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Commentary

Dietary protein and age-dependent female fertility: FGF21 trumps mTORC1

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In Western societies, women are tending to choose to have children later in their life [1]. As ageing reduces fertility [1] it is therefore important to understand how life-history leading up to the time of choice to reproduce influences reproductive potential. Given that nutrition profoundly influences reproduction [2], and nutrition can be controlled by the individual, it is of interest to know how and which foods might preserve fertility in later life. Concerning nutrition, even though total caloric intake can determine female reproductive potential, it is increasingly clear that balance of the dietary intake of the three macronutrients, namely protein (P), carbohydrate (C) and fat (F), has a profound impact on reproductive function [2]. In particular, in a study of mice confined to diets varying in macronutrient ratios from weaning, both oestrous cycling and ovulation rate were highest with low P:C ratio diets at middle-age [3]. Similarly, in the paper by Zhou and colleagues recently published in *EBioMedicine* [4], a similar relationship between dietary protein and reproductive potential was found. In particular, female mice were confined to diets varying in P:C ratio, and sacrificed at diestrous at selected ages up to 12 months of age. In this study, reproductive potential, as assessed by ovarian primordial follicle reserve, was maximised by a low P:C ratio [4]. This is important, as the activation of quiescent primordial follicles is the first step of folliculogenesis, and their activation must be regulated to prevent premature exhaustion of the ovarian follicular reserve. A highlight of this study was the conduct of a breeding assay, which demonstrated that the percentage of one-year old dams giving births to litters was higher when previously fed low P:C diets [4].

So, what could be the mechanism(s), by which the dietary P:C ratio influences fertility and ovarian reserve? Although there are cellular mechanisms which influence responses to amino acids such as mTORC1 and GCN2, the peptide hormone FGF21 has recently emerged as an endocrine signal of dietary protein supply and systemic amino acid balance [5,6]. Indeed, FGF21 was noted to be higher, and ovarian mTORC1 to be lower, on the low P:C ratio diets [4]. However, when liver-restricted FGF21 knockout mice were studied, these mice were refractory to the effects of the low P:C ratio diet on fertility; and this was independent of ovarian mTORC1 signalling [7]. This is similar to prior findings that disconnected reduced tissue mTORC1 signalling to FGF21 and associated improvements of metabolic health during dietary protein restriction [7]. Whether FGF21 also confers the effects of dietary protein restriction on breeding performance is yet to be determined and is a clear direction for future studies. In any case, FGF21 does not appear to have a direct effect on ovarian follicle reserve [4] which is in alignment with recent evidence that FGF21 does not have a direct role in fertility by rather may impact fertility by affecting energy balance [8]. It was shown that FGF21 can affect ovarian reserve at least partially via adiponectin [4]. However, the metabolic actions of FGF21 are not mediated by adiponectin [9], and thus may be due to direct actions of adiponectin on ovarian cycling [4].

While the results of these studies could be interpreted to suggest that one could eat a diet low in protein to preserve fertility in ageing there are certain considerations that should not be ignored. Firstly, the dosing of protein restriction needed for preservation of fertility with age would need to be empirically determined, and whether it affects other aspects of development and somatic function; especially in primates. Also, dietary protein is known to also influence male fertility [3], so breeding assays and the role of FGF21 would need to be conducted to properly assess male fertility. Lastly, dietary protein restriction can affect interuterine growth and can affect offspring traits in terms of health [10]. Thus, one would need to consider the 'life-timing' of when to adhere to certain diets to optimise certain traits without compromising one's own health, as well the health of one's offspring.

Author disclosure

The author declares no conflicts of interest. The author apologises to colleagues whose work was not cited due to reference limitations.

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