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Physiology: An atypical switch for metabolism and ageing

Colin Selman and

Institute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow,
Glasgow G12 8QQ, UK

Dominic J. Withers

MRC London Institute of Medical Sciences, Imperial College London, London W12 0NN, UK

Abstract

The enzyme S6K1 enzyme phosphorylates the enzyme glutamyl-prolyl t-RNA synthetase to modulate metabolic activity and lifespan, revealing an atypical role for this synthetase as a target of a key metabolic signalling pathway.

The observation a century ago that dietary restriction extends longevity in rodents¹ led to the realization that metabolism and ageing share a close relationship. We now know that biological signalling networks that respond to nutrients and hormones regulate lifespan in a highly evolutionarily conserved manner². The protein kinase S6K1 is a key target of one such network, the mechanistic target of rapamycin (mTOR) signalling pathway, but the mechanisms downstream of this kinase have remained obscure. In a paper online in *Nature*, Asif *et al.*³ show that another enzyme, glutamyl-prolyl t-RNA synthetase (EPRS), is a direct target of S6K1, and has a previously unidentified role in fat metabolism and lifespan.

Enzymes in the EPRS family have a key role in decoding the genome, catalysing the binding of amino acids to their relevant transfer RNAs for transport to the cell's translational apparatus. However, this family can also fulfil many atypical roles⁴. The group that performed the current study previously showed⁵ *in vitro* that EPRS can mediate the assembly of a protein complex that attenuates translation of certain inflammation-associated RNAs. This function depends on EPRS phosphorylation at one amino-acid residue, serine 999 (Ser⁹⁹⁹), but the identity of the kinase that catalyses this phosphorylation was unclear.

In the current study, Arif *et al.* identified S6K1 as this enzyme. Mice that lack S6K1 display reduced fat mass, resistance to nutrient excess, delayed ageing and increased healthy lifespan (healthspan) compared to control animals⁶, and the authors set out to investigate whether EPRS is a key mediator of these effects. They generated a pair of mouse models in which EPRS phosphorylation was either blocked or mimicked by mutating Ser⁹⁹⁹ to an alternative amino acid — in the first instance to alanine (a mutation dubbed S999A), which cannot be phosphorylated, and in the second to aspartate (S999D), which mimics permanent Ser⁹⁹⁹ phosphorylation.

Mice harbouring the S999A mutation displayed reduced fat mass, improved metabolism and increased lifespan compared to wildtype controls, in part resembling the S6K1-deficient animals. When the S999D mutation was introduced to rescue EPRS phosphorylation in S6K1-deficient mice, there was a partial restoration of fat mass in these animals. Together, these data suggest that EPRS phosphorylation by S6K1 has a key role in regulating fat mass in mice, and that such phosphorylation might mediate the beneficial effects of S6K1 deletion on metabolism and ageing.

Next, Arif *et al.* analysed the mutants in more detail, and discovered that insulin-stimulated lipid uptake was impaired in the fat cells of S999A mice compared to control animals. Motivated by this observation, the authors performed a screen to identify components of the lipid-metabolism machinery that interact with EPRS. This showed that EPRS binds to the protein FATP1, which is known to mediate uptake of lipid precursors called fatty acids into fat⁷, in an insulin-dependent and S6K1-dependent manner. These results implicate FATP1 as a key component of mTOR signalling, regulating metabolism in fat (Fig. 1).

Although this study provides insights into metabolism and ageing, unsurprisingly there are some unexpected findings and unanswered questions, together with avenues for future investigation. Perhaps the most pressing issues relate to longevity, given the increasingly aged human population and the recognition that ageing is the greatest risk factor for a range of diseases⁸.

It is somewhat surprising that the increased lifespan seen in S6K1-deficient mice can be mimicked by the mutation of a single target amino-acid residue in EPRS, given the many roles and substrates of S6K1. One potential explanation is that S6K1-deficient mice have a mixture of beneficial and detrimental traits, but the overarching output confers increased lifespan. In this scenario, the EPRS-dependent pathway might simply capture the beneficial effects. To bolster such an idea, it will be crucial to examine whether S999A mice show increased healthspan, in addition to increased lifespan. It will also be important to examine mice harbouring the S999D mutation in greater detail, as these surprisingly seem to lack traits that are associated with enhanced mTOR–S6K1 signalling in fat, such as insulin resistance and obesity.

The precise relationship between EPRS- and S6K1-dependent longevity could be further examined in genetic experiments using the mutants generated by Arif and colleagues. For example, is the increased longevity of S6K1-deficient mice abrogated by introduction of the S999D mutation, as would be expected if that longevity is dependent on EPRS phosphorylation? Likewise, if S6K1 and EPRS act in a linear pathway, S6K1-deficient mice that have the S999A mutation should have no additional metabolic or lifespan benefits over S6K1-deficient mice that have wildtype EPRS. Such complex genetic studies would bolster the idea that EPRS is a key regulator of ageing in the mTOR pathway.

The authors suggest that the metabolic and longevity changes seen in S999A mutants largely stem from altered fat-tissue biology and are caused by a lack of S6K1-mediated phosphorylation. But reduced fat mass in S999A mutants begins in adulthood, whereas S6K1-deficient mice are lean at an earlier age in part owing to defects in fat-cell

development⁹ — pointing to the possibility that EPRS also acts through other mechanisms. Furthermore, mice lacking FATP1 do not show the altered fat traits seen in S999A mice. Therefore, it is possible that EPRS also acts in other tissues. In support of this idea, S6K1 has roles in metabolic regulation in the liver, muscle and central nervous system^{10,11}. Specifically deleting S6K1 in fat and studying EPRS function in this tissue could give further insights into this issue.

The major excitement about the current study stems from the potential to target S6K1–EPRS signalling to treat metabolic disease and perhaps the pathology of ageing. Directly targeting Ser⁹⁹⁹ phosphorylation would be challenging, but it is well established that pharmacological blockade of mTOR–S6K1 signalling using the immunosuppressant drug rapamycin extends lifespan and increases healthspan in mice¹². It would therefore be useful to determine if any of the effects of rapamycin are mediated by EPRS-dependent mechanisms as this may help refine strategies aimed at the targeting of the mTOR pathway.

Finally, it would be interesting to assess whether there are alterations in EPRS function in ageing humans, and whether genetic variation in EPRS contributes to differences in human lifespan. Only then will we know the full potential of Arif and colleagues' discovery to give insights into the causes and potential treatments for age-related disease.

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Figure 1. A phosphorylation switch alters lipid uptake and longevity.

a. As part of a large protein complex, the protein mTOR can activate the kinase enzyme S6K1. Arif *et al.*³ report that S6K1 phosphorylates (P) the protein glutamyl-prolyl t-RNA synthetase (EPRS) on the amino-acid residue Serine 999 (Ser⁹⁹⁹). This switch promotes interaction with the fatty-acid transporter protein FATP1, leading to increased lipid uptake into fat tissue. **b.** If Ser⁹⁹⁹ is mutated to the amino-acid residue alanine in mice, such that it cannot be phosphorylated, the interaction with FATP1 does not occur — these animals have lower fat mass and live longer than controls.