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Preview

A Controlled Burn: Sensing Oxygen to Tune Fat Metabolism

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Animals must decide when to consume precious fat stores in order to sustain life. In this issue of *Cell Reports*, Witham et al. report how oxygen-sensing neurons ensure this decision is made under environmental conditions that favor metabolic efficiency.

A rudimentary gasoline engine delivers fuel and oxygen to a piston and ignites the mix in order to generate compressive force. Under ideal conditions, the air/fuel mix is such that the fuel in the chamber is completely combusted with no unburned fuel remaining. But if conditions change—let's say you step on the gas to accelerate and deliver more fuel to the piston or you drive to a mountaintop where the air is thinner—then the ratio of fuel to oxygen changes, and the efficiency of the engine can suffer. Modern engines neatly solve this problem by deploying sensors to monitor the amounts of oxygen and fuel in each piston with every engine cycle and adjusting the mix when it strays from the ideal. A biological version of this engineering marvel—with an unexpected twist—has now been discovered in the nematode *C. elegans*, where neurons that sense oxygen adjust the rate with which fat stores are converted into metabolic fuel.

Oxygen-sensing neurons were first discovered in *C. elegans* through landmark behavioral studies that dissected an innate behavioral preference for environments with oxygen concentrations in a specific range (Gray et al., 2004). Since their discovery, these neurons have been linked to behavioral responses to microbial food and pathogens (Meisel et al., 2014; Milward et al., 2011; Reddy et al., 2009), and they have also been shown to regulate lifespan through a poorly understood mechanism (Liu and Cai, 2013). In this issue of *Cell Reports*, Witham et al. (2016) report another critical function for oxygen-sensing neurons: controlling the conversion of fat stores into metabolic fuel.

The first inkling of this new function for oxygen-sensing neurons came from the authors' discovery that animals carrying a mutation that activates oxygen-sensing neurons, called URX neurons, display a striking depletion of fat stores in the intestine. A series of elegant molecular genetic analyses demonstrated that the low-fat phenotype of these mutants is caused by oxygen-sensing neurons generating a signal that upregulates expression of ATGL-1, an intestinal lipase that generates free fatty acids (FFAs) from stored lipids (Narbonne and Roy, 2009). This is a novel endocrine function for oxygen-sensing neurons. Moreover, the study suggests an elegant physiological control mechanism that couples oxygen availability with the molecular mechanisms that convert lipids into FFAs, which are fuel used by mitochondria to generate ATP. Harnessing the chemical energy of FFAs to synthesize ATP consumes a great deal of oxygen—tens of moles of oxygen per mole of FFA. The mechanism discovered by Witham et al. (2016) likely ensures that fat is broken down under conditions in which there is ample oxygen available to complete the metabolic reactions that ultimately generate ATP.

Additional study of the connection between oxygen-sensing neurons and fat stores revealed a surprising feature of this neuroendocrine circuit: just as oxygen-sensing neurons modulate the mobilization of fat stores, so too do fat stores modulate the function of oxygen-sensing neurons. The authors discover that, in animals replete with fat stores, the resting (or basal) activity of URX oxygen sensors is lower than those in animals with depleted fat stores. In other words, neuroendocrine control of fat metabolism is not mediated by top-down control of fat-storing cells by neurons but is rather controlled by a regulatory loop in which neurons control fat stores and fat stores control oxygen-sensing neurons.

What is the purpose of this reciprocal feedback between oxygen-sensing neurons and fat stores? In general, feedback can confer robustness and complex dynamics upon control systems. But it is interesting to consider that the reciprocal connections between fat stores and oxygen-sensing neurons might serve different functions. As discussed, there are good reasons to couple fat catabolism and oxygen availability. There are equally compelling reasons to couple the availability of fat stores with foraging behavior, which is heavily influenced by oxygen-sensing neurons. By modulating the basal activity of oxygen-sensing neurons, fat stores in the body might dynamically remodel food-seeking strategies in order to make them high-risk and high-reward when the coffers are full and more conservative when the cupboard is bare. Such a model, although unproved, would neatly integrate known roles of oxygen-sensing neurons in foraging and microbe sensing with the discovery of their role in metabolic control.

This study and the models it puts forth define new and exciting questions in the field of metabolic control. The authors find functional connections between oxygen-sensing neurons and fat stores, but the molecular agents are unknown. Fortunately, *C. elegans* is an organism perfectly suited to tackling such questions, and we can confidently predict that more molecular genetic studies of fat metabolism will

lead us to the factors released by oxygen-sensing neurons in order to control mobilization of fat stores. Perhaps most tantalizing is the question of whether these mechanisms are conserved between phyla, and, if so, how they are instantiated in vertebrates. Given the deep conservation of FFA metabolic pathways between species, it is more than plausible that control mechanisms are also conserved. The cellular and molecular basis of oxygen sensing in the vertebrate brain remains poorly understood, although great strides are being made toward understanding molecular mechanisms used by mammals to sense oxygen and control physiology (Chang et al., 2015). We anxiously await the discovery of vertebrate neurons that are counterparts of the URX neurons so we can begin to understand how such a mechanism might work in ourselves.

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