OBESITY

Looking at the epigenetic link between obesity and its consequences—the promise of EWAS

Epigenome-wide association studies (EWAS) provide an opportunity to uncover novel molecular mechanisms underlying human disease. The results of a new study of genome-wide DNA methylation patterns, published in *The Lancet*, highlight the usefulness of EWAS in the study of epigenetic effects of obesity in humans. The findings suggest that increased CpG methylation at three different sites in the *HIF3A* locus occurs as a consequence of increased BMI and might have a role in the development of obesity-associated metabolic dysfunction.

To date, many genome-wide association studies have been performed to investigate the contribution of genetic polymorphisms to a broad range of human diseases, but the feasibility of studying epigenetic variation in a similar way has been hampered by lack of appropriate tools. The study investigators have taken advantage of the new Infinium® HumanMethylation450 array (Illumina, San Diego, CA, USA) to explore associations between whole-genome epigenetic variation and BMI.

The researchers used blood collected from 479 adults of European ancestry (the discovery cohort) who either had a history of myocardial infarction ($n = 241$) or were healthy blood donors ($n = 238$). Two unrelated groups were used to validate the initial findings: a primary replication cohort of 339 white patients who had venous thrombosis (the MARTHA cohort) and a second replication cohort of 1,789 white participants without a specific disease (the KORA cohort). The researchers also obtained genome-wide single nucleotide polymorphism (SNP) data for all participants. Furthermore, they used methylation, genotype and genome-wide expression data from 635 subcutaneous adipose tissue and 395 skin tissue biopsy samples collected from another group of white women (from the MuTHER gene expression resource) to assess whether the associations between methylation patterns and BMI seen in blood cells were also present in other cell types.

Methylation at five sites in three genes—one in *CLUH*, one in *KLF13* and three in *HIF3A*—seemed to be associated with BMI in the discovery cohort; however, only the three sites located within the first intron of *HIF3A* were significantly associated with BMI in the primary and secondary replication cohorts. Interestingly, the effect of 10% increased methylation at one of these sites, cg22891070, on BMI was more dramatic than that associated with genetic variation in the ‘obesity gene’, *FTO* (0.98 kg/m² versus 0.39 kg/m² increased BMI, respectively, for a person with a BMI of 27 kg/m² in the discovery cohort).

To assess the causal direction of the relationship between methylation at *HIF3A* sites and BMI, the researchers sought for SNPs upstream of this gene that could be associated with methylation at the cg22891070 site. They identified two such genetic variants, rs8102595 and rs3826795, that were significantly

and independently associated with methylation at this site. As these SNPs were not associated with BMI, the researchers concluded that increased methylation at *HIF3A* is more likely to be a consequence, rather than a cause, of increased BMI. Analysis of tissue samples from the MuTHER cohort showed that BMI was also linked with methylation at the three *HIF3A* sites in adipose tissue but not in skin tissue, which corroborated the investigators’ idea that methylation at *HIF3A* is not a cause of increased BMI.

From their observations, the researchers suggest that increased body weight results in changed methylation patterns in *HIF3A*, a gene that encodes a subunit of hypoxia-inducible factor (HIF), a transcription factor involved in the cellular and physiological response to lack of oxygen. “To find that methylation of *HIF3A* is increasingly altered as someone becomes more obese is remarkable and raises the possibility that HIF may also be involved in mediating some of the deleterious effects of becoming overweight,” comments study leader Nilesch Samani (University of Leicester, UK) in the article’s press release. “Further studies are needed to understand how and when obesity affects methylation at *HIF3A* and what the consequences are, but the findings could eventually lead to new treatments that may tackle the adverse effects of obesity on health.”

The availability of tools with which to perform EWAS opens the way to large-scale studies of the pathways and mechanisms underlying the pathology and adverse effects of other diseases, and might reveal unsuspected roles for epigenetic regulation in these processes.

Joana Osório

Original article Dick, K. J. *et al.* DNA methylation and body-mass index: a genome-wide analysis. *Lancet* doi:10.1016/S0140-6736(13)62674-4

Svsiio/Thinkstock