

Abstract:

Diet has a profound influence on tissue regeneration and aging in diverse organisms. Low caloric states and intermittent fasting, for example, have beneficial effects on organismal health and slow down the progressive loss of tissue function observed in old age. Whether mammalian adult stem and progenitor cells respond to fasting and, if so, how these responses improve tissue regeneration in old age is unclear. Here, we find that in old mice intestinal stem cell (ISC) numbers are reduced and that aged ISCs are less functional in an organoid assay, suggesting that cell autonomous changes contribute to intestinal stem cell aging. Interestingly, a short-term fasting regimen augments ISC function in aged mice by inducing a peroxisome proliferator-activated receptor delta (PPAR- δ) driven fatty acid oxidation (FAO) program, and synthetic activation of this program mimics many of the effects of short-term fasting. Genetic disruption of *Cpt1a*, which encodes the rate-limiting step in FAO, abrogated the ISC-enhancing effects of short-term fasting. These observations provide a potential dietary and metabolic strategy for improving intestinal regeneration in old age.