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Editorial

Restricting the Possibilities for Mechanisms of Calorie Restriction

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Calubag M.F., et al. (2023). FGF21 Has a Sex-Specific Role in Calorie-Restriction-Induced Beiging of White Adipose Tissue in Mice, AgingBio, 1, doi: 10.59368/agingbio.20230002.

Calorie restriction (CR; a reduction in calorie intake without malnutrition) is a paradigm for lifespan extension by a lifestyle intervention. Although long-term CR in humans is extremely challenging and not generally recommended, more recent studies have presented evidence that more modest dietary interventions can still reap the benefits of CR. Time restricted feeding, intermittent fasting, and a fasting-mimicking diet are all feasible and potentially beneficial dietary interventions in humans that exert their effects, in part, by acute periods of CR. Accordingly, it is important to fully understand the molecular mechanisms underpinning the benefits of CR. Although inhibition of nutrient sensors, such as mechanistic target of rapamycin complex 1 (mTORC1), are at least in part responsible, the mechanisms are not fully understood.

Fibroblast growth factor 21 (FGF21) has been proposed as one mediator of the benefits of CR. FGF21 is induced by CR, and its ectopic expression extends longevity and induces metabolic reprogramming and signaling events that mimic CR. Considering these previous findings, Calubag et al set to ask whether FGF21 is required for CR-induced improvements in body composition, glucose homeostasis, and energy balance. The authors find that whole body inactivation of FGF21, by way of *Fgf21*$^{-/-}$ mice, does not abolish the effects of CR on body composition or energy balance and has only minor effects on glucose regulation. FGF21 is important for CR-induced beiging of inguinal white adipose tissue in males, but not females. Of note, the authors did not test an effect of FGF21 on lifespan extension itself.

This study eliminates FGF21 as candidate sole driver of the benefits of CR, thereby restricting the remaining possibilities. In fact, given the complexity of dietary sensing mechanisms and the pleiotropic effects of CR, it is perhaps not surprising that a single gene, *Fgf21*, is not required for many of the benefits of CR. FGF21 is likely involved in effects of CR, but is redundant with other pathways and effectors. Hence, these studies will now focus efforts on mechanisms that likely cooperate with FGF21, and potentially combinatorial interventions to promote healthspan and lifespan. In another interesting and important twist, this study further underscores the important of sex dimorphic effects when evaluating healthy aging interventions.

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