Exercise during pregnancy may have more benefits than we thought

Lingdi Wang,* and Lu Zhu †‡*

*Department of Physiology and Pathophysiology, Tianjin Key Laboratory of Cell Homeostasis and Major Diseases, School of Basic Medical Sciences, Tianjin Medical University, Tianjin 300070, China
†Department of Pharmacology, Tianjin Key Laboratory of Inflammatory Biology, The Province and Ministry Co-Sponsored Collaborative Innovation Center for Medical Epigenetics, School of Basic Medical Sciences, Tianjin Medical University, Tianjin 300070, China

Maternal obesity is a worldwide public health concern that may affect the health of both mother and offspring throughout their lifespan. In US and European countries, it was reported that the prevalence of maternal obesity had been 7–25%.1,2 Children born to obese mothers are at increased risk of metabolic disease and neuropsychiatric and cognitive disorders.3 Human and animal studies have shown that maternal interventions including nutrients intervention and exercise may reduce the adverse influence on the offspring by decreasing weight gain, cardiovascular disorders, and improving glucose tolerance.2 Exercise intervention in maternal obesity could reduce bodyweight and circulating levels of triglyceride and improve insulin sensitivity in liver and skeletal muscle. However, the underlying molecular mechanism remains elusive. In this issue of eBioMedicine, Son and Chae et al. demonstrated that maternal exercise improves metabolic homeostasis and muscle-based thermogenesis of the fetal and offspring by inducing the exerkine apelin function in fetal muscle and activating AMPK/CaMKK2 axis.4

Apelin, a peptide with 13 to 36 amino acids in length, is secreted by adipose tissue, skeletal muscle and other tissues. It is an endogenous ligand for the G-protein-coupled receptor APJ to activate Goq and Goq i.5 Emerging evidence have shown that apelin is an exercise-induced myokine that can enhance muscle cell metabolism6 and has metabolic beneficial effects by reducing obesity-related insulin resistance.7,8 Apelin has been shown to be induced by exercise in both maternal and fetal circulations, and function on fetal BAT development and offspring metabolic beneficial effects.9 Owing to the reduction of brown fat mass during ageing and the limited effect of brown fat on whole body metabolic homeostasis, exploration of apelin on fetal development and metabolic regulation is appreciated. Son and Chae et al. found maternal obesity downregulated fetal skeletal muscle temperature and the expression of thermogenic markers, which was recovered by maternal exercise. Moreover, the beneficial effects of maternal exercise could be persistent in offspring challenged with HFD to maintain the skeletal muscle thermogenesis and metabolic homeostasis. Interestingly, the authors found that maternal exercise directly induced the myokine apelin in fetal muscle, which played a critical role on fetal muscle thermogenesis. Meanwhile, administration of apelin during pregnancy mimicked maternal exercise and endowed the fetal skeletal muscle thermogenic capacity. CaMKK2 (calcium/calmodulin-dependent protein kinase kinase 2), as a classic downstream molecule of Goq i, was activated in the fetal muscle from obesity mothers and restored by either exercise or apelin administration, indicating that apelin mediates maternal exercise induced fetal muscle thermogenesis. Thus, apelin has clinical potential in improving long-term metabolic health of offspring born to mothers with obesity.

Apelin has been reported to activate AMPK in multiple organs as an underlying mechanic mediator in regulating metabolic pathways.10 To confirm the effect of apelin on fetal muscle thermogenesis, Son and Chae et al. showed impaired thermogenic capability due to decreased expression of thermogenic gene expression (Sarcolipin and UCP3) in APJ deficient myogenic cells. Furthermore, APJ deficient mice had lower average surface temperature, indicating the role of apelin/APJ in thermogenesis, consistent with previous finding of the function of apelin in fetal BAT.9 However, how much does the skeletal muscle contribute to thermogenesis? A tissue specific APJ knockout mouse model will be needed to answer this question. AMPKα ablation diminished the beneficial effect of apelin on fetal muscle thermogenesis as well as the expression of mitochondrial biogenetic and thermogenic genes. Taken together, these results indicate that maternal exercise activates Goq i /calcium signaling as well as apelin-APJ-AMPK axis to enhance mitochondrial biogenesis and thermogenesis in fetal muscle that impaired due to maternal obesity.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2022.103842
*Corresponding author.
E-mail address: zhulu@tmu.edu.cn (L. Zhu).
© 2022 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
In addition, the long-term effects of maternal exercise/apelin administration on sarcolipin and UCP3 activation in offspring muscle protect them from diet-induced obesity and metabolic disorders.

In summary, this study demonstrates a muscle-based thermogenic function of apelin mediating maternal exercise to provide metabolic benefits to offspring from obesity mothers through apelin-APJ-AMPK axis. Considering the general expression of APJ in major metabolic related organs such as liver, skeletal muscle and adipose tissues, apelin may possess function in other organs to benefit offspring of obese mothers in long term. In addition, the authors also identified apelin significantly induces muscle mitochondrial biogenesis, suggesting that the beneficial effects of apelin on metabolism may have unrevealed mechanisms independent of thermogenesis.

Contributors
Lingdi Wang and Lu Zhu wrote and revised the manuscript.

Declaration of interests
None.

References
1. Mitanchez D, Chavatte-Palmer P. Review shows that maternal obesity induces serious adverse neonatal effects and is associated with childhood obesity in their offspring. *Acta Paediatr*. 2018;107:1156–1165.
2. Shrestha A, Prowak M, Berlandi-Short VM, Garay J, Ramalingam L. Maternal obesity: a focus on maternal interventions to improve health of offspring. *Front Cardiovasc Med*. 2021;8:696812.
3. Melchor I, Burgos J, Del Campo A, Aiartzagüena A, Gutierrez J, Melchor JC. Effect of maternal obesity on pregnancy outcomes in women delivering singleton babies: a historical cohort study. *J Perinat Med*. 2019;47:625–630.
4. Son JS, Chae SA, Zhao L, et al. Maternal exercise intergenerationally drives muscle-based thermogenesis via activation of apelin-AMPK signaling. *eBioMedicine*. 2022;76:103842.
5. Yue P, Jin H, Xu S, et al. Apelin decreases lipolysis via G(q), G(i), and AMPK-dependent mechanisms. *Endocrinology*. 2011;152:59–68.
6. Vinel C, Lukjanenko L, Batut A, et al. The exerkine apelin reverses age-associated sarcopenia. *Nat Med*. 2018;24:1360–1371.
7. Yue P, Jin H, Aillaud M, et al. Apelin is necessary for the maintenance of insulin sensitivity. *Am J Physiol Endocrinol Metab*. 2010;298:E59–E67.
8. Dray C, Debard C, Jager J, et al. Apelin and APJ regulation in adipose tissue and skeletal muscle of type 2 diabetic mice and humans. *Am J Physiol Endocrinol Metab*. 2010;298:E1161–E1169.
9. Son JS, Zhao L, Chen Y, et al. Maternal exercise via exerkine apelin enhances brown adipogenesis and prevents metabolic dysfunction in offspring mice. *Sci Adv*. 2020;6:eaba2530.
10. Lou ZL, Zhang CX, Li JF, et al. Apelin/APJ-manipulated CaMKK/AMPK/GSKbeta signaling works as an endogenous counterinjury mechanism in promoting the vitality of random-pattern skin flaps. *Oxid Med Cell Longev*. 2021;2021:886098.