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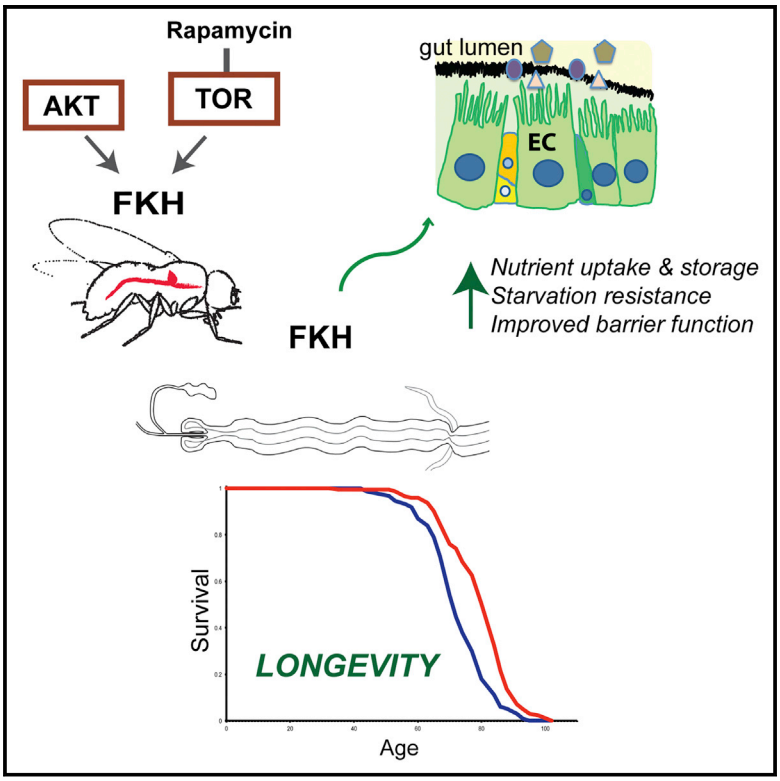
Cell Reports

Intestinal Fork Head Regulates Nutrient Absorption and Promotes Longevity

Graphical Abstract



Authors

Ekin Bolukbasi, Mobina Khericha, Jennifer C. Regan, ..., Janet M. Thornton, Nazif Alic, Linda Partridge

Correspondence

l.partridge@ucl.ac.uk

In Brief

Bolukbasi et al. identify the transcription factor FKH as a mediator of nutrient-sensing pathway signaling in *Drosophila*, and they characterize FKH's essential involvement in increased longevity via this network. They pinpoint FKH's pro-longevity effect to the gut, and they show increased expression of nutrient transporters and improvement of barrier function by FKH activity.

Highlights

- *Drosophila* FKH biochemically interacts with AKT and TOR
- IIS- and rapamycin-induced longevity requires FKH
- Gut tissue, specifically differentiated cells, mediates FKH's pro-longevity effects
- FKH activity in the gut upregulates intestinal nutrient transporters

Data and Software Availability

E-MTAB-6056

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Intestinal Fork Head Regulates Nutrient Absorption and Promotes Longevity

Ekin Bolukbasi,[1,2] Mobina Khericha,[1,2] Jennifer C. Regan,[1,2] Dobril K. Ivanov,[3] Jennifer Adcott,[1] Miranda C. Dyson,[1] Tobias Nespital,[2] Janet M. Thornton,[3] Nazif Alic,[1] and Linda Partridge[1,2,4,*]
[1]Institute of Healthy Ageing, Department of Genetics, Evolution and Environment, University College London, Gower St, London WC1E 6BT, UK
[2]Max Planck Institute for Biology of Ageing, Joseph-Stelzmann-Strasse 9b, 50931 Cologne, Germany
[3]European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SD, UK
[4]Lead Contact
*Correspondence: l.partridge@ucl.ac.uk
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SUMMARY

Reduced activity of nutrient-sensing signaling networks can extend organismal lifespan, yet the underlying biology remains unclear. We show that the anti-aging effects of rapamycin and reduced intestinal insulin/insulin growth factor (IGF) signaling (IIS) require the *Drosophila* FoxA transcription factor homolog Fork Head (FKH). Intestinal FKH induction extends lifespan, highlighting a role for the gut. FKH binds to and is phosphorylated by AKT and Target of Rapamycin. Gut-specific FKH upregulation improves gut barrier function in aged flies. Additionally, it increases the expression of nutrient transporters, as does lowered IIS. Evolutionary conservation of this effect of lowered IIS is suggested by the upregulation of related nutrient transporters in *insulin receptor substrate 1* knockout mouse intestine. Our study highlights a critical role played by FKH in the gut in mediating anti-aging effects of reduced IIS. Malnutrition caused by poor intestinal absorption is a major problem in the elderly, and a better understanding of the mechanisms involved will have important therapeutic implications for human aging.

INTRODUCTION

The signaling network of nutrient-sensing, insulin/insulin growth factor signaling (IIS) and Target of Rapamycin (TOR) influences healthy lifespan in diverse eukaryotic organisms, including mammals (Alic and Partridge, 2011). Specific alleles of IIS genes (Li et al., 2009; Pawlikowska et al., 2009; Suh et al., 2008; Willcox et al., 2008) and transcriptional variation of genes encoding components of the TOR pathway (Passtoors et al., 2013) are associated with survival to advanced ages in humans. Reduced network activity can induce a broad-spectrum resistance to age-related loss of function and disease in animal models (Clancy et al., 2001; Kenyon et al., 1993; Selman et al., 2008; Tatar et al., 2001), making it an attractive target for pharmacological intervention to improve human health during aging (de Cabo et al., 2014). Indeed, attenuation of TOR signaling by rapamycin extends lifespan in diverse species, including mice (Bjedov et al., 2010; Harrison et al., 2009), as does inhibition of the Ras-Erk branch of IIS by the drug trametinib in *Drosophila* (Slack et al., 2015).

In addition to its effect on aging, the IIS/TOR network regulates growth, metabolism, stress responses, and fecundity, potentially resulting in undesired side effects of reduction of network activity. For example, at some doses, rapamycin is a strong immunosuppressant (de Cabo et al., 2014) and can also impair wound healing (Squarize et al., 2010), while trametinib is a Mek1/2 inhibitor with anti-proliferative properties (Yamaguchi et al., 2011). Therefore, we need to uncover molecular and mechanistic outputs of nutrient-sensing networks in order to triage apart the positive effects of intervention from the negative effects inherent in manipulating upstream network nodes. In particular, we need to determine the tissue-specific effect of signaling activity in lifespan extension and the physiological processes underlying it.

Recent studies identified the intestinal tissue as pivotal in aging (Alic et al., 2014; Biteau et al., 2010; Rera et al., 2012), and they have mainly focused on hyperplastic intestinal pathology resulting from age-dependent intestinal stem cell (ISC) over-proliferation as a major determinant of lifespan (Biteau et al., 2010). However, while stem cell maintenance is no doubt important for intestinal homeostasis, hyperplasia may not occur early enough to influence the early tipping point between young and old metabolic states. Therefore, other aspects of intestinal physiology that determine lifespan still remain to be elucidated.

Outputs of the IIS/TOR signaling network are mediated by several transcription factors (TFs). For instance, in *C. elegans* and *Drosophila*, the single Fork Head Box O (FoxO) TF is required for extended lifespan from lowered IIS (Giannakou et al., 2004; Hwangbo et al., 2004; Murphy et al., 2003; Slack et al., 2011; Willcox et al., 2008). In *C. elegans* the heat shock TF HSF-1 (Hsu et al., 2003) and the Nrf-like xenobiotic response factor SKN-1 (Tullet et al., 2008) are also required. In *Drosophila*, lowered IIS increases lifespan through both the canonical IIS pathway and its FOXO effector, and through the Ras-Erk-ETS branch and its transcriptional repressor effector *anterior open* (AOP) (Slack et al., 2015). In *Drosophila*, at least one other TF is also likely to play a role, because the TF-binding sites