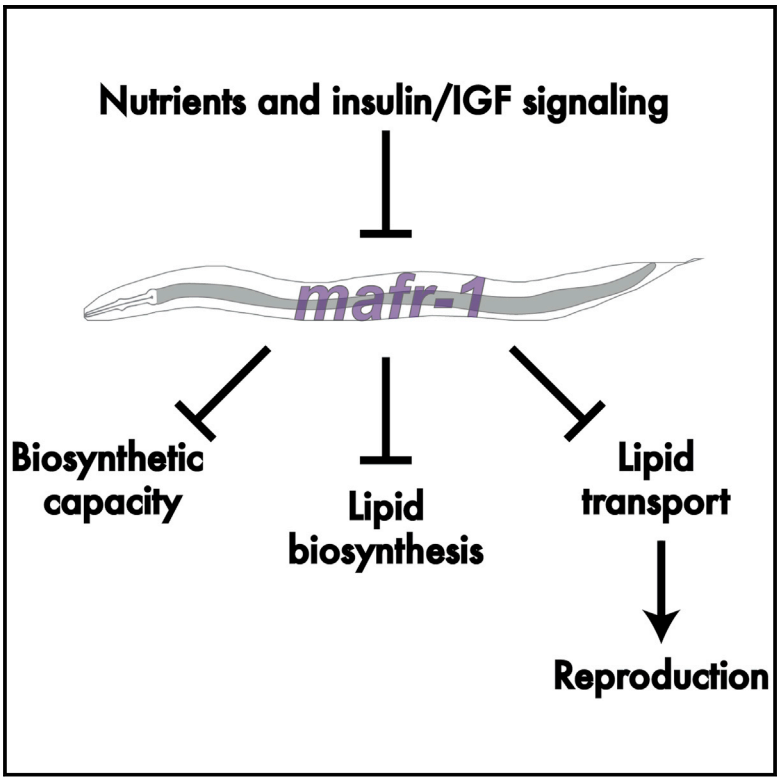
Article

Cell Reports

# Physiological Roles for *mafr-1* in Reproduction and Lipid Homeostasis

## Graphical Abstract




## Authors

Akshat Khanna, Deborah L. Johnson, Sean P. Curran

## Correspondence

spcurran@usc.edu

## In Brief

Maf1 is an evolutionarily conserved repressor of RNA polymerase III transcription that has been well characterized in single-cell models. The function of *mafr-1* in the context of a multicellular organism, however, is not well understood. In this study, Khanna et al. identify *mafr-1* as central node in the maintenance of *C. elegans* physiological homeostasis, where it functions as a potent regulator of reproduction and lipid homeostasis.

## Highlights

- *C. elegans* MAFR-1 regulates both RNA Pol II- and III-dependent transcription
- MAFR-1 levels impact de novo lipogenesis gene expression and lipid levels
- Dietary carbohydrates and insulin signaling regulate *mafr-1* levels
- MAFR-1 cell nonautonomously affects oogenesis and reproductive output

Khanna et al., 2014, Cell Reports 9, 2180–2191
December 24, 2014 
http://dx.doi.org/10.1016/j.celrep.2014.11.035

CellPress

OPEN ACCESS
CellPress

Cell Reports
Article

# Physiological Roles for *mafr-1* in Reproduction and Lipid Homeostasis

Akshat Khanna,[1,2] Deborah L. Johnson,[3] and Sean P. Curran[1,2,4,*]
[1]Leonard Davis School of Gerontology, University of Southern California, Los Angeles, CA 90089, USA
[2]Department of Molecular and Computational Biology, Dornsife College of Letters, Arts, and Sciences, University of Southern California, Los Angeles, CA 90089, USA
[3]Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX 77030, USA
[4]Department of Biochemistry and Molecular Biology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90089, USA
*Correspondence: spcurran@usc.edu
http://dx.doi.org/10.1016/j.celrep.2014.11.035


## SUMMARY

**Maf1 is a conserved repressor of RNA polymerase (Pol) III transcription; however, its physiological role in the context of a multicellular organism is not well understood. Here, we show that *C. elegans* MAFR-1 is functionally orthologous to human Maf1, represses the expression of both RNA Pol III and Pol II transcripts, and mediates organismal fecundity and lipid homeostasis. MAFR-1 impacts lipid transport by modulating intestinal expression of the vitellogenin family of proteins, resulting in cell-nonautonomous defects in the developing reproductive system. MAFR-1 levels inversely correlate with stored intestinal lipids, in part by influencing the expression of the lipogenesis enzymes *fasn-1*/FASN and *pod-2*/ACC1. Animals fed a high carbohydrate diet exhibit reduced *mafr-1* expression and mutations in the insulin signaling pathway genes *daf-18*/PTEN and *daf-16*/FoxO abrogate the lipid storage defects associated with deregulated *mafr-1* expression. Our results reveal physiological roles for *mafr-1* in regulating organismal lipid homeostasis, which ensure reproductive success.**

## INTRODUCTION

Initially characterized in *S. cerevisiae*, Maf1 is an evolutionarily conserved transcriptional corepressor of RNA polymerase (Pol) III-dependent genes, such as tRNA and 5S rRNA, which impact the biosynthetic capacity of the cell (Upadhya et al., 2002; Vannini et al., 2010). This function of Maf1 is conserved, as human, mouse, and *Drosophila* Maf1 also represses tRNA transcription (Boguta, 2013; Boguta and Graczyk, 2011; Marshall et al., 2012; Rideout et al., 2012). Mammalian Maf1 additionally regulates certain RNA Pol II-dependent promoters, including some Elk-1-regulated genes (Johnson et al., 2007). Given that Maf1 has extended roles in higher eukaryotes, we examined its function in a physiological context.

We were keen to investigate the physiological role of Maf1 in a genetically tractable system such as *C. elegans*. We examined the function of the related *C. elegans* MAF polymerase III Regulator-1 (MAFR-1) protein and elucidated the functional consequences of altered *mafr-1* expression on development, reproduction, and lipid homeostasis. In *C. elegans*, metabolic homeostasis is maintained by multiple evolutionarily conserved mechanisms (Barros et al., 2012; Brey et al., 2009; Brock et al., 2006, 2007; O'Rourke et al., 2009; Paek et al., 2012; Soukas et al., 2009; Walker et al., 2011; Watts, 2009; Zheng and Greenway, 2012), and *C. elegans* has become exceptionally useful for high-throughput screening studies of complex cellular processes relevant to human diseases (Anastassopoulou et al., 2011; Squiban et al., 2012; Wählby et al., 2012). We have discovered that MAFR-1 negatively regulates intracellular lipid accumulation and influences reproductive capacity. Taken together, these studies define the physiological roles for Maf1 and indicate the potential for targeting of Maf1 for therapeutic strategies for the prevention and treatment of metabolic diseases with deregulated lipid phenotypes.

## RESULTS

### *C. elegans* MAFR-1 Is a Conserved Modulator of RNA Pol III and Pol II Transcript Levels

Given the conserved role of Maf1 as a negative regulator of RNA Pol III in yeast, flies, and mammals, we investigated whether *C. elegans* MAFR-1 functions in an orthologous manner. We reduced *mafr-1* expression by RNAi and measured the transcript levels of established RNA Pol III transcripts, such as tRNAs. As predicted, when *mafr-1* expression was reduced by approximately 50% (Figure S1A), the expression of most tRNAs were significantly increased as compared to the internal normalization control, *snb-1*, whose expression was stable (Figures 1A and S1A). We further examined animals harboring an additional chromosomally integrated copy of *mafr-1*, which results in a ~80% increase in *mafr-1 over*expression (*mafr-1* O/E) (Figure S1B) and observed a striking reduction in all tRNAs tested (Figures 1B and S1B). Furthermore, the reduction of tRNA levels observed in *mafr-1* O/E animals was restored when animals were fed dsRNA targeting *mafr-1*, indicating that the effects