

Will branch for food—nutrient-dependent tracheal remodeling in *Drosophila*

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Mammalian vasculature, and the analogous tracheal system in *Drosophila*, can respond dynamically to hypoxic conditions to maintain a constant supply of oxygen to peripheral tissues. In a recent study published in *Cell*, Linneweber *et al* (2014) reveal that tracheal plasticity can also be regulated by nutrient availability, through both systemic and local insulin signaling. They also show that specific neurons innervating the intestine can respond to nutrient cues and direct long-lasting changes in tracheal morphology that provide metabolic benefits for the organism.

See also: **G Linneweber *et al*** (January 2014)

One of the most remarkable aspects of physiology is the ability of differentiated tissues to undergo remodeling in response to environmental signals. This has been extensively studied in the context of the vasculature, which expands dramatically under hypoxic conditions. Interestingly, recent evidence suggests that metabolic signals can also impact vascular architecture (Fraisl *et al*, 2009; De Bock *et al*, 2013). This relationship has been characterized in tumors, which depend on the circulatory system for delivering the nutrients and oxygen needed for proliferation, as well as the dramatic remodeling of adipose tissue that occurs under conditions of either weight loss or obesity (De Bock *et al*, 2013; Sung *et al*, 2013). Few molecular mechanisms, however, have been identified that explain the coordination between metabolism and vascularization, largely due to the technical difficulties of targeting genetic analysis to the blood vessels of specific tissues.

The tracheal system in the fruit fly *Drosophila* performs a function analogous to that of the mammalian vasculature. It does so through an extensive open tubular network that contacts all tissues in the body (Ghabrial *et al*, 2003). Tracheal placodes specified during embryogenesis develop into bilaterally symmetrical primary and secondary branches. These end in networks of terminal cells that act like capillaries to mediate gas exchange in target tissues. Tracheal cells respond to low oxygen through *Drosophila* Hypoxia Inducible Factor and Fibroblast Growth Factor (FGF) orthologs and can display dynamic remodeling in response to local hypoxic signals, similar to mammalian endothelial cells (Ghabrial *et al*, 2003). In spite of this evolutionarily conserved plasticity, however, no studies have demonstrated an effect of nutrition or metabolism on *Drosophila* tracheal morphology. A recent study by Linneweber *et al* (2014) provides the first steps in this direction.

In this paper, the authors pursue the intriguing observation that a reduction in dietary nutrients leads to dramatically reduced branching of the tracheal terminal cells in the larval gut, with no effect on tracheal architecture in the brain. This occurred under mild dietary nutrient depletion that had no effect on overall developmental timing or growth, suggesting that it occurred independently of tracheal development. The reduced intestinal tracheal network persisted into adulthood, even when the flies were transferred to a more nutritious medium. Moreover, transferring adults raised on normal medium to a one-week sugar diet resulted in increased terminal cell branching in intestinal tracheae, indicating

that nutrient-dependent tracheal remodeling is not restricted to the larval stage.

The authors then focus on defining the regulation of this tracheal plasticity during larval stages and show that it occurs independently of the major regulator of this pathway, FGF signaling. In contrast, inhibiting insulin signaling in the intestinal tracheal terminal cells results in reduced branching that resembles that seen with nutrient deprivation. Consistent with this, genetic disruption of the three major *Drosophila* insulin-like peptides (Dilps) that are secreted into the circulatory system in response to nutrients also leads to reduced gut tracheation (Fig 1). Curiously, however, the authors note that the posterior region of the intestine displayed normal tracheal morphology under these conditions. This region is innervated by two nerves, with some of the axons extending from neurons that produce a distinct insulin-like peptide, Dilp7, as well as the Pdf peptide hormone, which is related to mammalian vasoactive intestinal polypeptide (Fig 1). Genetic inactivation of these neurons resulted in reduced posterior gut tracheation, while increasing their neuronal activity resulted in increased terminal cell branching in this region, indicating that these neurons are sufficient to drive tracheal plasticity in their target tissue. Genetic studies of *dilp7* and *pdf*, together with the systemically secreted Dilps, indicated that the Dilps act together to coordinate anterior and posterior hindgut tracheal morphology, with Dilp7 and Pdf contributing to tracheal outgrowth in the posterior region (Fig 1). Using a genetically-encoded calcium indicator, the authors show that the posterior gut neurons can be activated by yeast in a manner that is

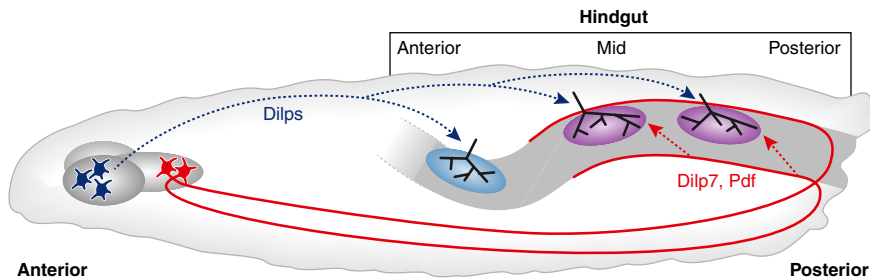


Figure 1. A lateral view of the *Drosophila* larva depicts the brain and hindgut in grey, located in the anterior and posterior regions of the larva, respectively. Cells in the brain, represented by blue circles, secrete Dilps in response to nutrients. These secreted Dilps (dotted blue arrows) promote tracheal remodeling in the intestine. Two nerves from the ventral ganglion of the brain, shown in red, extend to the intestine and innervate the mid- and posterior regions of the hindgut. These nerves release localized Dilp7 and Pdf (red arrows) that, in combination with secreted Dilps, modulate tracheal plasticity in the intestine in response to nutrients.

similar to, but qualitatively distinct from, their response to hypoxia. Finally, the authors link tracheal architecture to systemic metabolism. They show that a reduction in terminal cell branching that is restricted to intestinal cells results in no detectable effects on development, metabolism, or lifespan in adults. Remarkably, however, these flies display a significantly longer lifespan on a low-calorie diet, along with a lean phenotype, relative to controls. Thus, reduced intestinal tracheal branching appears to provide an adaptive advantage that allows the animal to survive more efficiently on a poor diet.

Several recent papers have reported important roles for insulin signaling in transducing nutritional cues to control tissue homeostasis in *Drosophila*. These include the reactivation of neuroblast proliferation in first instar larvae (Chell & Brand, 2010; Sousa-Nunes *et al*, 2011) and the dynamic regulation of intestinal growth in response to dietary signals (O'Brien *et al*, 2011). Taken together with the current study by Linneweber *et al* (2014), these papers demonstrate that insulin signaling plays a broad role in coupling nutrition with tissue remodeling, and raise the possibility that nutrient-responsive plasticity in different tissues might be integrated to properly coordinate tissue function and metabolism. It will also

be interesting to determine if the dynamic tracheal remodeling seen by Linneweber *et al* (2014) can be extended to different tissues. For example, although one experiment showed that a sugar diet can impact intestinal tracheal architecture in the adult fly, it is unclear how this is regulated and if this adult-specific remodeling has any effect on systemic metabolism. Linneweber *et al* (2014) also show, for the first time, that nerves can respond to dietary cues by secreting insulin and neuropeptide signals to promote target tissue remodeling. It will be interesting to determine if these neurons sense nutrients directly and further characterize how both systemic and local insulin signaling is integrated to provide appropriate regionalization of terminal cell shape changes. Finally, perhaps the most remarkable observation in this study is that tracheal remodeling is not only a response to nutritional cues but can also direct changes in metabolic homeostasis that affect overall fitness. Taken together with a recent publication, which shows that changes in mammalian adipose tissue vasculature can have similar beneficial effects on metabolism (Sung *et al*, 2013), it appears likely that the morphology of the vascular system may play a more direct and central role in metabolism

than had been previously expected. This publication by Linneweber *et al* (2014) provides an important new foundation for studying this pathway in detail and defining the molecular mechanisms by which nutrition and metabolic signals can drive vascular plasticity and regulate systemic metabolic homeostasis.

Conflict of interest

The authors declare that they have no conflict of interest.

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