Can we age well?

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Ageing is a malleable biological process. Research over the last two decades has revealed how several genetic, nutritional and pharmaceutical interventions can delay or accelerate ageing, together with many age-related pathologies and disorders. Many of these interventions act on nutrient sensing pathways that link macronutrient and energy intake with cellular mechanisms including mitochondrial function, translation, autophagy and oxidative stress. The main nutrient sensing pathways involve sirtuins, mTOR, AMPK and insulin/IGF-1/GH. In a study of 25 diets varying in macronutrients and energy content in mice, we found that diets that were low in protein and high in carbohydrate were associated with reduced mTOR phosphorylation, increased lifespan and improved latelife cardiometabolic health. Such diets were also associated with a younger profile of T and B cell subsets but reduced measures of reproductive health. These results support the concept of evolutionary life history trade offs between ageing and reproduction, in this case mediated by dietary macronutrients. In another study in a Cockayne progeria mouse model, we found that high fat diets are associated with reversal of the ageing phenotype. In this model, the mechanism involved increased ketones activating the sirtuin pathway. Pharmaceutical agents that act on these nutrient sensing pathways (resveratrol, metformin, rapamycin) increase lifespan without dietary manipulation in animal models, and are being explored for human intervention.