Genome-Wide Methylation and Body-Mass Index

Obesity is commonly viewed as influenced by lifestyle, environment, and genetic factors. Body-mass index (BMI, or Quetelet index), the most widely used index of obesity, shows a heritability value of > 30% (1). However, common genetic variants identified through genome-wide association studies (GWAS) account for only 1.5% of the variability that is attributable to genetics (2). A recent study probing the epigenome in relation to BMI could offer clues for such “missing heritability” as well as new informations about obesity (3).

Epigenetics defines functionally relevant changes in the genome that are not caused by changes in the nucleotide sequence. Deoxyribonucleic acid (DNA) methylation is a type of epigenetic change that most commonly involves the methylation of a cytosine in clusters of CpG (cytosine and guanine separated by 1 phosphate link) sites, often located in promoters of genes. In turn, these methylated areas tend to suppress the activity of some genes, which is critical during development and differentiation of tissues. Methylation itself is regulated by genetic and environmental factors, and it may be inherited.

Investigations of the association of genome-wide methylation patterns with diseases or physiological traits (epigenome-wide association studies, EWAS) have long been hampered by technological limitations. Taking advantage of a new, validated human methylation array (Infinium Human-methylation450 array from Illumina, including 485,000 methylation sites covering 99% of the genes), the group of NJ Samani *et al.* has

identified and replicated a specific association between BMI and 3 CpG methylation sites in the *HIF3A* locus, in 3 independent cohorts totalling more than 2,600 participants. Every 10% increase in the methylation level at 1 site was associated with a 3.6% increase in BMI (i.e. a 0.98 kg/m² higher BMI for a person with a mean BMI of 27 kg/m²). The association, which was primarily found in whole blood DNA, was also detected in DNA obtained from adipose – but not skin – tissue (3).

Although the cross-sectional design of the study did not allow to infer causality, the authors provided additional analyses suggesting that the increased methylation of *HIF3A* could be the consequence, rather than the cause, of increased BMI. The 3 methylation probes are located in the first intron of the *HIF3A* gene, which is a component of the hypoxia inducible transcription factor HIF but has also been involved in adipocyte differentiation (4). The association could thus reveal a new pathway mediating the effects of obesity.

Although these large studies are promising, it should be pointed out that interpretation of EWAS is much more complex than simple GWAS, as the methylation state is tissue or cell-dependent, and is influenced by age, gender, drug exposure, etc. Nevertheless, the possibility of assessing epigenetic alterations that are influenced by the environment will probably reveal mechanisms of disease that have remained elusive thus far.

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