Review of: "Small extracellular vesicles from young mice prevent frailty, improve healthspan and decrease epigenetic age in old mice"

Yang Wang

Potential competing interests: The author(s) declared that no potential competing interests exist.

The *bioRxiv*'s article entitled "*Small extracellular vesicles from young mice prevent frailty, improve healthspan and decrease epigenetic age in old mice*" by Consuelo Borras et al. reports that sEVs secreted from young adipose-derived stem cells (ADSCs-sEVs) improve several impaired performances and functions in aged mice. Moreover, ADSC-sEVs are shown to be beneficial to kidney and muscle as well as decrease oxidative stress, inflammation, and senescent markers. The epigenetic age and metabolome are both rejuvenated by ADSC-sEVs treatment. Furthermore, they propose that several miRNAs in ADSC-sEVs might be responsible for the therapeutic capacity.

This article is well written and provides intriguing results of the ADSC-sEVs function from multiple aspects. Following are some major concerns:

1. The title of this article makes it confusing for the readers to understand. As many organs and tissues in mice secret sEVs, the authors should point out the specific source of sEVs used in this article. "*Small extracellular vesicles from young adipose-derived stem cells prevent frailty, improve healthspan and decrease epigenetic age in old mice*" could be better.
2. In this study, an *in vitro* model of senescence in muscle progenitor cells was carried out to examine the anti-aging effect of ADSC-sEVs. As muscle progenitor cells play vital role in musculoskeletal system through myogenic differentiation, why didn't the authors examine the myogenic differentiation potential of senescent C2C12 cells before and after ADSC-sEVs treatment?
3. The authors outlined 6 miRNAs in ADSC-sEVs and predicted their possible targeted genes. But that's not enough for clarifying the underlying mechanisms of ADSC-sEVs. The authors should first verify the expression level of these miRNAs in ADSC-sEVs by miRNA-specific quantitative real-time PCR and secondly knockdown these miRNA one by one to investigate which one or ones could modulate the aging process and lifespan.