
GC–MS	gas chromatography–mass spectrometry
GWAS	genome-wide association studies
HDL	high density lipoprotein
HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
ICL	inner collagenous layer
IDL	intermediate density lipoprotein
INL	inner nuclear layer
INSIG	insulin-induced gene protein
IPL	inner plexiform layer
IS	inner segments
isoLGs	isolevuglandins
LCAT	lecithin: cholesterol acyltransferase
LDL	low density lipoprotein
LDL-R	low density lipoprotein receptor
LIPC	hepatic lipase
LXR	liver X receptor
MRM	multiple reaction monitoring
MS	mass spectrometry
NPC1	Niemann-Pick type C1
NFL	nerve fiber layer
NR	neural retina
ONL	outer nuclear layer
OPL	outer plexiform layer
OS	outer segments
PL	phospholipid
PR	photoreceptors
RPE	retinal pigment epithelium
SDD	subretinal drusenoid deposit
SNP	single nucleotide polymorphism
TG	triglycerides
UC	unesterified cholesterol
VLDL	very low density lipoprotein.

1. Introduction

Cholesterol is often viewed as a deleterious compound, mainly because its excess in systemic circulation is a risk factor for cardiovascular and Alzheimer's diseases (2002; Solomon et al., 2009; Zambon et al., 2010). Yet cholesterol is involved in many physiological processes and thus a lipid essential for normal human development, growth and physiology.

Studies of cholesterol will be moving to the forefront of vision research because of accumulating data implicating cholesterol homeostasis in the pathogenesis of age-related macular degeneration (AMD), the leading cause of irreversible vision loss and blindness in the elderly of industrialized world (Pascolini et al., 2004). Evidence linking cholesterol and AMD emerged more than a decade ago when cholesterol has been discovered to accumulate with age in human Bruch's membrane (BrM) (Curcio et al., 2001). Subsequent studies also established that esterified (EC) and unesterified cholesterol (UC) are significant components of the lipid-rich lesions associated with AMD (basal linear deposits, BLinD, and soft drusen) and comprise >40% of hard druse volume (Curcio et al., 2011a). The cholesterol-AMD link was confirmed when variants in the cholesterol-related genes were found to be associated with AMD by genome-wide association studies (GWAS) that suggested that these variants may play important roles in early AMD (Chen et al., 2010; Fritsche et al., 2013; Neale et al., 2010; Yu et al., 2012). As a result of all these