

## **Second round of revisions, reviewer comments:**

Thank you for taking the time to address all the comments from the reviewer. Your hard work is appreciated and acknowledged!

This review, titled 'The role and underlying mechanisms of irisin in exercise-mediated', has been since revised by the authors. The manuscript now reads very well and is a great summary of the work.

Although prose is a little repetitive at times, it does flow well and tells a logical story. Subsections are helpful in jumping to the information you need, and are ordered effectively.

I do have a few comments to add, (please see major and minor comments), however these are easily rectifiable.

### **Major points:**

As so much work has gone into making wonderful tables and figures, please reference them more in the main body of text. Will help direct the reader and provide more useful information.

Figure 1 says reference is taken from another source. Please check with editor / journal that no copyright rules are being broken (has permission been asked?).

### **Minor points:**

29: 'Cardiovascular diseases (CVDs) is a global burden of disease', first few words don't gel (grammar issue).

Try: 'Cardiovascular diseases (CVDs) are a clinical burden globally'

30: maybe worthwhile mentioning average age of study participants i.e., 'median age of 54.4'

35: intervention, not interventions

54: 'skeletal muscle fiber type transformation', do you mean 'switching' here?

71: check reference (typographical)

77-78: 'important crucial' delete one of these words (or add 'and' between the two)

80: may be interesting to include that ADAM10 cleaved FNDC5 in skeletal muscle (<https://doi.org/10.1186/s13578-020-00413-3>)

82-84: 'Both FNDC5 and irisin were first discovered in the skeletal muscle and serum of humans, rabbits, and mice (Hofmann et al. 2014).' potentially move to previous section of discovery?

125: already abbreviated myocardial infarction, so just use MI here

139: CVDs are highly correlated...

175: delete support (sentence doesn't make sense)

176: 'abnormal serum irisin levels can potentially be used'

210: remove full stop before Pekkala reference

210-212: Interesting point, I'm glad you included this. Are there any examples in humans whereby exercise was counter-intuitive to the beneficial release or effects of irisin? Or is this something only seen in mouse models?

From table 1 it seems apparent that in humans, blood irisin increases after all forms of exercise. Maybe worthwhile to make a note of this here

212: rephrase, i.e., Table 1 provides ....

220: grammar: effects

223: Be consistent with subscript for VO<sub>2</sub>max throughout manuscript

233: check formatting of 'PGC-1 $\alpha$ '

234: remove full stop before Luo reference

235: Be consistent with subscript for VO<sub>2</sub>max throughout manuscript

249: higher expression compared to what? Individual muscle weight? Potentially make clearer for reader

250: 'several studies have shown that exercise can promote CVD treatment., maybe can be worded better, e.g., 'several studies have shown that exercise can ameliorate CVD by ...'

256: 'In rats with...'

260: The autophagy component of this pathway (irisin/FNDC5-PINK1/Parkin-LC3/P62) can be deleterious to muscle if over activated, maybe worthwhile mentioning if authors of this paper saw it was activated to a beneficial level to improve regulatory mechanisms

264/273: Maybe worthwhile mentioning that AKT signalling is associated with muscle growth / hypertrophy in skeletal and cardiac muscle, may help to show why this pathway is important

290: double full stop noticed

293-294: sentence doesn't make sense? Try 'irisin, as it was shown that circulating levels were selectively boosted in subjects'

311: space required before 'were employed'