Research Highlights

Highlights from the latest articles in epigenomics and obesity research

Nutritional status affects the epigenomic profile of peripheral blood cells

Evaluation of: Wang X, Zhu H, Snieder H *et al.*: Obesity related methylation changes in DNA of peripheral blood leukocytes. *BMC Med.* 8, 87 (2010); Milagro FI, Campión J, Cordero P *et al.*: A dual epigenomic approach for the search of obesity biomarkers: DNA methylation in relation to diet-induced weight loss. *FASEB J.* 25(4), 1378–1389 (2011).

Obesity is characterized by excessive adiposity caused by a chronic, positive energy balance. In most cases, obesity is associated with a low-grade inflammatory state, with impaired leukocyte function and infiltration of nucleated blood cells at the site of insulin-sensitive tissues [1,2], leading to metabolic impairments and Type 2 diabetes. There is a growing appreciation that environmental factors may alter DNA methylation, and thereby influence the gene expression that controls the metabolic memory of skeletal muscle and adipose tissue [3,4]. Thus, epigenetic modifications through DNA methylation may contribute to the development of insulin resistance.

The immune system, largely because of its easy access to relevant cells, is one of the most frequently studied areas in the field of epigenetics. In healthy people, global DNA methylation in blood was shown to vary with age [5,6]. In pathological states, notably in chronic kidney disease and cancer, the DNA methylation profile is altered [7,8]. Alterations in inflammatory cytokines have also been associated with insulin resistance and obesity [9]. Thus, the immune system may reprogram metabolically active tissues through

epigenetic modifications that alter glucose and energy homeostasis in obesity and Type 2 diabetes.

Recently, Wang and colleagues have investigated the interindividual DNA methylation profiles of peripheral blood mononuclear cells from two separate cohorts of obese versus lean people [10]. Using a CpG chip covering 27,000 CpG sites, a subset of genes that have an altered DNA methylation profile in obese patients were identified. The promoters of these genes were either hyper- or hypo-methylated, suggesting obesity has a gene-specific influence. Of the identified genes, the most statistically significant changes were found on the *UBASH3A* and *TRIM3* genes, which were found to be hypermethylated and hypomethylated, respectively. In a larger, separate cohort of 91 individuals (14 were in the first cohort), *UBASH3A* and *TRIM3* methylation levels were altered, but to a lesser extent. The span in the BMI between the lean and obese subjects in the second cohort of 91 individuals was narrower than that of the first cohort of 14 individuals. Moreover, the distribution in BMI was more heterogeneous in the larger cohort (30.5–59.9 kg/m² in the obese group), which probably contributed to the smaller difference and higher statistical score between the analysis of the different groups. Nevertheless, the study of Wang and colleagues has highlighted the link between obesity and gene-specific DNA methylation changes in white blood cells. Whether the detected changes represent an epigenetic variation at the single cell level or generalized remodeling of the white blood cell subpopulation, remains to be determined. For instance, a previous report has provided evidence for a fivefold increase of CD34-positive cells in

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blood from obese individuals, suggesting that epigenetic changes could influence remodeling of the blood cell population [2].

One exciting, but still underexplored area is the potential utility of epigenetic markers in the prediction of future disease susceptibility or resistance. Milagro and colleagues have touched upon this by highlighting the potential utility of epigenetic patterns as predictors of disease phenotype or disease prevalence related to energy homeostasis [11]. These researchers determined the effect of an 8-week caloric restriction on CpG methylation in peripheral mononuclear blood cells in 25 overweight men. They identified responders to a caloric restriction and analyzed the DNA methylation status before and after the diet intervention to identify predictors of diet-induced weight loss. Before the dietary intervention, methylation on CpGs located in the region of *ATP10A* (also known as the ATPase class V) and *CD44* correlated with changes in fat mass, as well as levels of the inflammatory cytokine *TNF- α* and the adipose-tissue-derived hormone leptin after caloric restriction. The authors suggest that these sites could be used as biomarkers for the prediction of diet-induced weight loss.

Further highlighting the role of inflammatory factors and the development of obesity, Milagro and colleagues identified differences in DNA methylation after weight loss, notably in *TNFRSF9*, *ApoA-II* and transforming growth factor [11]. Irrespective of the response to caloric restriction, the genome-wide DNA methylation pattern was more homogeneous after (rather than before) the dietary intervention, suggesting that even though the caloric restriction affected body weight differently in individuals, it had a unifying effect on the epigenome. Nevertheless, the observed epigenetic variation could be a consequence of mononuclear subpopulation remodeling. Future studies designed to consider the use of methylation as a potential biomarker for the physiological response to weight loss should evaluate the possibility of a remodeling bias, so that tedious epigenetic testing procedures may be replaced by a simple blood formula.

The influence of epigenetic factors in the development of metabolic diseases such as obesity and Type 2 diabetes is a question of increasing interest. Future studies should consider the resolution of

tissue-specific epigenomes and epigenetic responses in metabolic diseases or whether these marks are transgenerational. The answer to these questions is not trivial, but it will one day allow for an understanding of how environmental and genetic factors collectively influence susceptibility to metabolic disease.

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