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Commentary

Mother smoking leads to methylation anomalies on 'smoke' genes in the offspring: Indelible traces of previous injuries

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Long-term consequences of exposure to smoke is a subject of increasing interest in medicine, especially so when the exposure occurs during prenatal life and there is a steady increase in the number of related publications. It is an important Public Health issue, since for instance in the US, 12.3% of women keep smoking daily during pregnancy.

At early terms (during pregnancy) it is known that nicotine has important impacts on human fetal development, potentially affecting different physiological systems such as the respiratory, the cardiovascular and the neurological system [1]. Exposure to tobacco derivatives has also early deleterious effects such as pregnancy losses, in utero fetal demise, increase morbidity and mortality [2,3]. Beside these gestational consequences, long term effects are of major interest and abundant epidemiological data accumulates about the putative risks.

A major scientific question is to be able to understand the mechanisms driving these long-term effects, inaccessible to the mere epidemiological analysis. A strong emerging idea is that epigenetics, particularly DNA methylation, might play a pivotal role in the fetal organic memory of the old injury originating from the mother smoking behavior. In a seminal paper of 2012, Joubert and coworkers demonstrated the existence of 26 significantly modified CpGs, from the systematic analysis of 1062 cord blood DNAs (representing marks on the newborn White Blood Cells). These CpGs were located in 10 genes, including *AHRR*, *CYPA1*, *MYO1G*, *CNTNAP2* and *GFI1* [4]. These differences were mild (around 20% of the methylation level at the maximum). Strikingly, and this is sufficiently rare to be stressed, further independent studies confirmed methylation anomalies at the same loci on 313 newborns [5]. About long-term effects, the same genes were found from birth until 17 years [6]. Following a drastic harmonization protocol, a meta-analysis performed in 2016 [7], that collected 13 newborn and 6 older children studies confirmed the previous findings. To note, it appeared that the gene *GFI1* encompassed 10 significantly modified CpG in the gene body that all presented a decreased methylation level in samples from smoker pregnancies.

The study published in this issue of *EBioMedicine* (Parmar et al., [8]) was coordinated by Sylvain Sebert in Oulu in Finland and Marjo-Ritta Järvelin, in London St Mary's campus at the Imperial College in UK. The study focuses on the GFI1 locus and connects the abnormal DNA methylation at 8 CpG positions of this gene that are induced by prenatal maternal smoking, with the adult cardiometabolic health. Cardiometabolic parameters were collected from 22 population-based studies from numerous centers (Finland, Italy, UK, Germany, Estonia, Sweden, the Netherlands, Australia, Singapore, USA, China, France, representing 18,212 patients). The participants were aged 16–81 years for the cardiometabolic measurements, 17% were smokers, 18% had been exposed prenatally to maternal smoking. Five cohorts were pregnancy-birth, and 20 were either 'pure' population studies or incorporated prenatal exposure patients. The aim was to identify the epigenomic impact of prenatal maternal smoking on the long-term on cardio-metabolic function. Four thousand two hundred and thirty individuals from five studies were used to meta analyze prenatal smoking exposure, allowing to identify 3 significantly hypomethylated CpG (max demethylation ~3%). On the other hand, 13,551 individuals could be used to evaluate the self-smoking methylation effects and revealed significant demethylation at the 8 CpG positions under scrutiny (max demethylation ~6%). Methylation at each CpG was then correlated with cardiometabolic parameters. The authors could demonstrate genome-wide significant associations between decrease methylation at specific CpGs with Body Mass Index, Waist Circumference and systolic Blood Pressure, that either increased (for a CpG associated with exposure to maternal smoking or decreased for the CpG most strongly associated to the own smoking). The eight CpG of GFI1 that were found significantly demethylated either prenatally or for the own smoker, were associated with higher TriGlycerid (TG) levels.

In sum, the study validates previous findings that smoking induces demethylation at specific genes and demonstrates a correlation with cardiometabolic parameters.

Two major limitations, that are not specific to the present study, are (i) the fact that the correlation found between demethylation and physiological measures, may not be the mark of an obvious functional impact, and (ii) these studies until today, do not address the fundamental question of the mechanical reason why and how smoking modifies methylation at specific positions.

Concerning the first point, *GFI1* encodes a zinc finger protein acting with histones to silence transcription in particular for Th1 cell differentiation [9], without known connections with detoxication mechanisms (which is quite different from *AHRR* or *CYP1A1*, factors that are directly involved in cellular detoxication mechanisms). In addition, the mild demethylation observed may not be enough to impact seriously gene expression, de-methylation in gene bodies (as is the case in GFI1) being often associated with decreased expression. Finally, the

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epigenetic measures carried out on blood cells may not represent alterations in other relevant tissues.

For the second point, the fact that altered methylation under smoking, consistently affects specific CpGs, indicates the existence of molecular mechanisms driving modifications at specific genomic positions. Whether these mechanisms necessitate specific chromatin editor molecules, for instance guided with non-coding RNA guides is not known today. Whether these mechanisms share tools with the imprinted gene toolbox (which also affects specific chromatin regions) is also a possibility that warrants further research [10]. Knowledge about these mechanisms could be a way of re-modifying DNA methylation with a targeted approach, differently that what is today envisaged by alterations of the diet, such as folate or vitamin C supplementation that may impact overall the DNA methylation pattern [11,12].

Conflict of interest

None declared.

Author contributions

Daniel Vaiman wrote this Editorial.

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