Journal of Molecular and Cellular Cardiology 79 (2015) 287–294

Contents lists available at ScienceDirect

Journal of Molecular and Cellular Cardiology

journal homepage: www.elsevier.com/locate/yjmcc

Original article

RIP140 contributes to foam cell formation and atherosclerosis by regulating cholesterol homeostasis in macrophages

Yi-Wei Lin [a], Pu-Ste Liu [a], Neeta Adhikari [b], Jennifer L. Hall [b], Li-Na Wei [a,b,*]

[a] Department of Pharmacology, University of Minnesota Medical School, Minneapolis, MN, USA
[b] Lillehei Heart Institute, University of Minnesota, Minneapolis, MN 55455, USA

ARTICLE INFO

Article history:
Received 21 June 2014
Received in revised form 26 November 2014
Accepted 10 December 2014
Available online 18 December 2014

Keywords:
RIP140
Atherosclerosis
Foam cell
Reverse cholesterol transport

ABSTRACT

Atherosclerosis, a syndrome with abnormal arterial walls, is one of the major causes that lead to the development of various cardiovascular diseases. The key initiator of atherosclerosis is cholesterol accumulation. The uncontrolled cholesterol deposition, mainly involving low-density lipoprotein (LDL), causes atheroma plaque formation, which initiates chronic inflammation due to the recruitment of inflammatory cells such as macrophages. Macrophages scavenge excess peripheral cholesterol and transport intracellular cholesterol to high-density lipoprotein (HDL) for excretion or storage. Cholesterol-laden macrophage-derived foam cell formation is the main cause of atherogenesis. It is critical to understand the regulatory mechanism of cholesterol homeostasis in the macrophage in order to prevent foam cells formation and further develop novel therapeutic strategies against atherosclerosis. Here we identified a protein, RIP140 (receptor interacting protein 140), which enhances macrophage-derived foam cell formation by reducing expression of reverse cholesterol transport genes, A TP-binding membrane cassette transporter A-1 (ABCA1) and ATP-binding membrane cassette transporter G-1 (ABCG1). In animal models, we found that reducing RIP140 levels by crossing macrophage-specific RIP140 knockdown (MϕRIP140KD) mice with ApoE null mice effectively ameliorates high-cholesterol diet-induced atherosclerosis. Our data suggest that reducing RIP140 levels in macrophages significantly inhibits atherosclerosis, along with markers of inflammation and the number of macrophages in a western diet fed ApoE null mouse. This study provides a proof-of-concept for RIP140 as a risk biomarker of, and a therapeutic target for, atherosclerosis.

1. Introduction

Hallmarks of atherosclerosis are abnormal cholesterol metabolism and inflammation [1]. Macrophages are critically involved in cholesterol metabolism and inflammation in the progression of atherosclerosis [2]. Macrophages scavenge excess peripheral cholesterol by uptake of LDL, and transport intracellular cholesterol to high-density lipoprotein (HDL), which can be stored or excreted by the liver through reverse cholesterol transport (RCT) [3]. However, when cholesterol levels are pathologically elevated, cholesterol-laden macrophages become inflammatory and turn to active foam cells [2,4]. Macrophage-derived foam cell formation marks the initiation of atherosclerosis. Cholesterol retention in the macrophage promotes foam cell formation. In macrophages, the ATP-binding membrane cassette transporter A-1 (ABCA1) and ATP-binding membrane cassette transporter G-1 (ABCG1) are the major transporters mediating RCT: ABCA1 regulates RCT to apolipoprotein A-I, and ABCG1 regulates RCT to mature HDL [5].

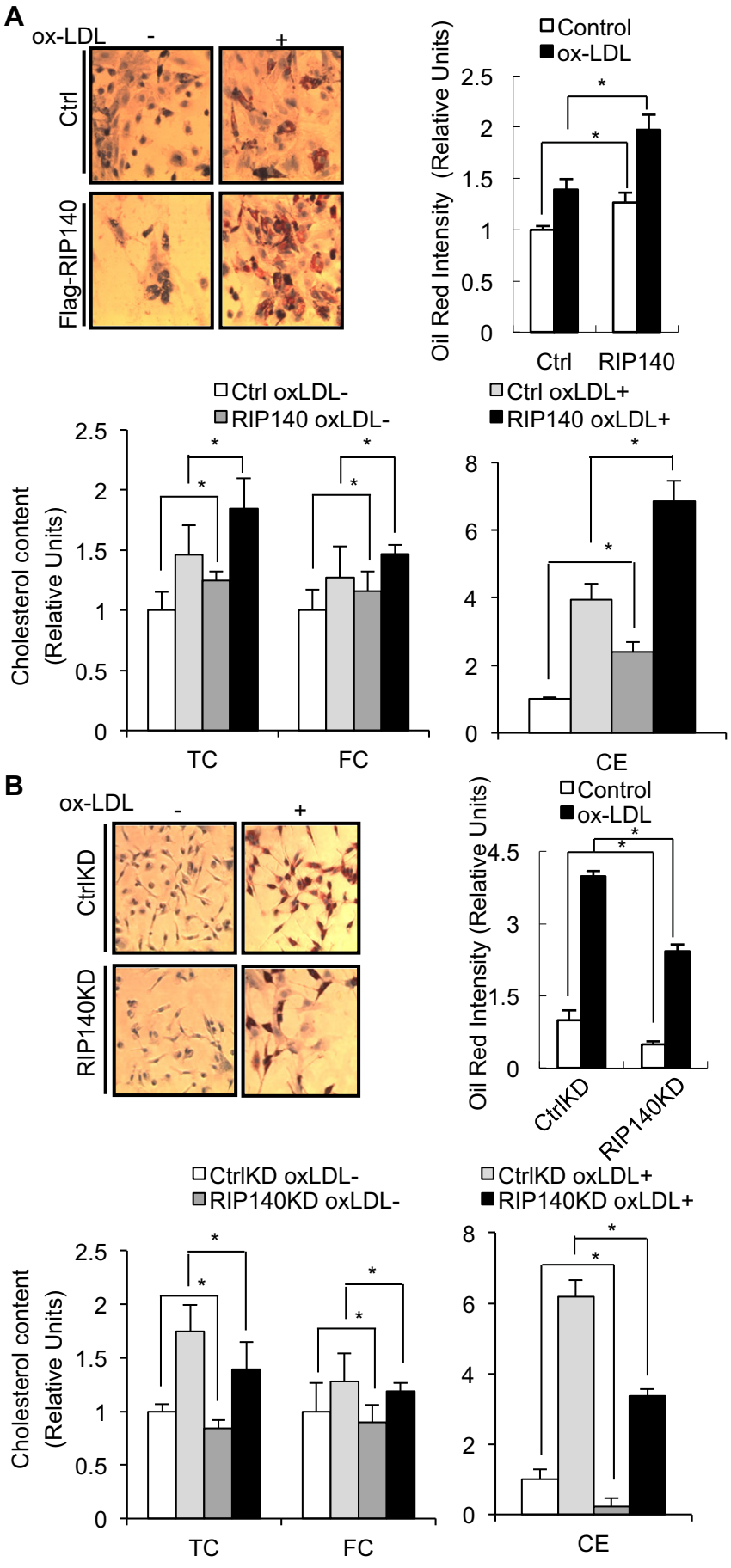
Receptor interacting protein 140 (RIP140) is a protein found in metabolic tissues, such as liver, muscle and adipose tissue [6,7]. As a versatile co-regulator of various transcription factors, RIP140 regulates metabolism, such as fat accumulation in adipocytes, by affecting the expression of metabolic genes [8–11]. RIP140 also exerts various regulatory functions through its extensive post-translational modifications, including various forms of phosphorylation, lysine-acetylation, lysine methylation, arginine methylation, vitamin B6 conjugation, and ubiquitination, etc [12–16]. RIP140 is also known to be expressed in the monocyte–macrophage lineage and can regulate inflammatory responses [17–19]. Our recent study indicated that accumulation of intracellular cholesterol in the macrophage elevated RIP140 and that RIP140 expression was sufficient to enhance inflammatory cytokine production and the inflammatory potential of the macrophage [20].

In this study, we provide novel data showing that RIP140 promotes foam cell formation by reducing cholesterol efflux. This process is mediated through the repression of ABCA1 and ABCG1. Further, cholesterol loading stimulates RIP140's post-translational modification

Abbreviations: LDL, low density lipoprotein; HDL, high density lipoprotein; RIP140, receptor interacting protein 140; ABCA1, ATP-binding membrane cassette transporter A-1; ABCG1, ATP-binding membrane cassette transporter G-1; RCT, reverse cholesterol transport; oxLDL, oxidized low density lipoprotein; AcLDL, acetylated-low density lipoprotein; ApoE, apolipoproetin E; ApoA-I, apolipoprotein A-I; LXR, liver X receptor; ERK2, extracellular-signal-related kinase 2.

* Corresponding author at: 612 Jackson Hall, 321 Church St. SE, Minneapolis, MN 55455, USA. Tel.: +1 612 625 9402; fax: +1 612 625 8408.
E-mail address: weixx009@umn.edu (L.-N. Wei).

http://dx.doi.org/10.1016/j.yjmcc.2014.12.009
0022-2828/


A
ox-LDL
-
+
Ctrl
Flag-RIP140
Control
ox-LDL
Oil Red Intensity (Relative Units)
2.5
2
1.5
1
0.5
0
Ctrl
RIP140
Ctrl oxLDL-
RIP140 oxLDL-
Ctrl oxLDL+
RIP140 oxLDL+
Cholesterol content (Relative Units)
TC
FC
CE
B
CtrlKD
RIP140KD
CtrlKD oxLDL-
RIP140KD oxLDL-
CtrlKD oxLDL+
RIP140KD oxLDL+
4.5
3
1.5
0
8
6
4
2