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Packing on the Pounds in Response to Bacterial Growth Conditions

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Reporting in *Nature Cell Biology*, Lin and Wang (2017) show that bacterial methyl metabolism impacts host mitochondrial dynamics and lipid storage in *C. elegans*. The authors propose a model whereby bacterial metabolic products regulate a nuclear hormone receptor that promotes lipid accumulation through expression of a secreted Hedgehog-like protein.

C. elegans is a beautifully simple model with which to explore organismal responses to environmental factors. For *C. elegans*, bacteria serve as both diet and microbiota. Although not all bacteria are equally capable of colonizing the *C. elegans* gut, animals live in the bacterial lawn and are constantly exposed to bacterial products, making them an ideal model for the study of host-bacteria interactions. Reporting recently in *Nature Cell Biology*, Lin and Wang (2017) use this system to uncover molecular links between the bacterial environment and its effects on the host.

The bacterial growth environment is often neglected in studies examining host-microbe interactions, although it can have pronounced effects on bacterial metabolism. Lin and Wang (2017) demonstrate that a single strain of *E. coli* can have dramatically different effects on *C. elegans* lipid metabolism and mitochondrial dynamics, depending on bacterial growth conditions. When *C. elegans* are fed *E. coli* MG1655 grown in the minimal media M9 (*E. coli*-M9), they accumulate twice as much fat as animals fed *E. coli* cultured in Lysogeny broth (*E. coli*-LB) and also display fragmentation of intestinal mitochondria, an indication of increased mitochondrial fission. The bacterial diets have similar caloric content and similar levels of protein and triacylglycerides, and although carbohydrate levels were slightly increased in *E. coli*-M9, supplementing LB media with glucose did not increase fat storage in *C. elegans*. Thus, the observed effects were unlikely to be due to differences in macronutrient levels, but more likely the result of a specific metabolite.

Comparison of the two bacterial diets identified metabolites—including methionine and all components of the bacterial methyl cycle—that were decreased in the *E. coli*-M9 diet. Methionine is a precursor to S-Adenosyl Methinone (SAM) and supplementing the *E.coli* M9 diet with methionine or SAM inhibited increased fat storage. SAM acts as a methyl donor for proteins, lipids, and metabolites and is required for biosynthesis of phosphatidylcholine (PC) from phosphatidylethanolamine (PE) by phosphoethanolamine methyltransferases (PMTs). Lin and Wang (2017) show that limiting PC production by knocking down *pmt-1* increased fat storage in animals fed *E. coli*-LB, but the effect of methionine supplementation on lipid accumulation in animals fed *E. coli*-M9 is blocked, demonstrating that the influence of methionine in this system is likely through the production of PC. Indeed, supplementing the bacterial diet with either diundecanoyl PC (DUPC) or dilauroyl PC (DLPC) restored normal fat levels in animals fed *E. coli*-M9. DUPC and DLPC are agonists of mammalian Liver Receptor Homolog-1 (LRH-1), a member of the NR5A family of nuclear hormone receptors (NHRs) (Lee et al., 2011). In *C. elegans*, NHR-25 is the sole member of the NR5A family of NHRs, and genetic and transcriptional assays presented by the authors suggest that DUPC and DLPC may act as ligands for NHR-25. Lipid accumulation and mitochondrial morphologies characteristic of growth on *E. coli*-M9 were observed in *nhr-25* mutants grown on *E. coli*-LB. Further, the authors show that *nhr-25* is required to mediate the effects of methionine, DUPC, or DLPC in preventing increased lipid accumulation. Together, these results suggest that NHR-25 mediates the organismal response to methionine metabolic by-products.

Curiously, *pmt-1* is expressed in hypodermal cells (Li et al., 2011), and decreasing PC production by specifically knocking down *pmt-1* in the hypodermis was sufficient to induce increased fat accumulation. The authors also observed that a NHR-25 GFP fusion construct localizes to the nuclei of hypodermal cells. These findings suggest that endocrine signaling mediated by NRH-25 activity in the hypodermis may control lipid mobilization/storage. To identify factors regulated by NHR-25 that could mediate endocrine signaling, Lin and Wang (2017) combined expression analysis of animals fed both diets with ModEncode ChIP-seq data for NHR-25. From these analyses, they identified GRound-Like-21 (GRL-21), a Hedgehog-like secreted protein whose expression is repressed by NHR-25 (Figure 1). Knockdown of *grl-21* suppressed lipid accumulation in animals fed *E. coli*-M9 and the mitochondrial fragmentation phenotypes in *nhr-25* mutants. The authors then used a targeted RNAi screen to identify the Patched family receptor PTR-24 as a candidate receptor for GRL-21, finding that knockdown of *ptr-24* also increased fat accumulation and mitochondrial fragmentation in animals fed *E. coli*-LB (Figure 1).

These genetic analyses indicated that the increased lipid accumulation and mitochondrial fragmentation that occur in intestinal cells in response to the *E. coli*-M9 diet are regulated through a

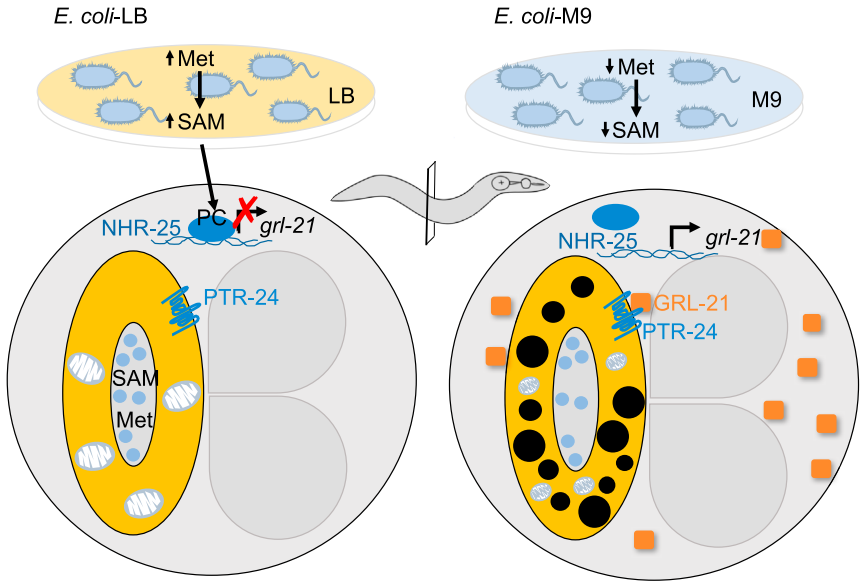

Figure 1. Bacterial Growth Media Influences Lipid Metabolism and Mitochondrial Dynamics
E. coli grown on the minimal media M9 (*E. coli* M9) produce reduced levels of methyl metabolites relative to *E. coli* grown on Lysogeny broth (*E. coli*-LB). Diagram represents a cross-section of *C. elegans*, depicting NHR-25-mediated repression of *grl-21* in the hypodermis in the presence of Phosphatidylcholine (PC) when bacteria are grown in rich media (LB). By contrast, when bacteria are grown in minimal media, *grl-21* repression is lifted and GRL-21 is released from hypodermal cells and acts on PTR-24 in the intestine (yellow). GRL-21 induced mitochondrial fragmentation and subsequent lipid accumulation (black) in the intestine.

common mechanism requiring NHR-25. Mitochondria play an important role in lipid metabolism, leading the authors to ask whether alterations in intestinal lipid metabolism were influencing the mitochondria or whether alterations in mitochondrial function were influencing lipid metabolism. To test this, the authors genetically inhibited mitochondrial fission specifically in the intestine and found that this prevented lipid accumulation in animals fed *E. coli*-M9. These data support a model in which endocrine signaling from the hypodermis to the intestine influences mitochondrial dynamics in order to regulate lipid accumulation.

Previous studies showed that decreasing SAM or PC biosynthesis in *C. elegans* induced transcriptional upregulation of SBP-1 (the *C. elegans* ortholog of SREBP) target genes that promote lipid synthesis and accumulation (Walker et al., 2011). Based on these findings, *sbp-1* would be a likely candidate mediator of the lipid accumulation induced by mitochondrial fragmentation. However, lipid accumulation was increased in response to the *E. coli*-M9 diet in *sbp-1* mutants, leading the authors to conclude that SBP-1 plays a negligible role in this response. Although the absence of SBP-1 could not inhibit lipid accumulation, it seems likely that some crosstalk exists between the NHR-25/GRL-21/PTR-24 pathway and SBP-1 because both regulate lipid metabolism in response to PC and SAM levels. Specific PC molecules likely act as ligands for NHR-25, which may allow NHR-25 and GRL-21 to act as an early warning system, signaling animals to prepare for changing nutrient conditions before cellular metabolites are depleted. NHR-25 may also link nutrient availability to global control of development, because NHR-25 is a regulator of developmental progression and molting (Gissendanner and Sluder, 2000; Asahina et al., 2000). This study highlights the importance of considering diet at a molecular level, focusing on the molecules present rather than on caloric content.

REFERENCES

Asahina, M., Ishihara, T., Jindra, M., Kohara, Y., Katsura, I., and Hirose, S. (2000). Genes Cells *5*, 711–723.

Gissendanner, C.R., and Sluder, A.E. (2000). Dev. Biol. *221*, 259–272.

Lee, J.M., Lee, Y.K., Mamrosh, J.L., Busby, S.A., Griffin, P.R., Pathak, M.C., Ortlund, E.A., and Moore, D.D. (2011). Nature *474*, 506–510.

Li, Y., Na, K., Lee, H.-J., Lee, E.-Y., and Paik, Y.-K. (2011). J. Biochem. *149*, 529–538.

Lin, C.J., and Wang, M.C. (2017). Nat. Cell Biol. *19*, 550–557.

Walker, A.K., Jacobs, R.L., Watts, J.L., Rottiers, V., Jiang, K., Finnegan, D.M., Shioda, T., Hansen, M., Yang, F., Niebergall, L.J., et al. (2011). Cell *147*, 840–852.