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The Multidimensional Organization of Interorgan Communication Networks

Ilia A. Droujinine[1,*] and Norbert Perrimon[1,2,*]
[1]Department of Genetics, Harvard Medical School, Boston, MA 02115, USA
[2]Howard Hughes Medical Institute, Boston, MA 02115, USA
*Correspondence: droujinine@g.harvard.edu (I.A.D.), perrimon@genetics.med.harvard.edu (N.P.)
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Secreted molecules coordinate organ function. In a recent issue of *Cell*, Hudry et al. (2019) uncover a *Drosophila* testis-midgut interaction via cytokine and citrate signaling that regulates intestinal metabolism, spermatogenesis, and food intake. This impressive study is a striking example of the role of spatial organization in sex-specific interorgan communication.

Organs are specialized, interdependent, and regulated by an interorgan communication network (ICN) of secreted molecules that are beginning to be revealed from work in both vertebrates and invertebrates (Droujinine and Perrimon, 2016). For instance, to regulate growth, metabolism, immunity, and digestive enzymes, the *Drosophila* gut secretes hedgehog, insulin growth factor binding protein-like ImpL2, PDGF- and VEGF-related factor 1 (Pvf1), activin, and, from gut-associated *corpora cardiaca*, limostatin and adipokinetic hormone and senses activin-like dawdle (Daw) and peptidoglycan recognition proteins (PGRPs) (Droujinine and Perrimon, 2016; Rodenfels et al., 2014; Song et al., 2019).

The midgut consists of multiple interacting cell types: intestinal stem cells (ISCs) and differentiated enterocytes (ECs) and enteroendocrine cells. Interestingly, male and female guts show sex differences; for example, there is more ISC proliferation in female guts than in male guts, and ECs located in the posterior R4 region of the male midgut show increased expression of genes involved in carbohydrate metabolism (Hudry et al., 2016). Interestingly, while the sex determination pathway controls differences in ISC proliferation cell autonomously, male-specific expression of genes involved in sugar metabolism does not depend on the sex of the ECs themselves. Puzzled by this observation, Hudry et al. (2019) observed that the apical tip of the testes and the posterior R4 region of the midgut are in close proximity to one another and made the remarkable hypothesis that signaling from the male somatic gonad may be responsible for the pattern of expression of sugar genes in the male gut. In a search for such a signal, they found that the testis soma produces the cytokine Upd1, which induces JAK-STAT signaling in the R4 region of the midgut, which is in turn essential for sugar gene expression.

In determining the physiological consequences of the testis-gut interaction, Hudry et al. (2019) found that intestinal glucose metabolism and JAK-STAT signaling affect food intake through extracellular citrate. This metabolite was found to be downstream of glycolysis, pyruvate, and the pyruvate-citrate pathway and secreted from ECs and imported to neurons through the Indy channel. In addition, intestinal citrate production and uptake play a role in the testis soma to promote sperm maturation (Figure 1). These remarkable findings have significant implications for interorgan communication studies and raise a number of questions.

The importance of citrate for spermatogenesis and food intake suggests that gonads may regulate metabolism to promote reproductive capacity (Hudry et al., 2019). Given that sexual dimorphism can be altered in adults and has significant effects on reproduction and feeding behavior, are there dietary or environmental cues affecting these carbohydrate metabolism-related phenomena? Other processes and cell types may be regulated by sexually dimorphic intracellular or extracellular cues. For instance, yolk proteins are expressed in female but not male midguts, and oxidative stress genes are increased in male R4 over female midguts. Also, enteroendocrine cells show male-biased Maltase-A3 glucoside hydrolase expression, suggesting that cell types other than ECs are regulated sex specifically (Hudry et al., 2019). Interestingly, in non-R4 gut regions in males or females, JAK-STAT signaling was neither necessary nor sufficient for carbohydrate metabolism gene expression, suggesting the involvement of factors unrelated to sex determination in these regions (Hudry et al., 2019).

Broadly, this work has implications for interorgan regulation of sexually dimorphic phenotypes. Reproduction in female flies regulates motility, food intake, lipid metabolism, and lifespan, suggesting that gonads may produce additional physiologically significant interorgan factors (Avila et al., 2011; Reiff et al., 2015). This paper also has relevance to mammals, in which cytokine production can differ between sexes (Couillard et al., 1997).

The work of Hudry et al. (2019) is a striking example of a metabolite, in this case citrate, that is derived from a central metabolic process and affects systemic physiology. Systemic roles of other metabolites such as succinate have also been documented (Mills et al., 2018). While it is unclear how spermatogenesis is affected by citrate, it could function as a substrate for the TCA cycle or fatty acid generation, or affect histone acetylation (Hudry et al., 2019). Furthermore, the neural mechanisms of the effect of citrate on food intake are unclear. Finally, citrate also has a neuronal role in affecting food intake, although the precise neural populations that detect it and the intracellular mechanisms are unknown. The paper by Hudry et al. (2019) will inspire studies of the roles of citrate on food intake and spermatogenesis in mammals.

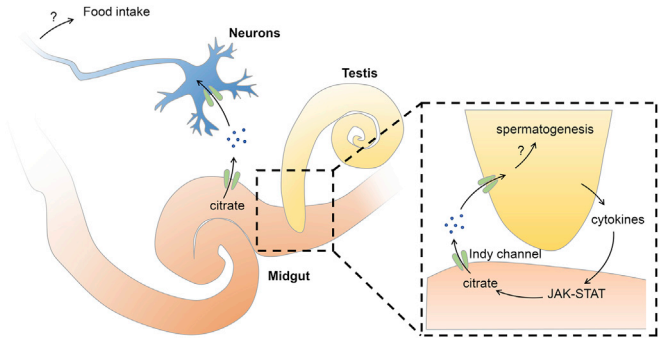

Figure 1. Interactions among the *Drosophila* Midgut, Neurons, and Testis Regulate Carbohydrate Metabolism, Food Intake, and Spermatogenesis

The Upd1 cytokine secreted from the testis soma leads to activation of JAK-STAT signaling in posterior midgut enterocytes, expression of male-biased sugar metabolism genes, and secretion of citrate (blue dots) through the Indy channel. Citrate regulates food intake and spermatogenesis in the testis.

The spatial proximity of the testis to the gut R4 region is likely to be physiologically significant, as male JAK-STAT activity is adjacent to the testis tip and citrate concentrations are regulated in the gut and testis, but not in the hemolymph (Hudry et al., 2019). It would be interesting to determine the effects of diet, regeneration, age, reproductive status, and putative interorgan adhesion molecules on gut-testis co-localization, as well as to determine the effects of changes to this co-localization on gut-testis crosstalk. There is potential for additional interorgan proximal communication from other extended organs, including among other gut regions, Malpighian tubules, accessory glands, and the crop, and between the brain and a head-capsule-localized fat body, and between ovary and posterior midgut (Droujinine and Perrimon, 2016; Reiff et al., 2015). In vertebrates, the blood or lymphatic vessel organization of one organ relative to another could also be significant in interorgan communication. Moreover, the observation that incorrect orientations of organs in human patients can impact health, including effects on metabolism, suggests that interorgan contacts could also be important for interorgan communication in humans (Jung et al., 2017). Could changes in spatial organization or proportions during obesity, anorexia, disease, injury, deformation, or mechanical forces result in defects in interorgan signaling? In addition, it would be interesting to determine the extent of changes to interorgan contacts that occur during development and aging, and the effects of these changes on interorgan communication (Hudry et al., 2019).

We previously hypothesized that interorgan communication enabled and coevolved with organ specialization (Droujinine and Perrimon, 2016). The work by Hudry et al. (2019) suggests that spatial organization of organs may facilitate interorgan communication. Therefore, could interorgan communication influence the positioning of organs? Altogether, the work of Hudry et al. (2019) will inspire future studies on interorgan regulation of sex-specific growth, physiology and metabolism, and organ spatiotemporal organization.

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