Asialoglycoprotein receptor 1 gene expression in peripheral blood monocytes associates with serum total cholesterol and low-density lipoprotein cholesterol levels

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To the Editor: Asialoglycoprotein receptor 1 (*ASGR1*) is the major subunit of *ASGR*, it is predominantly expressed by liver parenchymal cells and relatively lower expression was found in peripheral blood monocytes.[1] A genetic study recently revealed that *ASGR1* haploinsufficiency resulted from loss-of-function (LOF) variants was strongly associated with the pronounced reductions in serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels,[2,3] suggesting that *ASGR1* may play a key role in cholesterol metabolism. However, the function of *ASGR1* remains largely unclear. This study was focused on the association of *ASGR1* gene expression in monocytes and plasma cholesterol level.

This study followed the principles of the *Declaration of Helsinki* and was approved by the Ethics Committee of the First People's Hospital of Huaihua, University of South China (KY-2017060101). The written inform consents were obtained from the included individuals.

A total of 104 patients who were hospitalized in Cardiology Department, the First People's Hospital of Huaihua from July 1 to August 31, 2017 were recruited. Whole blood samples were collected at the 7 AM after overnight fasting on admission for routine clinical detections and monocytes separation. Demographic and clinical characteristics and laboratory parameters were collected from electronic medical record. The test of *ASGR1* gene in monocytes was referred to the description of previous study.[1,4] Statistical analyses were performed by R (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc., Boston, MA, USA)

The mean age of included patients was 58 years, 34 (33%) were females. The relative expression of *ASGR1* gene ranged from 0.21 to 3.87. When stratified by the tertiles of *ASGR1* gene expression [Supplementary Table 1, http://links.lww.com/CM9/A232], TC and LDL-C levels were higher in top tertile than those in middle and bottom tertiles ($P < 0.001$). The differences in *ASGR1* gene expression between subgroups which stratified by age, gender, and clinical diagnoses were not significant, but a lower *ASGR1* gene expression was observed in the subjects with cholesterol-lowering therapy than that in the patients without cholesterol-lowering therapy [Supplementary Figure 1, http://links.lww.com/CM9/A232].

Single factor linear regression showed log-transformed *ASGR1* gene expression was significantly associated with TC and LDL-C but not associated with the other lipids [Supplementary Table 2, http://links.lww.com/CM9/A232]. Multiple linear regression after adjusting for gender, clinical diagnoses and cholesterol-lowering therapy showed a pronounced association of *ASGR1* gene expression with TC and LDL-C levels among patients who aged <60 years [Table 1]. As for 1-SD increase in log-transformed *ASGR1* gene expression, TC increased 2.11 mmol/L (95% CI, 0.61–3.61) and LDL-C increased 1.77 mmol/L (95% CI, 0.65–2.90). When regarded bottom tertile as reference, TC levels increased 0.44 and 1.10 mmol/L from the middle to top tertile, respectively, LDL-C levels increased in parallel with the tertiles of

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Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000862

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Chinese Medical Journal 2020;133(12)
Received: 26-12-2019 **Edited by:** Li-Shao Guo

Table 1: Multivariable adjusted analysis of the associations between *ASGR1* gene expression and TC and LDL-C.

Items	<60 years		≥60 years		Total		
	Non-adjusted	Adjust I*	Non-adjusted	Adjust I*	Non-adjusted	Adjust I*	Adjust II†
TC							
Per-SD increase	1.88 (0.76, 3.00)	2.11 (0.61, 3.61)	–0.25 (–1.27, 0.76)	–0.27 (–1.50, 0.96)	0.99 (0.17, 1.82)	1.10 (0.14, 2.07)	1.30 (0.39, 2.21)
Tertiles							
Bottom tertile	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Middle tertile	0.41 (–0.37, 1.19)	0.44 (–0.52, 1.40)	–0.18 (–0.75, 0.40)	–0.21 (–0.85, 0.43)	0.15 (–0.36, 0.66)	0.12 (–0.41, 0.66)	0.12 (–0.39, 0.64)
Top tertile	1.01 (0.23, 1.80)	1.10 (0.04, 2.15)	0.24 (–0.34, 0.81)	0.30 (–0.39, 0.99)	0.66 (0.15, 1.17)	0.76 (0.16, 1.35)	0.74 (0.17, 1.30)
P trend	0.01	0.04	0.42	0.42	0.01	0.02	0.01
LDL-C							
Per-SD increase	1.50 (0.67, 2.34)	1.77 (0.65, 2.90)	0.01 (–0.66, 0.68)	0.24 (–0.58, 1.05)	0.89 (0.30, 1.47)	1.06 (0.37, 1.74)	1.19 (0.53, 1.84)
Tertiles							
Bottom tertile	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Middle tertile	0.35 (–0.23, 0.93)	0.34 (–0.38, 1.07)	0.11 (–0.27, 0.49)	0.12 (–0.30, 0.54)	0.26 (–0.11, 0.63)	0.23 (–0.16, 0.61)	0.22 (–0.16, 0.59)
Top tertile	0.86 (0.28, 1.44)	0.91 (0.12, 1.71)	0.23 (–0.15, 0.61)	0.40 (–0.05, 0.85)	0.57 (0.20, 0.94)	0.65 (0.22, 1.07)	0.63 (0.22, 1.04)
P trend	<0.01	0.03	0.24	0.09	<0.01	<0.01	<0.01

*Adjust I, adjusted for gender, clinical diagnoses and cholesterol-lowering therapy. †Adjust II, adjusted for age, gender, clinical diagnoses and cholesterol-lowering therapy. TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol.

ASGR1 gene expression (β were 0.34 and 0.91 for the middle and top tertile). However, the association was lost the significance among patients aged ≥60 years [Table 1]. Multivariate smoothing spline plots after adjusted for gender, clinical diagnosis, and cholesterol-lowering therapy demonstrated that plasma TC and LDL-C increased with the increasing expression of log-transformed *ASGR1* gene in a linear dose-response manner in patients aged <60 years but not in patients who aged ≥60 years [Supplementary Figure 2A and 2B, http://links.lww.com/CM9/A232].

ASGR1 knockout-mice and humans carrying LOF variants of *ASGR1* all displayed a much lower TC and LDL-C levels,[2,5] suggesting that *ASGR1* involves in cholesterol metabolism. Previous study all focused on the hepatic *ASGR1*. Particularly, this study focused on the monocyte *ASGR1* and showed that *ASGR1* gene expression in monocytes was positively associated with plasma TC and LDL-C levels in a dose-response manner in the patients aged <60 years, indicating that monocyte *ASGR1* may also play a role in cholesterol metabolism. However, the physiological function of *ASGR1* remains unclear.

Monocytes are the source of macrophages. Whether macrophages express functional *ASGR1* is important to clarify the roles of *ASGR1* in cholesterol metabolism. Genetic study showed that LOF variants of *ASGR1* has a larger effect on the risk of coronary artery disease than is anticipated by its effect on the reduced levels of cholesterol.[2] If the LOF variants resulted in a defective functional *ASGR1* both in hepatocyte and in monocytes (macrophages), these phenotypes may be reasonably interpreted. In addition, cholesterol-lowering drugs have a suppressive effect on *ASGR1* gene expression, whether the decreased *ASGR1* gene expression induced by cholesterol-lowering drugs involves in the cholesterol-lowering effect by these drugs deserved to be explored.

Of note, though these findings provide new insights that the monocytes *ASGR1* may play a role in deaminating TC and LDL-C levels, but whether *ASGR1* could be a target for lowering cholesterol, much work has to be done to clarify the molecular mechanism.

Funding

This work was supported by grants from the Natural Science Foundation of Hunan Province in China (Nos. 2017JJ3250 and 2019JJ40230), and the Science and Technology Plan Project of the Health commission of Hunan Province in China (Nos. B2019034 and B2019035).

Conflicts of interest

None.

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How to cite this article: Zhao X, Tang B, Shi ZH, Deng ZW, Deng Y, Tan LM, Jiang SL, Shu YL, Qiu CF. Asialoglycoprotein receptor 1 gene expression in peripheral blood monocytes associates with serum total cholesterol and low-density lipoprotein cholesterol levels. Chin Med J 2020;133:1505–1506. doi: 10.1097/CM9.0000000000000862