

## **Section 1: Cholesterol chemistry and cell function**

Chapter 1: Cholesterol chemistry and laboratory synthesis

Abstract

Introduction

Cholesterol structural characterization

Cholesterol laboratory synthesis

Concluding remarks

References

Chapter 2: Molecular evolution of cholesterol and other higher sterols in relation to membrane structure

Abstract

Acknowledgments

Introduction: The overlooked lipids

Key features of the cholesterol molecule

Evolution and streamlining of a molecule

Phase equilibria in lipid membranes

Cholesterol and lipid membrane phase equilibria: The liquid-ordered phase

Cholesterol, transverse membrane order, permeability, and mechanics

Cholesterol and lateral membrane organization

Other higher sterols: Universality in sterol function

A case study: Cholesterol, lateral membrane structure, and the functioning of Na<sup>+</sup>/K<sup>+</sup>-ATPase

Cholesterol and membrane evolution

References

Chapter 3: Role of cholesterol in maintaining the physical properties of the plasma membrane

Abstract

Acknowledgments

Introduction

Phase diagram for cholesterol/phospholipid mixtures

Basic membrane physical properties and how cholesterol regulates them

Lateral organization of membranes: Effect of cholesterol

New information from the saturation recovery electron paramagnetic resonance stretched exponential function approach

Concluding remarks

References

Chapter 4: The fundamental interaction of cholesterol with lipid membranes: The umbrella model

Abstract

Acknowledgments

Introduction

Maximum solubility of cholesterol in phosphatidylcholine (PC) and phosphatidylethanolamine (PE) bilayers

The umbrella model

Monte Carlo simulation of chemical potential of cholesterol using multibody interactions

A family of small headgroup molecules: Sterols, ceramides, and diacylglycerols

Molecular dynamics (MD) simulation of the umbrella effect  
Measurement of the chemical potential of cholesterol in PC bilayers  
Concluding remarks  
References

#### Chapter 5: Model peptides and cholesterol

Abstract  
Acknowledgment  
On the energy and entropy parameters of the free energy of the membrane  
References

#### Chapter 6: Cholesterol and ceramide: An unlikely pair

Abstract  
Acknowledgments  
Introduction: Membrane heterogeneity  
Sphingolipids and cholesterol: Biological impact  
Sphingolipids and cholesterol: Membrane biophysics  
Cholesterol and ceramide in fluid membranes  
Conclusions and future perspectives  
References

#### Chapter 7: Cholesterol-recognizing amino acid consensus motifs in transmembrane proteins: Comparative analysis of in silico studies and structural data

Abstract  
Introduction  
Cholesterol: Bifacial structure, multifaceted functions  
Cholesterol footprint on a membrane protein: Starting the investigation  
CARC and CRAC algorithms: Basic principles at work  
Cholesterol-binding motifs in 3D: What structural studies reveal  
Moving to the 3rd dimension  
Conclusion  
References

#### Chapter 8: Effects of cholesterol on the GPCR AT1 receptor and its interplay with AT1 antagonists

Abstract  
Introduction  
Experimental results and their discussion  
Cholesterol influence on the physicochemical properties of the cell membrane in the presence of AT1R and sartans  
Molecular dynamics (MD) simulations on AT1R embedded in a DPPC:Cholesterol (60:40 mol%) bilayer reveal a putative binding site for AT1R blockers on the receptor  
Conclusions  
References

#### Chapter 9: Principles of cholesterol regulation of ion channels

Abstract  
Acknowledgments

## Introduction

Lipids as structural components and functional regulators of membrane proteins

A thermodynamic consideration of lipid-binding sites on ion channels and their generic effects on the gating of the channels

Cholesterol-binding sites on ion channels

Functional impact of cholesterol on the activities of ion channels

Technical limitations and potential solutions for further developments

Conclusions

References

## Chapter 10: Fluorescent probes for microscopy visualization of cholesterol topography and dynamics in membranes

Abstract

Acknowledgments

Author contributions

Declaration of interests

Introduction

The elusive ideal probe

Cholesterol probes

Indirect cholesterol probes

Direct imaging of intrinsic fluorescent cholesterol analogs

Concluding remarks

References

## Chapter 11: Cholesterol transport in blood, lipoproteins, and cholesterol metabolism

Abstract

Author contributions

Introduction

Lipoproteins an overview

Low-density lipoprotein cholesterol

High-density lipoprotein cholesterol

How does aging impact cholesterol metabolism?

Obesity and aging: Two sides of the same coin?

Using mathematical modeling to explore cholesterol metabolism

Discussion of future perspectives

References

## Chapter 12: Common laboratory research methods for detection and quantification of cholesterol

Abstract

Introduction to cholesterol detection and quantification

The early era of cholesterol detection and quantification: Colorimetric approaches

MS-based approaches

Imaging-based approaches

Enzymatic methods

Summary and concluding remarks

References

Chapter 13: Approaches for modifying cellular cholesterol levels and their application to mechanistic studies: Examples from the ion channel field

Abstract

Introduction

In vitro methods for modifying cholesterol levels in cell membranes

In vivo modification of cholesterol levels

Applications to mechanistic studies on the effect of cholesterol on ion channel targets

Outlook

References

## **Section 2: Cholesterol homeostasis and its disruption**

Chapter 14: Diet-induced hypercholesterolemia in small laboratory animal models

Abstract

Introduction

Mouse models

Rat models

Hamsters

Guinea pigs

Rabbits

Additional diet considerations

Control diets

References

Chapter 15: Nutrition and cholesterol metabolism

Abstract

Acknowledgments

Introduction

Cholesterol structure

Nutritional recommendations for maintaining healthy blood cholesterol levels

Dietary cholesterol intake

Saturated fat intake

Cholesterol functions

Digestion and absorption of cholesterol

Transport of cholesterol

Endogenous cholesterol synthesis

Blood cholesterol and atherosclerosis

Guinea pigs as a preclinical model

Advances in cholesterol research

Explanatory and predictive models approach

Conclusions

References

Chapter 16: Cholesterol and early development

Abstract

Introduction

The fetus and cholesterol

Steroid hormones in reproduction and early life

Extraembryonic structures, secondary yolk sac and placenta, and materno-fetal cholesterol transport

Maternal cholesterol levels in healthy pregnancies, maternal hyper- and hypocholesterolemia, and consequences for the fetus  
Effect of selected medicines related to cholesterol metabolism on the fetal development  
Summary  
References

Chapter 17: Clinical and biochemical diagnostic methods: What do blood lipid levels tell us?

Abstract  
Introduction  
Use of conventional laboratory methods to measure lipoproteins by determining their cholesterol content  
Beyond standard lipid profiles: Determination of atherogenic lipoproteins by advanced lipoprotein testing  
Fasting versus nonfasting lipid measurements  
Lipid and lipoprotein testing in laboratory animals  
What do lipid/lipoprotein levels tell us?  
References

Chapter 18: Familial hypobetalipoproteinemia and abetalipoproteinemia

Abstract  
Introduction  
ApoB gene mutations causing familial hypobetalipoproteinemia  
Familial hypobetalipoproteinemia (FHBL) and coronary heart disease (CHD)  
FHBL and hepatic steatosis  
FHBL and insulin sensitivity  
FHBL, hepatic cirrhosis, and hepatocarcinoma  
FHBL and psychiatric disease  
Heterozygous FHBL and neurological manifestations  
Proprotein convertase subtilisin kexin 9 gene (PCSK9) mutations  
Familial combined hypolipidemia (FHBL2)  
ANGPTL3 S17X  
Abetalipoproteinemia (ABL) and homozygous hypobetalipoproteinemia (HHBL)  
Diagnosis and management  
Heterozygous FHBL  
Pregnancy management  
Conclusion  
References

Chapter 19: Critical illness and cholesterol levels

Abstract  
Acknowledgments  
Introduction  
Clinical implications of hypocholesterolemia  
References

Chapter 20: Familial hypercholesterolemia

Abstract  
Introduction

Genetic and molecular background of FH  
Familial hypercholesterolemia diagnosis  
Familial hypercholesterolemia treatments  
Nutrition and familial hypercholesterolemia  
Management of homozygous familial hypercholesterolemia  
Familial hypercholesterolemia-related diseases  
Familial hypercholesterolemia current status and future perspectives  
References

#### Chapter 21: Niemann-Pick type C disease (NPC)

Abstract  
Acknowledgment  
Introduction  
Clinical picture of NPC disease  
Genetic background of NPC  
Biochemical aspects of NPC1 and NPC2 proteins  
Pathomechanisms underlying NPC disease  
Diagnostics  
Treatment  
References

#### Chapter 22: Rare monogenic disorders of cholesterol metabolism

Abstract  
Introduction  
Monogenic hypercholesterolemia  
Sterol storage diseases  
Bile acid biosynthesis disorders  
Hypocholesterolemia  
References

#### Chapter 23: Secondary (acquired) hypercholesterolemia

Abstract  
Introduction  
Causes of secondary hyperlipidemias and their treatment  
Conclusions  
References

#### Chapter 24: Blood lipids and molecular pathways of atherogenesis

Abstract  
Introduction  
Cholesterol metabolism  
Pathophysiology of atherosclerosis  
Low-density lipoprotein cholesterol and cardiovascular disease  
Oxidized low-density lipoprotein cholesterol and cardiovascular disease  
High-density lipoprotein cholesterol: Marker or risk factor?  
Triglycerides and cardiovascular disease  
Genetics and dyslipidemia  
Conclusions  
References

## Chapter 25: Lysosomal acid lipase: Roles in rare deficiency diseases, myeloid cell biology, innate immunity, and common neutral lipid diseases

Abstract

Historical background: Lysosomal acid lipase (LAL)

Structure, properties, and biology of LAL

LAL roles in disease states

Molecular biology and genetics

LAL in diseases beyond the LALDs

References

Further reading

## Chapter 26: Cholesterol and pathogens

Abstract

Acknowledgments

Introduction

The role of cholesterol-rich membrane microdomains in infectious diseases

Cholesterol recruitment to pathogen-containing vacuoles

Targeting cellular cholesterol metabolism

Systemic cholesterol levels and pathogens

Cholesterol-lowering agents as potential therapeutics in infectious diseases

Cholesterol and immune response

Summary

References

## Chapter 27: Involvement of cholesterol and $\beta$ -amyloid in the initiation and progression of Alzheimer's disease

Abstract

Neurodegenerative diseases are a significant health problem: Alzheimer's disease (AD)

The amyloid cascade as a central cause for Alzheimer's disease

Cellular domains important for the formation of A $\beta$  and cholesterol

Interactions of A $\beta$  with the neuronal membrane and the initiation of synaptic failure

Participation of membrane lipids in the initiation of A $\beta$ -mediated neurotoxicity

How A $\beta$  and cholesterol might lead to neurodegeneration

Cholesterol affects a number of membrane proteins that fine tune neuronal excitability

The  $\epsilon$ 4 isoform (ApoE4) factor in disease onset and progression

References

## Chapter 28: Cholesterol and alcohol

Abstract

Introduction

Alcohol pharmacology

Alcohol use disorder

Alcohol and cholesterol interactions

Alcohol and lipoproteins

Alcohol and PCSK9

Fetal alcohol spectrum disorders (FASDs) and cholesterol

Targeting lipids for treatment of alcohol-related diseases

Conclusion  
References

### **Section 3: Pharmacological considerations and perspectives**

Chapter 29: Cholesterol stiffening of lipid membranes and drug interactions:  
Insights from neutron spin echo and deuterium NMR spectroscopy

Abstract

Acknowledgment

Introduction

Neutron spin echo spectroscopy of lipid membranes

Solid-state  $^2\text{H}$  NMR spectroscopy of lipid membranes

Membrane stiffening effect of cholesterol from molecular dynamics simulations

Cholesterol effects on drug uptake and drug delivery applications

Conclusions

References

Chapter 30: Cholesterol in drug delivery systems

Abstract

Introduction

The common synthesis chemistry of modifying cholesterol into the polymers

Cholesterol in the form of drug delivery vehicles

Conclusion

References

Chapter 31: Modification of vascular receptor pharmacology by cholesterol: From  
molecular determinants to impact on arterial function

Abstract

Introduction

Cholesterol modulation of vasoactive drug action in which the underlying  
pharmacodynamic process(es) is not fully determined

Cholesterol modulation of vasoactive drug action occurring at the cell membrane  
where the vasoactive drug receptor of interest is embedded

Cholesterol modulation of vasoactive drug action occurring at the vasoactive drug  
receptor protein itself

Conclusions and prospective

References

Chapter 32: Clinical strategies for reducing cholesterol levels

Abstract

Introduction

Epidemiology

Major guidelines for lipid-lowering therapy in the United States

Pharmacologic treatment of lipids

Other lipid-lowering therapies

Nonprescription and dietary supplements

Patient education

Clinical pearls

Screening for lipid disorders

Summary

References

General patient education resources for understanding cholesterol disorders and treatment options  
Clinician tools

### Chapter 33: Medicinal chemistry and pharmacology of statins

Abstract  
Introduction  
Medicinal chemistry of statins  
Pharmacology  
Future drugs and concluding remarks  
References

### Chapter 34: Cyclodextrins as promising therapeutics against cholesterol overload

Abstract  
Acknowledgments  
Introduction  
Cyclodextrins in general  
Cyclodextrins in the treatment of Niemann-Pick type C disease  
Cyclodextrins with great potential in the treatment of neurodegenerative diseases  
Cyclodextrins as promising therapeutics in atherosclerosis  
Role of cyclodextrins in the treatment of kidney diseases  
Role of cyclodextrins in the treatment of eye disorders  
Potential effects of cyclodextrins against coronavirus  
Concluding remarks  
References

### Chapter 35: Hyperlipidemia and rheumatoid arthritis

Abstract  
Introduction  
Pathophysiologic mechanisms in rheumatoid arthritis (RA)  
Articular and extra-articular manifestations of RA  
Rheumatoid arthritis treatment  
Comorbidities in RA  
CVD: A major comorbidity in RA  
CVD risk assessment in RA  
CVD and atherosclerosis in RA  
Lipid profile in RA patients  
Mechanisms related to dyslipidemia in RA  
Lipid concentration and inflammatory markers  
Atherosclerosis and inflammation  
Lipid metabolism and inflammation  
The impact of cytokines on LDL  
Lipid peroxidation  
Altered HDL function and structure  
Effects of antirheumatic therapy on serum lipid levels  
Glucocorticoids (GCs)  
DMARDs  
Antitumor necrosis factor-alpha (anti-TNF- $\alpha$ ) agents  
Anti-interleukin-6 (IL-6) agents  
Janus kinase inhibitors (JAK inhibitors)

Other agents  
Mediterranean diet and RA  
The role of exercise in RA  
Conclusions  
References

Chapter 36: Management of hypercholesterolemia in individuals living with HIV/AIDS

Abstract  
Introduction  
Nucleoside reverse transcriptase inhibitors (NRTIs)  
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)  
Diabetes mellitus, metabolic syndrome and HIV  
Conclusion  
References  
Index