

Comment on: “Fibroblast growth factor 21 controls mitophagy and muscle mass” by Oost et al.

We have read with great interest the article by Oost *et al.*, in which the authors demonstrated that fibroblast growth factor 21 (FGF21) induces muscle atrophy and weakness via up-regulation of mitophagy protein Bnip3.¹ Although the study design and conclusions are reasonable, we have the following concerns that need to be addressed.

FGF21, a member of the FGF family, consists of 209 amino acids and is physiologically decomposed into 181 amino acids for maturity, which is mainly secreted by and acts on target tissues such as liver, fat, pancreas, and muscle.² Importantly, there are still great divergences in the physiologic role and mechanism of FGF21. Similarly, Liu and colleagues also observed that FGF21 facilitated muscle mass loss, while the muscle mass loss was mediated by peroxisome proliferators-activated receptor- γ coactivator-1 α (PGC-1 α) caused transition of myofibrillar types.³ Moreover, much different from that FGF21 induces mitophagy in Oost's study,¹ Ji *et al.* reported that mitochondrial respiratory chain deficiency in skeletal muscle could upregulate the FGF21 expression, which compensatively enhanced mitochondrial function via the mammalian target of rapamycin (mTOR)-Yin Yang 1 (YY1)-PGC1 α -dependent pathway.⁴ In addition, increasing evidence revealed that increasing the muscle-derived FGF21 level would enhance glucose uptake, fatty acid oxidation and insulin sensitivity in skeletal muscle, thereby improving lipid metabolism and reducing body weight.^{5,6} It therefore seems that FGF21 has multiple biological functions and metabolic pathways, thus leading to different outcomes. We totally agree with the conclusion that FGF21 could induce muscle atrophy and weakness,¹ while the role of classical FGF21 signalling pathway in muscle atrophy and weakness cannot be ignored.

The FGF21 signalling pathway is mediated by FGF receptor (FGFR) in the cell membrane, requiring the participation of the co-receptor β -Klotho. The N-terminus of FGF21 binds to FGFR while the C-terminus binds to β -Klotho to form a complex, which phosphorylates the receptor and activates downstream signalling pathways, thereby exerting physiologic effects.⁷ Similar to FGF21, β -Klotho is mainly expressed in liver, fat, pancreas, and muscle tissues,⁸ which suggests that

β -Klotho is necessary for FGF21 to exert physiologic functions. As an anti-aging protein, β -Klotho could retard the aging process through a wide variety of mechanisms, such as antioxidation, antisenescence, antiautophagy, and regulation of many signalling pathways (including insulin-like growth factor and Wnt).⁸ Furthermore, β -Klotho plays an important role in the progression of aging-related diseases such as vascular diseases and neurodegeneration.^{9,10} It is well known that aging is always accompanied by muscle atrophy and weakness. Thus, we speculate that extremely elevated FGF21 level may cause a relative deficiency in the levels of β -Klotho, which would weaken the anti-aging effect, thus leading to muscle mass loss; in other words, muscle atrophy may be attributed to the imbalance in FGF21- β -Klotho signalling caused by relative up-regulation of FGF21. In addition, a cross-sectional study enrolling 184 healthy individuals indicated that circulating FGF21 levels were increased with aging independently of bone mineral density and fat mass,¹¹ which indirectly supported a causal linkage between FGF21, β -Klotho, and muscle atrophy caused by aging.

In conclusion, the mechanism underlying muscle atrophy and weakness may be related to the elevated level of FGF21 and relative low level of β -Klotho. Further detailed studies on the role of FGF21- β -Klotho signalling in muscle atrophy and weakness are greatly needed.

Author Contributions

All the authors conceived the scientific ideas, critically reviewed, approved the final version.

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