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 without cholesterol-lowering therapy than that in the patients with 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...
ASGR1 gene expression ($\beta$ were 0.34 and 0.91 for the middle and top tertile). However, the association was lost the significance among patients aged $\geq 60$ 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 $\geq 60$ 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 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.

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**Conflicts of interest**

None.

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

| Items          | <60 years | ≥60 years | Total |
|----------------|-----------|-----------|-------|
| TC Per-SD increase Tertiles | Non-adjusted | Adjust I† | Non-adjusted | Adjust I† | Non-adjusted | Adjust I† | Non-adjusted | Adjust I† |
| Bottom tertile | 0 (reference) | 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) | 0.24 (−0.34, 0.81) | 0.42 | 0.18 (−0.75, 0.40) | 0.21 (−0.85, 0.43) | 0.30 (−0.39, 0.99) | 0.42 |
| Top tertile    | 1.01 (0.23, 1.80) | 1.10 (0.04, 2.15) | 0.42 | 0.42 | 0.24 (−0.34, 0.81) | 0.30 (−0.39, 0.99) | 0.42 | 0.42 |
| P trend        | 0.01 | 0.04 | 0.24 | 0.03 | 0.01 | 0.02 | 0.01 | 0.01 |
| LDL-C Per-SD increase Tertiles | Non-adjusted | Adjust I† | Non-adjusted | Adjust I† | Non-adjusted | Adjust I† | Non-adjusted | Adjust I† |
| Bottom tertile | 0 (reference) | 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) | 0.24 | 0.12 (−0.30, 0.54) | 0.12 (−0.30, 0.54) | 0.40 (−0.05, 0.85) | 0.57 (0.20, 0.94) |
| Top tertile    | 0.86 (0.28, 1.44) | 0.91 (0.12, 1.71) | 0.23 (−0.15, 0.61) | 0.24 | 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 | <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.

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