Cell

Epigenetic ON/OFF Switches for Obesity

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http://dx.doi.org/10.1016/j.cell.2016.01.006

Heritable epigenetic mechanisms might contribute to the worldwide increase in the prevalence of obesity. Dalgaard et al. identify an epigenetic molecular switch that controls body weight control. The discovery suggests the existence of mammalian polyphenism in energy metabolism and might have implications for strategies to limit the obesity epidemic.

Alternative phenotypes can originate from genetically identical organisms, as a response to environmental cues. This phenomenon, called polyphenism, is a hallmark of epigenetic potential. In insects, environmental cues driven by hormonal or dietary changes can be "sensed" by chromatin-based mechanisms that trigger morphological changes allowing better adaption to the environment (Simpson et al., 2011). However, it is not clear whether such fixed genomic plasticities regulate physiological processes or pathological states in mammals. In an important breakthrough in this issue of *Cell*, Dalgaard et al. (2016) report one of the first examples of a mammalian polyphenism in body weight regulation.

Obesity is a multifactorial disease influenced by the interaction of genetic predisposition and environmental cues, including lifestyle choices. Epigenetic mechanisms inherited or acquired during early life can govern energy metabolic processes and determine body adiposity (Vogt et al., 2014). Moreover, epigenetic marks at specific genes can correlate with body adiposity in humans (Dick et al., 2014). Such marks are implicated in the transmissions of alterations in energy metabolism to progeny (Desai et al., 2015). Recent evidence suggests that the epigenome of somatic cells in obese subjects can be remodeled by anti-obesity therapeutic interventions, such as bariatric surgery (Donkin et al., 2015). Therefore, understanding the mode of action of chromatin-based networks and their role in regulating metabolic processes might be a critical step toward developing preventive and therapeutic approaches to combat the obesity epidemic.

Before formulating therapeutic strategies based on epigenetic modulators, several basic questions need to be addressed. What are the main epigenetic players involved in energy metabolism? Are epigenetically inherited alterations causally linked to metabolic syndrome in humans? Finally, are epigenetic mechanisms implicated in polyphenism and disease occurrence in mammals?

Dalgaard et al. (2016) elucidate an epigenetic network capable of triggering obesity in an ON/OFF bimodal manner. The authors observe that genetically identical (syngenic) mice bearing a mutation in the KRAB-zinc-finger transcription factor Trim28 ($Trim28^{+/D9}$) exhibit a bimodal distribution in their body weight. Adult $Trim28^{+/D9}$ mice randomly switch their phenotype from a normal body weight (obese-OFF) to increased body weight and adiposity (obese-ON). Intriguingly, this "polyphenism" is non-Mendelian and remains stable over many generations, resisting segregation, suggesting the presence of epigenetic mechanisms.

In order to uncover genes involved in this switching, the authors analyze different RNA-sequencing datasets from adipose tissue samples of obese-ON versus obese-OFF mice. Several paternally imprinted genes are differentially expressed in the two groups and specifically downregulated in the obese-ON mice. Interestingly, among different imprinted gene networks (IGNs), an in-silico-based analysis reveals a cluster named IGN1 that is uniquely downregulated in adipose tissue samples of obese-ON mice. Intriguingly, syngenic mice deficient for two genes of the IGN1 network (*Nnat* and *Peg3)* recapitulates the ON/OFF mode of regulation of body weight observed in $Trim28^{+/D9}$ mice. Thus, the authors show that epigenetic alterations of the IGN1 network might underlie the phenotypic switches in the body weight observed in $Trim28^{+/D9}$ mice.

How does the TRIM28 genetic deletion determine alterations in the IGN1 cluster, and what are the mechanisms behind imprinting in these genes? At a molecular level, the authors showed that obese-ON $Trim28^{+/D9}$ mice display altered expression of several factors that form a complex with TRIM28. Therefore, the authors propose a model in which insufficiency of the TRIM28-ZFP57 complex leads to switch-like dysregulation of IGN1 and body weight control. However, they do not show the mechanisms underlying dysregulation of the IGN1 genes. Imprinting typically results from discordant maternal versus paternal DNA methylation in germline defined genomic regions. Surprisingly, in obese-ON mice, no difference in the DNA methylation levels of such imprinting control regions is observed in the IGN1 genes. Therefore, a ''non-classical'' imprinting gene program is proposed. Future work will be required to understand the mechanisms underlying this "non-classical imprinting."

By identifying a TRIM28/IGN1 axis relevant for body weight control (Figure 1), the work of Dalgaard et al. (2016) paves the way for future studies aimed at understanding the metabolic contribution of single or combined genetic components of the IGN1 gene cluster. IGN1 genes

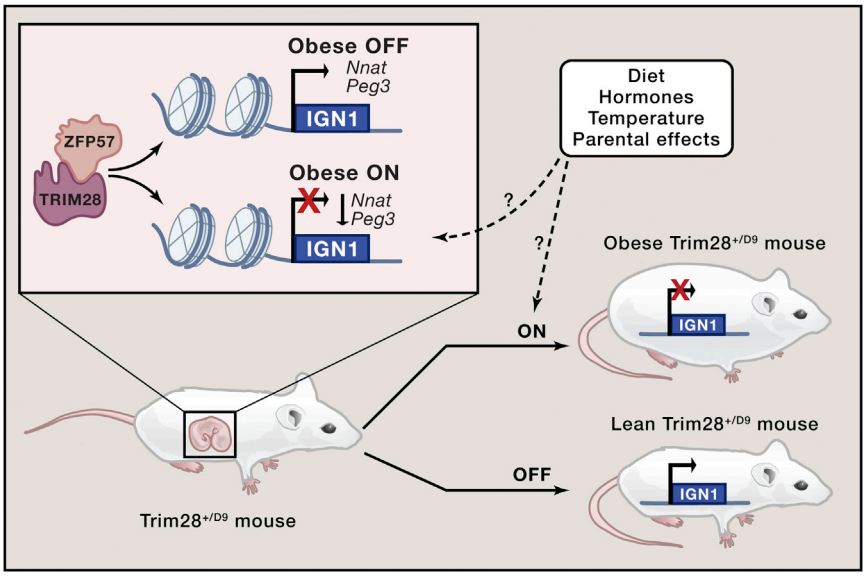

Figure 1. An ON/OFF Switch for Obesity

Mutations in the chromatin-associated co-repressor Trim28/KAP1 (Trim28$^{+/D9}$) affect the formation of a functional TRIM28-ZFP57 complex, which in turn affects chromatin states and modifications during embryonic development. Such (not yet identified) epigenetic alterations might be linked to a down-regulated expression of an imprinted cluster of genes named IGN1. Reduced levels of components of the IGN1 network, including Nnat and Peg3, could lead to an obese-ON program. This program of obesity susceptibility is linked to a phenotypic switch in the body weight in adult genetically identical Trim28$^{+/D9}$ mice, rendering them either normal or obese but without an intermediate phenotype. Such polyphenism might be influenced by environmental signals including dietary conditions, hormonal signaling, and changes in the environmental temperature, occurring in early life stages, during development, or potentially in the prior generation.

have been implicated in metabolic regulation (Curley et al., 2005), but their functional contribution to energy balance is far from being completely understood. Moreover, TRIM28 and IGN1 factors might be involved in several processes such as placentation, developmental growth, control of behavior, and cancer (Cleaton et al., 2014). Thus, more work will be required to test whether and which epigenetic marks may be transmitted to control biological functions such as development and behavior and pathological states such as cancer, in the context of this novel Trim28/IGN1 axis.

Do these findings in mice have implications for humans? After examining the transcriptional profiles of adipose tissue samples derived from multiple human cohorts, the authors observe that humans, like mice, appear to stratify into subpopulations defined by adipose Trim28 expression. Subjects displaying low Trim28 levels exhibited increased obesity incidence and a distinct transcriptome characterized again by IGN1 dysregulation. To further address this epigenetic system in humans, the authors analyzed adipose tissue samples form monozygotic twins displaying differences in their body weight. They observed both reduced Trim28 levels and reduced IGN1 gene expression in obese relative to lean isogenic co-twins. Altogether, these data support a possible role of the Trim28/IGN1 axis in increasing the susceptibility to obesity in humans.

The work of Dalgaard et al. (2016) shows that in mammals and possibly in humans, a switch in the regulation of body weight can occur in genetically identical individuals as a consequence of impairment of the chromatin-sensitive Trim28/IGN1 molecular axis (Figure 1). One critical question remains to be addressed. Can environmental factors contribute to this epigenetic-based mechanism of body weight regulation? The authors believe that this might be the case, as they notice that changes in housing temperature and density of housing affect the frequency of ON/OFF body weight switches observed in Trim28$^{+/D9}$ mice. In support of the potential impact of environmental factors on this epigenetic axis, a recent study has shown that mutations in the insulin and insulin-like growth factor 1 receptors lead to impaired expression of a subset of IGN-1 genes (Boucher et al., 2014), indicating a possible link between Insulin/IGF1 signaling and the phenotype observed in Trim28$^{+/D9}$ mice.

Humans are continuously exposed to environmental factors, such as hormones, metabolic factors, or dietary conditions, that might induce epigenetic re-modeling. More research is needed to establish whether environmentally regulated epigenomic ON/OFF switches for obesity via the Trim28/IGN1 axis operate in humans. Knowing this could help develop preventive or therapeutic strategies to counteract obesity. Or, in a bleaker assessment, epigenetic remodeling might already be driving the obesity epidemic to a point of no return, with the promising therapeutics we discover today ceasing to work in future generations.

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