Correspondence on Editorial regarding “Macrophage ATG16L1: potential candidate for MASH treatment”

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Dear Editor,

We very appreciate it to receive the insightful comments from Professor Junjie Yu on our publication, providing an editorial\(^1\) to summarize the major findings of our publication in the same issue.\(^2\) Regarding the body weight of macrophage *Atg16l1* knockout mice is significantly increased with less energy expenditure after high fat and high cholesterol diet (HFHCD) feeding compared to the control group, and as *Lyz2-Cre* is expressed in all macrophages, the contribution of macrophage ATG16L1 from other tissues such as white adipose tissue (WAT) in metabolic dysfunction-associated steatohepatitis (MASH) may need more investigation. The authors would provide more discuss to refine this concern.

Previous study has been reported that global or brown adipocyte-specific deletion of pink1, a key molecular for mitophagy, could suppress the energy expenditure of mice,\(^3\) indicating autophagy might account for body weight. Our study found that macrophages *Atg16l1* knockout increased the weight and liver weight of HFHCD feeding mice, there were significant difference of energy expenditure between the different groups of mice with HFHCD provision, indicating that energy expenditure may account for the difference of body weight or liver weight for macrophages *Atg16l1* knockout mice fed with HFHCD compared to the controls. Meanwhile, inflammation of visceral adipose tissues was decreased in macrophages *Atg16l1* knockout MASH mice as compared to floxed MASH mice. Moreover, we found that macrophage *Atg16l1* depletion promoted lipid loading in hepatocytes by aggravating inflammatory response, which may also account for more body weight and liver
weight gain in macrophage *Atg16l1* knockout mice than that in macrophage *Atg16l1* floxed mice fed with HFHCD.

As pointed out by Professor Yu, *Lyz2-Cre*-mediated conditional knockout affects all *Lyz2*+ cells. Therefore, macrophage ATG16L1 in other tissues, such as adipose tissue and the cardiovascular system, may regulate the progression of MASH through autophagy. Previous study has demonstrated that the role of autophagy in the differentiation of white adipose tissue was studied by deleting the autophagy-related 7 (*atg7*) gene from adipose tissue in mice. *Atg7* deletion results in a striking phenotype at the cellular, tissue and whole-organism levels. For example, adipose tissue deposits in the mutant mice are much smaller in mass than those observed in their wild-type counterparts and the knockout mice are noticeably slimmer than their wild-type littermates. The mutant mice also exhibit higher basal physical activity levels and an array of metabolic changes. These findings establish a new function for autophagy and provide a new model system for use in the search for treatments for obesity and diabetes.

Moreover, another study by Liu et al. demonstrates that macrophage-specific ATG5 deficiency exacerbates hepatic inflammation in MASH, while the level of inflammation in WAT shows no significant difference. This may be due to the unique histological and immunological characteristics of the liver. The study only used a 12-week HFD feeding protocol, so the role of macrophage ATG5 in WAT during the progression of MASH requires further investigation. Liao et al.'s study indicates that macrophage-specific ATG5 deficiency exacerbates atherosclerosis, possibly due to defective autophagy in macrophages decreasing their phagocytic


clearance capacity. Considering the differential roles of macrophage autophagy in tissues outside the liver, the tissue-specific role of macrophage ATG16L1 still requires further investigation.

To sum up, MASH might be tightly associated with other pathophysiologically changes affected by HFHCD, such as adipose tissue deposition, atherosclerosis, obesity and diabetes. Autophagy-related proteins might play an important role in these diseases, which needs further investigation in the future.

**Authors’ contributions**

Qi Wang, Qingfa Bu, Haoming Zhou and Ling Lu are responsible for manuscript preparation, concept synthesis and finalization. All the authors have read and approved the final manuscript.

**Acknowledgments**

This work was supported by grants from the National Natural Science Foundation of China (81971495, 82370668, 82071798), the CAMS Innovation Fund for Medical Sciences (No. 2019-I2M-5-035) and the Postgraduate Research & Practice Innovation Program of Jiangsu Province (KYCX24_2030).

**Conflicts of interest**

The authors have no conflicts to disclose.
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