Epigenetics and obesity: the devil is in the details

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Epigenetics and obesity: the devil is in the details

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Abstract
Obesity is a complex disease with multiple well-defined risk factors. Nevertheless, susceptibility to obesity and its sequelae within obesogenic environments varies greatly from one person to the next, suggesting a role for gene × environment interactions in the etiology of the disorder. Epigenetic regulation of the human genome provides a putative mechanism by which specific environmental exposures convey risk for obesity and other human diseases and is one possible mechanism that underlies the gene × environment/treatment interactions observed in epidemiological studies and clinical trials. A study published in BMC Medicine this month by Wang et al. reports on an examination of DNA methylation in peripheral blood leukocytes of lean and obese adolescents, comparing methylation patterns between the two groups. The authors identified two genes that were differentially methylated, both of which have roles in immune function. Here we overview the findings from this study in the context of those emerging from other recent genetic and epigenetic studies, discuss the strengths and weaknesses of the study and speculate on the future of epigenetics in chronic disease research.

See research article: http://www.biomedcentral.com/1741-7015/8/87/abstract

Introduction
Obesity is highly prevalent in most industrialized nations where labor-saving devices and calorically dense diets are common [1]. The impressive results from randomized clinical trials of intensive lifestyle modification on short- to medium-term weight loss [2,3] give us good reason to believe that traditional hunter-gatherer or subsistence farming lifestyles might be a panacea for the obesity epidemic. However, programs of lifestyle modification are notoriously difficult to implement and maintain on a large scale for prolonged durations, and the public health message of “eat less and exercise more” appears to have fallen on deaf ears. Thus, despite the apparently simple explanation and remedy for obesity, this knowledge is not enough. So we are saddled with a challenge, which is to unravel the mechanisms by which obesity emerges and to understand how its presence causes disease and death, with the hope that somewhere within the details hides the solution to the problem.

Although obesity is widespread, certain ethnic groups appear much more susceptible than others to the condition [4]. Striking differences in the rates of obesity are often seen between genetically distinct subpopulations, such as American Indians and people of northern European ancestry living within comparable environments, indicating that obesity may be the consequence of gene × environment interactions. More concrete evidence of such interactions has emerged from epidemiological cohort studies, most notably for the interaction between a polymorphism at the FTO (fat mass and obesity gene) locus and physical activity levels [5]. Nevertheless, even where rare examples of statistically reliable gene × environment interactions have emerged from epidemiological studies, causal inference is often difficult and little is revealed about the underlying mechanisms driving the interaction.

Mechanisms of gene × environment interactions in disease
So what mechanisms might underlie the gene × environment interactions observed in epidemiological studies or clinical trials? Clearly, the manner in which an interaction is defined and quantified will affect our ability to understand the cellular mechanisms which underlie it. However, assuming the interaction is a consequence of environmental effects (for example, smoking, physical activity, or dietary whole grains intake) on a disease trait that are dependent on the genotype of an individual,
there are probably at least two closely related mechanisms that might give rise to the interaction (Figure 1).

The first involves differential transcription rates across genotypes in response to environmental stimuli. During aerobic exercise, as an example, subsets of genes, particularly those involved in oxidative energy metabolism, are upregulated [6]. If the rates of transcription or translation of these genes were to differ by genotype, one might, at a population level, observe a gene × lifestyle interaction on a clinical phenotype such as blood glucose concentrations. The second mechanism by which genes and environmental factors might interact involves epigenetic factors, such as DNA methylation and histone modifications.

The word **epigenetics** describes the phenomena of inherited changes in gene function that occur independently of changes in the nucleotide sequence [7]. Initially, it was believed that epigenetic modifications were unidirectional, but recent studies have demonstrated that the epigenome is in fact highly dynamic, changing in response to nutrient availability, physical exercise and aging, among other exposures [8-22]. While nearly all cells in the body have the same nuclear genome, different cell types have their own epigenomes, a characteristic essential for the development of cell-specific phenotypes. In differentiated mammalian cells, DNA methylation occurs primarily to cytosines in CpG-dinucleotides[23]. DNA methylation of gene promoters has also been implicated in transcriptional silencing, mainly through repressed transcription factor binding to gene promoters or by recruiting methyl-CG-binding proteins, which in turn recruit histone deacetyltransferases (HDACs) and corepressors. By virtue of the cell’s capacity for histone modification, it can control its chromatin structure and either activate or suppress the transcription of its genes. Early-life nutrition represents an intriguing example of how environmentally augmented epigenetic events might affect an individual’s response to environmental triggers.

**Figure 1** The mechanisms that underlie observations of gene × environment interactions made in epidemiological studies (or gene × treatment interactions in clinical trials) likely involve a combination of epigenetic and transcriptional modifications. Although environmental exposures may be the primary triggers of these perturbations, the phenotypes themselves may also feed back to trigger both epigenetic and transcriptomic events, thus modulating the expression of disease phenotypes. The figure shows a simplification of how these processes might fit together. HDAC, histone deacetyltransferase; NCoR, nuclear receptor corepressor; MeCP2, methyl CpG binding protein 2.
to metabolic load and disease susceptibility in adult-
hood, with numerous studies lending weight to this
hypothesis [14-16,24,25]. Nevertheless, our understand-
ing of how epigenetic events early in life influence the
development of obesity and its comorbidities remains
fairly rudimentary.

This month in *BMC Medicine*, Wang et al. [26] report
a study in which they examined DNA methylation in
isolated blood leukocytes and its relationship with obe-
sity-induced immune dysfunction in seven lean and
seven obese African American male adolescents. Specifi-
cally, the authors examined DNA methylation in periph-
eral blood leukocytes at approximately 27,000 CpG sites
spread across more than 14,000 genes and compared
methylation patterns between the two groups. Epigenetic
studies are often constrained in their size by the high
costs of the methylation chips (although this obstacle is
receding as the technology becomes less expensive).
This, in combination with the multitude of hypothesis
tests that are performed in multiplex experiments and
the corresponding procedures to correct for type 1
errors, render almost all existing epigenetic studies
underpowered to detect statistically robust effects. Such
is the case with the study conducted by Wang et al.;
indeed, none of the findings from the first phase of their
experiment remained statistically significant after correc-
tion for multiple testing. Despite this, the authors car-
ried forward their most promising findings (defined as
either genes yielding association *P* values ≤2×10⁻⁴ or
those with differences in DNA methylation ≥27.1%) for
replication in a cohort composed of 45 obese and 46
lean individuals. In these replication analyses, two of six
genes were differentially methylated in obese compared
with lean individuals; the levels of DNA methylation for
*UBASH3A* (ubiquitin-associated and SH3 domain-
containing A) and *TRIM3* (tripartite motif-containing 3)
were higher and lower, respectively, in obese compared
with lean individuals, findings that were directionally
consistent with those from the first phase of the study.

Interestingly, recent genome-wide scans have impli-
cated DNA variants proximal to *UBASH3A*, which
encodes a T-cell signaling- and activation-regulating
protein [27], in the development of type 1 diabetes [28].
Thus, the findings of Wang et al., when placed in con-
text with existing genetic data, suggest that *UBASH3A*
may play a role in obesity-induced immune dysfunction.
Intriguingly, *TRIM3*, which belongs to the superfamily
of TRIM proteins, is also involved in immune response
[29], which may explain why differential methylation
patterns of these genes were visible in blood leukocytes.

The study by Wang et al. is small and probably
underpowered to detect all but the largest differences in
DNA methylation. It may be, therefore, that with a lar-
ger sample size, statistically significant differences in
DNA methylation patterns for many other genes that
are smaller in magnitude than for *UBASH3A* and
*TRIM1* would be observable. The detection of other
CpG sites and genes might also be facilitated by the
application of methods that afford greater genomic cov-
verage, such as deep sequencing combined with either
bisulfite-treated DNA or immunoprecipitation of methyl-
ated DNA.

While peripheral blood leukocytes are attractive for
epigenetic studies, not least because they can be easily
obtained, there are many other cell types and tissues
involved in the pathogenesis of obesity and its comor-
bidities, such as adipose tissue, skeletal muscle and
hypothalamus, the examination of which could be well
worthwhile in the context of epigenetics. Along these
lines, Bouchard et al. [17] recently provided some of
the first evidence that DNA methylation in adipose tissue
differs in people who respond well and those who
respond poorly to caloric restriction for weight loss.
Elsewhere, a high-fat diet lasting 5 days was shown to
affect DNA methylation of a major transcriptional coac-
tivator (peroxisome proliferator-activated receptor-γ
corepressor 1-α) of genes involved in oxidative energy
metabolism [13]. Furthermore, in studies examining
early life overnutrition and obesity, DNA methylation of
the hyperthalamically expressed pro-opiomelanocortin
promoter, which plays an important role in hunger and
satiation [30], was observed. While these studies imply
that epigenetic modifications cause obesity, metabolic
disease and its complications, it is virtually impossible
to establish whether changes in methylation precede
the development of obesity or *vice versa*. Indeed, these
relationships may not be causal at all, but consequences of
confounding by factors correlated with obesity and
DNA methylation, such as physical inactivity, nutrition
or smoking.

Elucidating causal relationships between DNA methy-
lation and obesity will be necessary if observations of
the nature described by Wang et al. are to be of clinical
value. Inevitably, this probably means that randomized,
controlled trials of weight loss or weight gain interven-
tions, where DNA methylation patterns are assessed
before and after the intervention and subsequently com-
pared between the treatment and control arms of the
trial, are required. It will also be necessary to examine
whether changes in DNA methylation correspond with
changes in gene transcription and/or translation, as well
as more distal, clinically relevant phenotypes. Assessing
these relationships in diverse tissues and cell types and
in different demographic groups and environmental
contexts will further advance our understanding of how
epigenetic events affect an individual’s predisposition to
obesity, or how obesity impacts the epigenome. Whether
changes in DNA methylation are associated with
obesity-induced histone modifications of the same genes (that is, whether DNA methylation coincides with the presence of closed histone marks) represents another interesting but as yet unanswered question.

**Concluding remarks**

In summary, Wang et al.’s study provides tentative evidence that DNA methylation at two loci, IABASH3A and TRIM3, may be implicated in the pathogenesis of obesity. Replication of these findings in independent settings will be necessary to ensure that these findings are true positives, and to fairly conclude that the relationships are causal will require appropriately designed experimental studies. Because of these and other hurdles facing the field of epigenetics, identifying a meaningful clinical application for epigenetics in the prevention or treatment of obesity is likely to remain more vision than reality for some time to come.

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**Authors’ contributions**

PWF wrote the first draft of the article. Both authors contributed to the development of the draft.

**Competing interests**

The authors declare that they have no competing interests.

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