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Preview

For Intestinal Homeostasis, You Are What You Eat

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Nutrients play a central role in controlling the form and function of the intestinal epithelium. In this issue of *Developmental Cell*, Mattila et al. (2018) and Obniski et al. (2018) uncover important mechanisms by which *Drosophila* intestinal stem cells respond to dietary signals, linking nutrients to tissue homeostasis.

Dietary nutrition can have wide-ranging effects on aging and health. This is particularly evident in the intestine where nutrients influence multiple processes, including intestinal mass, absorptive capacity, and proliferation. For example, in mammalian models of small bowel resection, the remaining intestinal mucosa will increase absorptive capacity in a compensatory manner, including changes in proliferation as well as crypt and villus morphology (Drozdowski and Thomson, 2006). Over the past decade, genetic studies in simple model systems have provided major breakthroughs in our understanding of the molecular mechanisms that connect diet to intestinal homeostasis. These include a central role for insulin signaling in mediating the effects of diet on adaptive growth of the adult intestine in *Drosophila* (Shim et al., 2013). Similarly, S-adenosyl methionine, derived from dietary methionine, can promote intestinal stem cell (ISC) proliferation and maintain intestinal homeostasis (Obata et al., 2018). In this issue of *Developmental Cell*, Mattila et al. (2018) and Obniski et al. (2018) provide important new insights into the mechanisms by which dietary nutrients can affect intestinal cellular responses in *Drosophila*.

Mattila et al. (2018) start with the remarkable observation that dietary N-acetyl-D-glucosamine (GlcNAc), an intermediate metabolite of the hexosamine biosynthesis pathway (HBP), is sufficient to reverse the intestinal growth defects normally seen under nutrient-deprived conditions. To understand the mechanisms by which dietary GlcNAc has these effects, the authors perform clonal analysis using mutants for *gfat2*, which encodes a rate-limiting enzyme in the HBP pathway. Together with overexpression studies, this revealed that *gfat2* is necessary and sufficient in the ISC lineage to promote proliferation. The decrease in clone size of *gfat2* mutant lineages was rescued by either dietary GlcNAc or genetic expression of *gfat2*, demonstrating the specificity of the phenotype. RNA-seq analysis revealed that dietary GlcNAc induces the lactate dehydrogenase gene and suppresses the expression of genes that act in the TCA cycle and mitochondrial oxidative phosphorylation. This metabolic profile is diagnostic of a switch toward glycolytic metabolism, known as the Warburg effect in cancer cells, which supports the biosynthetic pathways needed for growth and proliferation. Genetic mosaic studies of genes in these pathways support this model. Finally, the authors show that dietary GlcNAc, or *gfat2* expression, is sufficient to rescue the reduced clone size seen under conditions of reduced insulin signaling. Taken together, these findings from Mattila et al. (2018) lead to the model that the HBP is required in ISCs for a metabolic switch toward glycolytic metabolism to support the biosynthetic pathways needed for intestinal growth in response to nutrient signaling. The mechanisms by which the HBP promotes glycolytic metabolism, however, remain unclear. Studies in hematopoietic cells have shown that flux through the HBP is required to maintain growth factor signaling and nutrient uptake to support anabolic metabolism and cell growth (Wellen et al., 2010). Alternatively, N- or O-linked protein glycosylation mediated by the HBP could have a wide range of downstream effects on metabolism and cell growth. It will be interesting to further examine this pathway to better define its important role in linking the HBP to a pro-growth metabolic state in ISCs.

In contrast to the effects of dietary carbohydrates reported by Mattila et al. (2018), Obniski et al. (2018) focus on the role of lipids on cell fate specification in the ISC lineage. They show that young adults raised on a lipid-depleted diet have reduced numbers of the differentiated secretory cell type in the fly intestine, enteroendocrine cells (EEs). Dietary lipids are sufficient to restore EE numbers, whereas a high cholesterol diet leads to elevated numbers of EEs. This does not, however, appear to occur through a change in the rates of ISC division or apoptosis. Rather, the authors use a Notch reporter to show that low lipid levels lead to elevated Notch signaling, whereas high lipids result in low Notch signaling, consistent with the known role of this pathway in cell fate specification (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). Moreover, the authors show that a nuclear receptor important for sterol uptake and utilization, Hr96, is necessary and sufficient for the effects on EE cell number.

The established role for Notch signaling in specifying EE cell fate suggests that a lipid-depleted diet could result in elevated levels of the Notch ligand Delta while a high sterol diet might have the opposite effect (Ohlstein and Spradling, 2007). The authors show that this is indeed the case. In addition, clonal analysis using an *Hr96* mutant showed that this receptor is required in the ISC lineage for maintaining reduced levels of Delta in animals on a control diet. These findings support the model that dietary lipids modulate Notch signaling in progenitor cells, mediated by Hr96, specifying the appropriate number of EEs in the intestine. When dietary lipids are low, Delta is stabilized, reducing EE cell number. A corresponding increase in the alternative cell fate, absorptive enterocytes, could facilitate lipid uptake and utilization under these nutrient-deprived conditions.

The authors go on to explore how dietary lipids might impact the long-term

adaptive physiology of the intestine. Interestingly, flies initially exposed to a lipid-depleted diet and then shifted to a normal yeast diet after 1 week maintained their reduced number of EEs for at least 2 more weeks. This appears to be of physiological significance since these animals accumulate significantly more cholesterol than controls kept on a yeast diet. This provides an intriguing parallel with the well-established association between nutritional deprivation early in development and the later onset of obesity and suggests that this association could arise from the effects of diet on intestinal cell fate specification.

Finally, Obniski et al. (2018) note that their study provides a mechanistic framework to understand the association between a high-fat diet and cancer. In *Drosophila*, this is seen in the lipid-rich region of the intestine where a loss of Notch signaling in ISCs leads to hyperplastic enteroendocrine tumors (Micchelli and Perrimon, 2006; Ohlstein and Spradling, 2006). Interestingly, Obniski et al. (2018) show that this tumor burden can be greatly reduced by exposing these animals to a lipid-depleted diet. In addition, at least some aspects of this pathway appear to be conserved through evolution. Treatment of tissue culture cells with an agonist for an Hr96 homolog, the LXR oxysterol receptor, leads to decreased levels of a Delta family member, DLL4. Given that inhibition of DLL4 is sufficient to reduce tumor growth in mouse models, these results suggest that dietary intervention or potential therapeutic application of LXR agonists might provide a means of reducing cancer risk (Hoey et al., 2009).

This study by Obniski et al. (2018) demonstrates that the nutritional environment can act through known signaling pathways to modulate tissue development and physiology. This work sets a foundation for future studies to address the mechanisms by which dietary lipids act through Hr96 to shift Notch signaling toward low Delta levels and EE cell fates. The authors propose that this could be due to diet-induced changes in membrane lipid composition that impact Delta protein stability and turnover. In support of this model, they present intriguing genetic evidence suggesting that this acts through the ERAD pathway. Further experiments could clarify this important association and demonstrate how the Hr96 transcriptional program regulates Notch signaling and directs the ISC lineage toward an EE cell fate.

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