Does skeletal muscle stop ageing physiologically?

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Ageing is associated with an exponential increase in mortality, but paradoxically, in many organisms mortality rates decline late in life, a phenomenon known as late-life mortality deceleration. How late-life differs to ageing physiologically, and if mortality deceleration implies that ageing stops or reverses at a specific point of an organism's life remains unknown. Therefore, to examine the cellular and metabolic basis for mortality deceleration, we used a novel model of ageing – that of the African killifish, an extremely short-lived vertebrate that displays mortality deceleration. Using skeletal muscle, where the stereotypic hallmarks of ageing are well characterized, we highlight that ageing and late-life phases are physiologically distinct. Using a systems metabolomics approach, we demonstrate that during ageing there is a striking depletion of triglycerides, mimicking a state of calorie restriction, which triggers mitohormesis, a reactive oxygen species mediated stress resistance mechanism. This improves lipid and mitochondrial metabolism, subsequently maintaining nutrient homeostasis during late-life and driving mortality deceleration. Our results not only provide evidence of mitohormesis in regulating lifespan in vertebrates that naturally live-longer, but they also collectively show that the metabolic hallmarks of ageing are reversible.

Keywords: sarcopenia, skeletal muscle, killifish. mitohormesis, longevity.