Dear Editors

Thank you very much for your email with which you sent us the reviewers' comments on our paper. We also wish to take this opportunity to thank the reviewer for his constructive comments and valuable recommendations. The comments have been carefully taken into account and a new revised submission have been uploaded. We responded point by point to the comments.

Our responses are listed below:

Reviewer #1:

Comments 1-3: 1 Title: Appropriate. 2 Abstract: Well described in the manuscript. 3 Key words: Appropriate.

Answering: Thank you very much for your review.

Comments 4: Background: Please add references about review article related to similar issue.

Answering: We have added references about review article related to similar issue in the background.

We add "*Cluster of differentiation 36 a highly glycosylated 80kD membrane protein responsible for lipid transport and lipid sense [14]. The amino terminus of CD36 contains a domain that binds to fatty acids, low-density lipoprotein, and phosphatidylcholine. Lysine 164 and 166 are key sites [15]. RAGE is a multi-ligand receptor. These ligands bind to the extracellular V-C1-C2 domains of RAGE and mediate pathogenic signaling in a variety of diseases [16]. RAGE is abnormally elevated under high-fat conditions. RAGE-related signals further aggravate lipid metabolism disorders and lipid accumulation [17].* (Introduction, Paragraph 3)"

Reference 14. Li Y, Huang X, Yang G, Xu K, Yin Y, Brecchia G, Yin J. CD36 favours fat sensing and transport to govern lipid metabolism. Prog Lipid Res 2022;88:101193 [DOI: 10.1016/j.plipres.2022.101193]

Reference 15. Pepino MY, Kuda O, Samovski D, Abumrad NA. Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. Annu Rev

Nutr 2014;34:281-303 [DOI: 10.1146/annurev-nutr-071812-161220]

Reference 16. Egaña-Gorroño L, López-Díez R, Yepuri G, Ramirez LS, Reverdatto S, Gugger PF, Shekhtman A, Ramasamy R, Schmidt AM. Receptor for Advanced Glycation End Products (RAGE) and Mechanisms and Therapeutic Opportunities in Diabetes and Cardiovascular Disease: Insights From Human Subjects and Animal Models. Front Cardiovasc Med 2020;7:37 [DOI: 10.3389/fcvm.2020.00037]

Reference 17. Asadipooya K, Lankarani KB, Raj R, Kalantarhormozi M. RAGE is a Potential Cause of Onset and Progression of Nonalcoholic Fatty Liver Disease. Int J Endocrinol 2019;2019:2151302 [DOI: 10.1155/2019/2151302]

We add "*Lipid metabolism in macrophages includes three processes: lipid uptake, esterification and efflux [22]. When these processes are disturbed, macrophages will form lipid-rich foam cells.* (Introduction, Paragraph 4)"

Reference 22. Maguire EM, Pearce SWA, Xiao Q. Foam cell formation: A new target for fighting atherosclerosis and cardiovascular disease. Vascul Pharmacol 2019;112:54-71 [DOI: 10.1016/j.vph.2018.08.002]

Comments 5-6: 5 Methods: Appropriate. 6 Results: Appropriate.

Answering: Thank you very much for your review.

Comments 7: Discussion: I am not familiar the hypothesis proposed in this study. The authors should clarify this concern for discussion.

Answering: We have added the hypothesis of this study in the Discussion section.

We added "*Previous literatures have confirmed that CD36 and RAGE are closely related to lipid metabolism. So, we speculate that CD36 and RAGE may also be involved in CML-promoted lipid uptake of macrophages.* (*Discussion, paragraph 1*)" in the Discussion section.

Comments 8: Illustrations and tables: I am not familiar in vivo model. Please introduce commonly used illustrations and tables for predictive model. Does any

vitro model involve the similar topic?

Answering: Thank you very much for your review. In this study, in order to verify the binding of CD36 to CML and the binding of RAGE to CML, and then to compare the affinity of CML to CD36 and to RAGE, we chose to use a cell model and a cell-free system of radioactive receptor ligand experiments. There is currently no suitable in vivo experimental model for exploring receptor-ligand affinity.

In addition, we also used neutralizing antibodies to verify the lipid uptake ability of macrophages after blocking CD36 or RAGE. To show the lipid uptake of macrophages more intuitively, we used an in vitro model. In vivo lipid uptake by macrophages can be reflected by animal models of some diseases. Detection of atherosclerosis in macrophage-specific CD36 or RAGE knockout ApoE-deficient mice can reflect lipid accumulation in macrophages. In addition, the use of bone marrow transplantation model can also reflect the effect of CD36 and RAGE on CML-induced macrophage lipid uptake.

Our study is original and innovative, so there are no other studies and in vitro models that are similar to our topic. We used cell model, receptor-ligand cell-free system and molecular docking simulation to verify the interaction of CML with CD36 and RAGE, and these results can fully support the conclusion.

Comments 9: Biostatistics: Does the manuscript examined by experienced biostatistics? ANOVA's assumption satisfied for this data?

Answering: Thank you very much for your review. Yes, our statistics are examined by experienced biostatistics。The statistical methods of this study were reviewed by a member of biomedical statistic service from the Department of Central Laboratory. A biostatistics statement was uploaded to the submission system. We used one-way ANOVA to compare the differences between CML + IgG group, CML + Anti-CD36 group and CML + Anti-RAGE group in Figure 4.

Comments 10: Units: Does the manuscript meet the requirements of use of international system of units?

Answering: Yes, we have revised the unit to meet the requirements of the international unit system.

Comments 11: References: Please cite appropriately the latest, important and authoritative references in the introduction and discussion sections.

Answering: We added 6 the latest, important and authoritative references in the introduction and discussion section. The references are:

5. Schalkwijk CG, Micali LR, Wouters K. Advanced glycation endproducts in diabetes-related macrovascular complications: focus on methylglyoxal. Trends Endocrinol Metab 2023;34(1):49-60 [DOI: 10.1016/j.tem.2022.11.004]

10. Jia W, Guo A, Zhang R, Shi L. Mechanism of natural antioxidants regulating advanced glycosylation end products of Maillard reaction. Food Chem 2023;404(Pt A):134541 [DOI: 10.1016/j.foodchem.2022.134541]

19. Xu Z, Li X, Ding Z, Zhang Y, Peng Z, Yang X, Cao W, Du R. LRPPRC inhibits autophagy and promotes foam cell formation in atherosclerosis. FEBS J 2022;289(23):7545-7560 [DOI: doi: 10.1111/febs.16567]

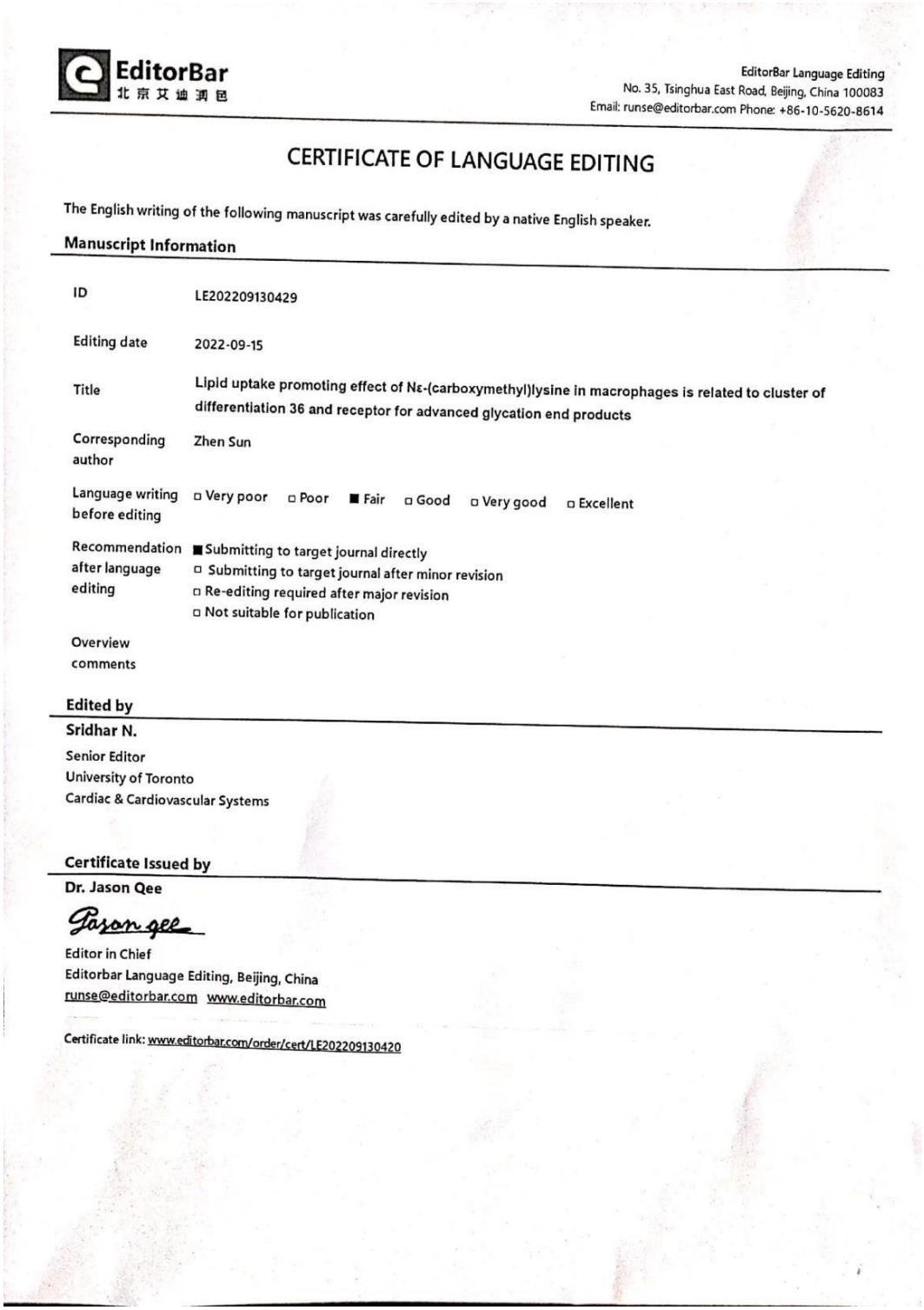
29. Liang B, Zhou Z, Yang Z, Liu J, Zhang L, He J, Li H, Huang Y, Yang Q, Xian S, Wang L. AGEs-RAGE axis mediates myocardial fibrosis via activation of cardiac fibroblasts induced by autophagy in heart failure. Exp Physiol 2022;107(8):879-91 [DOI: 10.1113/EP090042]

40. Singh S, Siva BV, Ravichandiran V. Advanced Glycation End Products: key player of the pathogenesis of atherosclerosis. Glycoconj J 2022;39(4):547-63 [DOI: 10.1007/s10719-022-10063-x]

46. Yu XH, Tang CK. ABCA1, ABCG1, and Cholesterol Homeostasis. Adv Exp Med Biol 2022;1377:95-107 [DOI: 10.1007/978-981-19-1592-5_7]

Comments 12: Quality of manuscript organization and presentation: Please provide English editing certificate.

Answering: Our manuscript has been revised by native speakers of English. The editing certificate is shown below.



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CERTIFICATE OF LANGUAGE EDITING

The English writing of the following manuscript was carefully edited by a native English speaker.

Manuscript Information

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Title	Lipid uptake promoting effect of Nε-(carboxymethyl)lysine in macrophages is related to cluster of differentiation 36 and receptor for advanced glycation end products
Corresponding author	Zhen Sun
Language writing before editing	□ Very poor □ Poor ■ Fair □ Good □ Very good □ Excellent
Recommendation after language editing	■ Submitting to target journal directly □ Submitting to target journal after minor revision □ Re-editing required after major revision □ Not suitable for publication
Overview comments	

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Comments 13: Research methods and reporting: Please provide appropriate research methods and reporting. Authors should have prepared their manuscripts according to manuscript type and the appropriate categories, as follows: (1) CARE Checklist (2013) - Case report; (2) CONSORT 2010 Statement - Clinical Trials study,

Prospective study, Randomized Controlled trial, Randomized Clinical trial; (3) PRISMA 2009 Checklist - Evidence-Based Medicine, Systematic review, Meta-Analysis; (4) STROBE Statement - Case Control study, Observational study, Retrospective Cohort study; and (5) The ARRIVE Guidelines - Basic study.

Answering: Thank you very much for your review. We have provided appropriate research methods and reporting

Comments 14: Ethics statements: Please provide appropriate ethics approval.

Answering: Thank you very much for your review. Our study did not report in vivo experiments or clinical trials on humans or animals, so no ethical approval was required.