Commentary: Marking the epigenome—in search of the fingerprints of intrauterine nutritional deficiencies

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Epigenetics is increasingly attracting the attention of epidemiologists for many reasons: unlike the genetic code, epigenetic marks are modifiable; environmental exposures influence the epigenome; epigenetics may provide the mechanistic underpinning for certain exposure–disease associations; and, the epigenome provides a wealth of opportunities to identify new disease risk and early detection biomarkers.1 Moreover, the relevance of epigenetic aberrations for health and disease has been suggested in numerous studies, linking epimutations to a variety of illnesses ranging from childhood disorders to cancer. The prenatal establishment of the epigenome has made it a favourite also among researchers of the Developmental Origins of Health and Disease (DOHaD), as transient perturbations during intrauterine life may affect the reprogramming of the epigenetic code.2
In this issue of the *International Journal of Epidemiology*, Lumey et al. trace epigenetic mechanisms as possible explanations of DOHaD observations using data from the Dutch famine. Lumey et al. identified individuals whose mothers were exposed to the Dutch famine of 1944–45 during their pregnancy or during the time of conception. Controls were individuals not exposed to the famine in utero who were conceived either before or after the famine. Blood samples were collected from the study participants at an average age of 58 years and DNA was extracted from white blood cells. The investigators then proceeded to assess DNA methylation of repetitive elements throughout the genome and found no differences in study participants exposed to the famine and those not exposed.

Intrauterine famine exposure has been linked to adult obesity, coronary heart disease and schizophrenia. Several mechanisms have been proposed for these observations including intrauterine metabolic reprogramming, mismatch between pre- and postnatal environment, and developmental plasticity. However, the molecular details remain elusive and epigenetic modulations offer a tempting conduit to connect early nutritional deficiencies to distant disorders. As we sort through the potential candidates in the epigenetic toolbox, we may consider functionally relevant genes and explore their transcriptional control by DNA methylation, histone modification or non-coding RNAs. A first’ approach’ is often to look at so-called ‘global methylation’ to potentially pick up some crude signals. Whereas little is known about the functional relevance of methylation of repetitive elements such as LINE-1, Alu or Sat2, it is diminished in patients with cancer, and also declines with age, making it a frailty index. Indeed, the term global methylation is somewhat of a misnomer since genome coverage is limited and cytosine methylation of different repetitive elements is little and may even be inversely correlated as also observed in the study by Lumey et al. The lack of specificity precludes a role of repetitive element methylation as biomarker other than of ageing or possibly of cancer in general. Why methylation of repetitive elements should be particularly vulnerable to intrauterine starvation remains unclear and no rationale is offered by the authors. Nevertheless, the lack of association in this latest study from the Dutch famine does not preclude gene-specific methylation changes following prenatal deprivation.

In a previous study of the same population, these and other investigators examined DNA methylation of the imprinted *IGF2* gene among individuals prenatally exposed to the Dutch famine and their unexposed siblings. At the age of 58 years, methylation of the *IGF2* DMR0 in the blood was 2.7% lower among the participants exposed to the famine relative to their siblings. The authors concluded that ‘early-life environmental conditions can cause epigenetic changes in humans that persist throughout life’. To support the link between prenatal deficiencies and epigenetic marks six decades later, the same adaptive responses of the epigenome would have to be present immediately following the exposure. Although logarithically difficult to obtain, biological samples at birth are necessary to separate intrauterine from life course effects on DNA methylation. Of course, whether the modest difference in methylation observed has any functional relevance would require verification of (allele-specific) expression changes, but RNA was not collected by the investigators. It will be interesting to explore the relation between *IGF2* DMR0 methylation and other adult methylation changes identified among famine-exposed individuals and the classic DOHaD diseases such as hypertension, cardiovascular disease, diabetes and obesity. Unfortunately, limited data are yet available on the epigenetic regulation of these disorders.

The choice of the tissue that may reflect traces of developmental experiences is another important consideration since the timing of early environmental insults may affect tissues of the various germ lineages differently. White blood cells are of mesodermal origin and although their DNA is most easily accessible and commonly collected in long-term studies or biobanks, the reproducibility of their epigenetic profile in repeated blood samples collected over (even short) periods of time represents another challenge. Given the cell type specificity of epigenetic marks, the ever-changing composition of the different white blood cell fractions following infection, inflammation and preclinical disease makes inter- and intra-individual comparisons difficult to interpret.

The growing interest in epigenetics in the DOHaD community calls for the careful planning of well-designed long-term cohorts that can provide the necessary data and biological samples to answer relevant questions. The epigenetic epidemiology of DOHaD has the potential to identify important associations between early environmental stimuli during sensitive developmental periods and persistent changes in epigenetic regulation. Whereas the nature of epigenetic control mechanisms makes them prime targets for periconceptional and prenatal experiences, in particular intrauterine nutritional deficiencies, pertinent epidemiologic studies lending support to the role of such primary imprints have yet to be conducted.

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References


