EBioMedicine 45 (2019) 15–16

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Genetic and epigenetic regulation of *CRTC1* in human eating behaviour and fat distribution: Methodological and clinical insights and considerations

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Obesity constitutes a significant challenge for individual and public health and the prevalence has been dramatically increasing globally. Prevalence rates of overweight and obesity are estimated to be 39% globally [1]. It is now being increasingly recognized that obesity results from a complex interplay between genetics and environmental factors and that epigenetic processes may constitute a physiological mechanism by which these genetic and environmental factors interact [2,3]. Recent studies in individuals with obesity indicate that various genes implicated in both metabolic regulation and brain function may be involved [2,3]. As such, the CREB regulated transcription coactivator 1 (CRTC1) – an important mediator in the hypothalamus of the effects of hormones and nutrient signals on energy balance [4] – is an interesting candidate for improving the understanding of molecular mechanisms of obesity.

Following up on animal studies and the reported associations between genotypic *CRTC1* variation and BMI and fat mass in humans (e.g. [4,5]), the aim of the study by Rohde et al. [3] in *EBioMedicine* was to investigate genetic and epigenetic (DNA methylation) regulation of the *CRTC1* gene in relation to eating behaviours and physiological parameters relevant to obesity. Research questions were studied in two independent community samples and in individuals with obesity. Interestingly, DNA methylation was assessed in whole blood and in two types of adipose tissue (omental/visceral and subcutaneous).

The study yielded various methodological and clinical insights:

One of the novel findings was that DNA methylation levels of a CpG within the *CRTC1* rs7256986 polymorphism and in a neighbouring CpG were allele/genotype-dependent, suggesting a methylation quantitative trait locus (meQTL). This result complements previous studies that have identified various other SNPs involved in metabolic traits that may play a causal role in the regulation of DNA methylation in adipose tissue [6]. Identifying a meQTL in blood and adipose tissue in relation to eating behaviours and obesity is of interest since it could provide mechanistic insight into how SNPs influence the (clinical) phenotype. It may also constitute one of the possible mechanisms explaining how DNA methylation patterns could be transferred to subsequent generations.

Whereas the MeQTL was present in both blood and in the two types of adipose tissues, DNA methylation and gene expression levels in the three tissues were somewhat differentially associated with the various outcome measures. The reason for this cross-tissue divergence is unclear, but may further underscore the importance of collecting multiple samples when studying peripheral tissue DNA methylation in association with behavioural and physiological outcome [7].

Interestingly, animal studies have shown that (unlike other CREB coactivators such as Crtc2) Crtc1 is primarily expressed in the brain [4,8]. The various associations reported by Rohde et al. [3] with blood and adipose tissue-based (epi)genetic measures of CRTC1 are in line with the obese phenotype observed in *Crtc1* knockout mice [4,8]. Yet, as DNA methylation cannot be assessed directly in the living human brain, an important avenue for future work is the use of animal models of obesity to validate current methylation findings in brain tissue.

It may still be too early to know whether findings could be applied in clinical practice. Effect sizes and sample sizes were generally small and many of the reported associations did not withstand multiple comparison correction. On the other hand, small effect sizes in this domain of research are common given that eating behaviour / obesity are highly complex behaviours / disorders with multiple genetic and environmental determinants [1,2]. Studies with larger sample sizes and including measures such as early-life adversity, mental health and socioeconomic status may further help to adjust for confounding factors in the reported (epi)genetic associations. Furthermore, we know very little about how stable peripheral methylation samples (including but not limited to *CRTC1* methylation) are over time and methylation stability could be different depending on tissue. Longitudinal studies assessing DNA methylation at various points in time may provide insight into the dynamic nature of *CRTC1* methylation and into whether peripheral *CRTC1* methylation patterns are prone to changes in environmental conditions such as diet.

Lastly, animal models suggested that *Crtc1* may play a role in the bidirectional relation between obesity and depression [8]. An interesting question for future research is to what extent *CTRC1* dysregulation is associated with psychiatric disorders such as Anorexia Nervosa (AN) where weight dysregulation, restraint eating and altered energy metabolism are key symptoms. Although AN and obesity are considered at the opposite ends of the spectrum of weight regulation, both disorders have

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.05.050.

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https://doi.org/10.1016/j.ebiom.2019.06.019

been shown to share genetic and epigenetic correlations with metabolic phenotypes [2,9,10]. Yet, it is not known whether *CRTC1* plays a role in AN.

In sum, the study by Rohde et al. [3] provides some interesting insights into the (epi)genetic regulation of *CRTC1* in humans and its possible relevance for (mal)adaptive eating and energy metabolism. Results could help to guide the design of future (epi)genetic studies on the role of *CRTC1* in disorders where altered metabolic function may play a role.

Declaration of Competing Interests

The author has no conflict of interest.

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