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Irx3, a new leader on obesity genetics

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Over the past 40 years, the prevalence of overweight and obesity has tripled. The latest World Health Organization (WHO) estimates suggest that 1.9 billion adults (18 years or older) were overweight and 650 million were obese in 2016 (http://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight). Overweight and obesity are associated with early death through increased risk of many chronic diseases, including type 2 diabetes (T2D), cardiovascular disease and cancer [1]. Obesity is therefore a major international public health threat and economic burden. The scientific community believes that identifying the genetic factors underlying the heritable risk of obesity will contribute to our basic knowledge of the biology of energy balance, and might even highlight molecules and pathways that can be targeted for therapeutic intervention.

On this regard, GWAS studies for type 2 diabetes identified a strong association between common single nucleotide polymorphisms (SNPs) in the fat mass and obesity-associated (FTO) gene region and risk of T2D [2–4]. Importantly, later analyses have shown that this association is closely related to body mass index (BMI) rather than T2D [3]. In fact, several studies have confirmed this observation in several human populations [2,3,5]. Noncoding variation in SNPs within a 47-kb region of high linkage disequilibrium in introns 1 and 2 of FTO is still the strongest association with risk to polygenic obesity in humans [6]. Smemo et al. 2014, has previously demonstrated how the promoters of Iroquois homebox gene 3 (Irx3) directly interact with FTO in multiple species, including humans [6]. In consonance with these results, authors demonstrate that not only full body but also hypothalamic-specific genetic deficiency in Irx3 expression leads to 30% weight loss, establishing Irx3 as a novel determinant of body mass and composition.

Here, Araujo T.M. et al. [7] studies the role of Irx3 in the hypothalamus by means of a different approach. Authors demonstrate that viral-mediated partial deletion of Irx3 in the hypothalamus results in the opposite phenotype of the total Irx3 deletion described by Smemo et al. [6] These results suggest the existence of at least two possible scenarios: i) Global or Ins2-Cre deletion of Irx3 performed by Smemo et al. [6] results in embryonic developmental defects that are affecting the development of the hypothalamus and therefore leading to profound alterations in energy balance. A careful analysis of adult deletion of Irx3 compared to the one performed by Smemo et al. [6] through Tamoxifen induced mouse models could be useful to rule out potential developmental alterations. Several lines of evidence can be found in the literature showing that alterations in specific genes during development have different behavioral outputs when compared to alterations performed in adult mice [8]. ii) The extent of deletion or the cells being affected by the deletion can lead to a differential regulation of energy balance mediated by Irx3. Different subsets of neurons expressing Irx3 in the hypothalamus might have diverse physiological outputs, as they are responsible for different functions through partially overlapping circuits. Therefore, it is still conceivable that the results of Araujo T.M. et al. [7] and Smemo et al. [6] can be interpreted differently when a POMC conditional knockout for Irx3 is performed. This neuron-specific ablation of Irx3 might be helpful to parse out the exact roles of Irx3 in energy balance-related neurons. Importantly, authors report that Irx3 is depleted in fasting, similar to POMC/CART, and opposite to AgRP/NPY. Additionally, authors provide evidence that POMC neurons are the main subset of neurons in the arcuate nucleus expressing Irx3. Ideally, this selective deletion of Irx3 should be performed using Tamoxifen induced Cre-LoxP mediated conditional knockouts in POMC neurons in order to sort out the specific roles of Irx3 in relation to energy balance only in adult mice.

It is also worth pointing out the effects observed by a short-term exposure to HFD in hypothalamic neurons. Other publications have also pointed out that quick changes occur when there is an overload of nutrients for a short period of time [9]. These changes might lead to permanent and long lasting effects regarding metabolism that would be worth studying. Several of the genes and/or proteins that quickly change (neuropeptides, regulatory factors such as Irx3, etc.) might be key to fully understanding the alterations that ultimately lead to weight gain and obesity. Finally, it is already known that Irx3 sits in a region with strong association to polygenetic obesity in humans. Additionally, recent results from Araujo T.M. et al. [7] regarding energy homeostasis claims for a necessity to fully understand Irx3 function and mechanism, specifically in energy balance regulating populations of neurons (POMC). I therefore believe that future advances in understanding Irx3 roles might lead to the development of novel therapies regarding one of the most debilitating diseases in western societies by targeting its expression and ultimately modulating energy balance.

Author disclosure

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