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Estradiol signaling mediates gender difference in visceral adiposity via autophagy

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Abstract

Excessive adiposity (particularly visceral fat mass) increases the risks of developing metabolic syndrome. Women have lower deposit of visceral fat than men, and this pattern becomes diminished postmenopausally, but the underlying mechanism remains largely unknown. Here, we show that the gender difference in visceral fat distribution is controlled by an estradiol–autophagy axis. In C57BL/6J and wild-type control mice, a higher visceral fat mass was detected in the males than in the females, which was associated with lower expression of estrogen receptor α (ER α) and more active autophagy in males vs. females. However, deletion of ER α normalized autophagy activity and abolished the gender difference in visceral adiposity. In line with the adiposity-reducing effect of the ER α –autophagy axis, we found that downregulation of ER α and increased autophagy activity were required for adipogenesis, while induction of estradiol signaling dampened autophagy and drastically prevented adipogenesis. Mechanistically, the estradiol–ER α signaling activated mTOR, which phosphorylated and inhibited ULK1, thereby suppressing autophagy and adipogenesis. Together, our study suggests that the lower visceral adiposity in the females (vs. the males) arises from a more active estradiol–ER α signaling, which tunes down autophagy and adipogenesis.

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Electronic supplementary material

supplemental data - https://static-content.springer.com/esm/art%3A10.1038%2Fs41419-018-0372-9/MediaObjects/41419_2018_372_MOESM1_ESM.docx

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