HDLC AND CELL SIGNALING IN THE HEART: ROLES IN CARDIOPROTECTION

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Learning objectives:

- To review the role of HDL and the HDL receptor SR-B1 in regulating reverse cholesterol transport
- To understand the role of HDL and SR-B1 in protection against atherosclerosis
- To discuss emerging evidence that HDL and SR-B1 mediate direct cardioprotection
Causes of Heart Failure

- Ischemic Heart Disease/
  Coronary artery disease/
  Myocardial Infarction
- Cardiotoxic substances
- Hypertension
- Diabetes
- Valvular disease
- Others
Heart Disease Risk Versus LDL- and HDL-Cholesterol Levels

Incidence of CHD (per 1000 in 6 yrs)

HDL-C (mg/dL)

LDL-C (mg/dL)

<35
35-55
>55
<135
135-154
155-195
>195

124 Suppl. S11-S20
Events in the formation of atherosclerotic plaques

- Monocyte
- LDL
- HDL
- OxLDL
- Foam Cell
- Efflux
- Inflammation
- Migration
- Apoptosis
- Rupture/thrombosis

EC

SMC
Scavenger Receptor Class B, Type 1: SR-B1


SR-B1 Knockout in Mice Increases HDL Cholesterol and Reduces Cholesterol in Bile

Atherosclerosis in SR-B1/LDL R dKO Mice Fed Atherogenic Diets

<table>
<thead>
<tr>
<th>Diet</th>
<th>Fat Content</th>
<th>Cholesterol Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFCC</td>
<td>15%</td>
<td>1.25% Cholesterol, 0.5% Cholate</td>
</tr>
<tr>
<td>HFC</td>
<td>15%</td>
<td>1.25% Cholesterol</td>
</tr>
<tr>
<td>HC</td>
<td>2%</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Normal</td>
<td>6%</td>
<td>Fat, traced cholesterol</td>
</tr>
</tbody>
</table>

Fuller et al 2014 ATVB 34:2394-403

Mark Fuller
Atherosclerosis in Aortic Sinuses of SR-B1/LDL R dKO Mice Fed Atherogenic Diets

Fuller et al 2014 ATVB 34:2394-403
Atherosclerosis in Coronary Arteries of SR-BI/LDL R dKO Mice Fed Atherogenic Diets

15 % Fat, 1.25 % Cholesterol, 0.5 % Cholate; 3.5 weeks

Fuller et al 2014 ATVB 34:2394-403
Cardiac Fibrosis in SR-B1/LDLR dKO Mice Fed Atherogenic Diets

15 % Fat, 1.25 % Cholesterol, 0.5 % Cholate; 3.5 weeks

Fuller et al 2014 ATVB 34:2394-403
Doxorubicin Induced Cardiotoxicity

Doxorubicin

Apoptosis

Tumor

Heart

Heart Failure
Doxorubicin Induced Cardiotoxicity - *In Vitro*
HDL Protects Cultured Cardiomyocytes against Doxorubicin-Induced Apoptosis


Kristina Durham
HDL Induces Akt Phosphorylation in Cardiomyocytes in an SR-B1 Dependent Manner


Kristina Durham
In Vivo Repeated Doxorubicin Exposure Model

1. ApoA1\textsuperscript{+/+} vs ApoA1\textsuperscript{Tg/Tg}

2. SR-B1\textsuperscript{-/-} ApoA1\textsuperscript{+/+} vs SR-B1\textsuperscript{-/-} ApoA1\textsuperscript{Tg/Tg}

Kristina Durham

ApoA1 Overexpression Protects WT Mice Against Dox-Induced Cardiomyocyte Apoptosis In Vivo

Saline

DOX

ApoA1 +/+  

ApoA1 Tg/Tg  

TUNEL

Cardiac TnT

DAPI

50μm

% TUNEL Positive Cardiomyocytes

Saline

DOX

ApoA1 +/+  

ApoA1 Tg/Tg

Kristina Durham

ApoA1 Overexpression fails to Protect SR-B1-KO Mice from Dox-Induced CM Apoptosis In Vivo

HDL Protects Against Dox-induced Cardiac Dysfunction in WT but not SR-B1-KO Mice

Kristina Durham

SR-B1 Mediated HDL Signaling in the Heart

- HDL
- SR-B1
- Src
- PDZK1
- S1PR1
- Gαi
- PI3K
- Akt 1
- Cell Death
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