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Previews

Thermogenesis by THADA

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THADA has been associated with cold adaptation and diabetes in humans, but the cellular and molecular basis of its function has been unknown. Moraru and colleagues (2017) report in this issue of *Developmental Cell* that it triggers thermogenesis by uncoupling ATP hydrolysis from calcium transport into the endoplasmic reticulum.

Obesity and associated metabolic disorders, such as type 2 diabetes, pose a great public health risk in many parts of the world, including in North America. Although excess dietary intake and lack of physical activity are the major causes of obesity, as energy intake exceeds energy expenditure, genetic predisposition to obesity is also a contributing factor. A better understanding of the molecular mechanisms that regulate obesity is therefore critical for its effective management. In this issue of *Developmental Cell*, Moraru et al. (2017) use *Drosophila* as a model to examine the in vivo function of the gene *Thyroid Adenoma Associated* (*THADA*), a strongly selected gene in human evolution that is associated with cold adaptation and type 2 diabetes. They show that THADA is an important determinant of obesity and shed lights on the underlying cellular and molecular mechanism of its function.

One mode of obesity control is non-shivering thermogenesis, which increases sedentary energy expenditure. Normally, the proton gradient generated across the inner mitochondrial membrane during the transport of electrons through the electron transport chain is used by ATP synthase to generate ATP. In non-shivering thermogenesis, mitochondrial uncoupling proteins cause proton leakage across the inner mitochondrial membrane and dissipate the electrochemical gradient in the form of heat in brown and "beige" adipose tissues. This uncoupling of mitochondrial respiration from ATP synthesis thus increases energy expenditure to improve glucose metabolism and promotes weight loss (Kajimura et al., 2015). On the other hand, ATP-dependent calcium pumps such as SERCA use the energy from ATP hydrolysis to transport Ca^{2+} from the cytosol into the lumen of the endoplasmic reticulum (ER). In muscles, the protein Sarcolipin interacts with SERCA and prevents accumulation of Ca^{2+} in the ER lumen without affecting ATP hydrolysis. This uncoupling of ATP hydrolysis from Ca^{2+} transport also leads to non-shivering thermogenesis, improving glucose tolerance and preventing obesity (Bal et al., 2012; Maurya et al., 2015). Non-shivering thermogenesis, therefore, plays a role both in metabolic homeostasis and in thermoregulation.

In addition to non-shivering thermogenesis, genome-wide association studies (GWAS) identified THADA as an important factor in type 2 diabetes, as well as in cold adaptation during human evolution, suggesting that THADA plays a role in energy homeostasis (Cardona et al., 2014; Zeggini et al., 2008). *THADA* is a poorly characterized gene that codes for an evolutionary conserved 220 kDa protein. Chromosomal aberration affecting *THADA* is associated with benign thyroid adenomas (Rippe et al., 2003). To study the role of THADA in metabolism and thermogenesis in vivo, Moraru and colleagues (2017) generated *THADA* knockout flies. In line with the GWAS studies, *THADA* knockout in *Drosophila* leads to obesity accompanied by hyperphagia, reduced thermogenesis, and an increase in lipid storage mostly in the fat body. Interestingly, both fat-body- and neuron-specific expression of THADA in *THADA* knockout mutants partially rescued the obesity phenotype, and only neuron-specific expression of THADA partially rescued the hyperphagic phenotype. Altogether, these data suggest that elevated lipid storage in the fat body and increased food intake contribute to the obesity phenotype of *THADA* mutant flies.

In order to understand the molecular function of THADA, Moraru et al. (2017) examined its subcellular localization. Both immunostainings in fly tissues and western blots on microsomal preparations revealed that THADA localizes to the ER. Moreover, THADA colocalizes with SERCA, which was also found to physically interact with THADA in the immunoprecipitation experiments. Because an increase in ER calcium levels also leads to obesity and hyperphagia, the authors tested whether THADA exerts its metabolic effects by regulating SERCA. Strikingly, a SERCA activity assay, which measures Ca^{2+}-dependent ATP hydrolysis, showed that the loss of THADA leads to elevated SERCA activity. This was accompanied by an increase in ER calcium levels, indicating that THADA acts either as an inhibitor or as an uncoupler of SERCA. Microcalorimetry experiments then showed that the heat production was reduced in *THADA* knockout flies, resulting in enhanced cold sensitivity. Collectively, these experiments demonstrate that THADA acts as a SERCA uncoupler.

Mild and ubiquitous knockdown of *SERCA* completely rescued obesity in *THADA* knockout flies, suggesting that the metabolic effects of THADA are mediated through SERCA. In addition, overexpression of IP_3R, which pumps Ca^{2+} from the ER lumen into the cytosol, partially rescued the *THADA* mutant obese phenotype, suggesting that elevated Ca^{2+} levels in the ER lumen contribute to obesity in *THADA* knockout flies. Notably, the obese phenotype of *THADA* knockout flies can be rescued by expression of human THADA. Moreover, *THADA* knockdown in human HeLa cells resulted in an increase in ER calcium levels, mimicking its effect in *Drosophila* cells. These data indicate that the effect of THADA on Ca^{2+} transport into the ER lumen and on

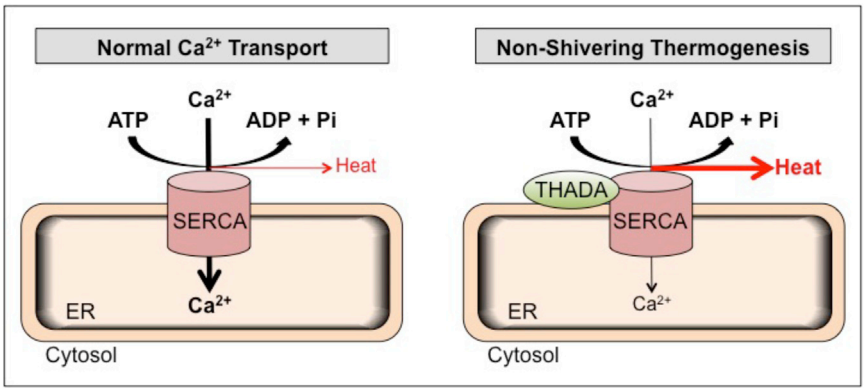

Figure 1. Non-shivering Thermogenesis Triggered by THADA
SERCA uses the energy of ATP hydrolysis to pump Ca^{2+} into the ER lumen. THADA uncouples ATP hydrolysis from Ca^{2+} transport, and that results in reduced Ca^{2+} transport into ER and in thermogenesis due to dissipation of the energy from ATP hydrolysis in the form of heat.

associated metabolic parameters such as adiposity is conserved between flies and humans.

The study by Moraru et al. (2017) is an important in vivo characterization of the physiological function of THADA. It shows that THADA physically interacts with SERCA to uncouple ATP hydrolysis from Ca^{2+} transport and reduces the levels of Ca^{2+} in the ER (Figure 1). In this regard, THADA is reminiscent of Sarcolipin, which is absent in *Drosophila*. This study highlights the fact that multiple non-shivering thermogenic mechanisms, including thermogenesis mediated by mitochondrial uncoupling proteins (Da-Ré et al., 2014), are present in *Drosophila*. Interestingly, single-nucleotide polymorphism (SNP) alleles in human THADA show the strongest positive selection in the evolution of modern humans when compared to Neanderthals (Green et al., 2010). Similarly, the evolution of THADA is associated with adaptation to colder climates (Cardona et al., 2014). The findings by Moraru et al. (2017) are especially interesting in the context of human evolution because they uncover a link between the evolution of THADA and the associated adaptation in energy metabolism.

Unlike UCP1 and Sarcolipin (Pant et al., 2015), THADA is not induced by cold. An exciting question for future studies will be to identify the physiological and environmental signals that trigger THADA-mediated thermogenesis. Both enhanced thermogenesis and reduced ER calcium prevent obesity. The anti-obesity effect of THADA reported by Moraru and colleagues (2017) is possibly mediated through either or both mechanisms. Further characterization of the metabolic effects of THADA in mammals and a better understanding of its regulation might provide new therapeutic targets for the treatment of obesity.

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