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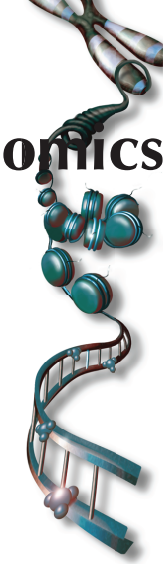
Commentary

Epigenomics



The epigenome as a biological candidate to incorporate the social environment over the life course and generations

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"Identifying biological responses to the social environment will give the opportunity to identify direct, objective information on physiological mechanisms that eventually contributes to disease onset before its clinical diagnostics, which could in turn help to design preventive interventions (before disease development)."

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"*Epigenetics modifications in response to the social environment: a potent tool to tackle social inequalities in health and break the generational transmission?*"

Social inequalities in health relate to the systematic relationship that exists between socioeconomic groups and a wide range of adverse health conditions and mortality both between and within countries worldwide [1,2]. The social gradient in health indicates that health is progressively better the higher the socioeconomic position (SEP) of people as reflected by, for example, their educational attainment, occupation or levels of income, or by the characteristics of the places where they live. These differences between social groups are systematic, unfair and avoidable [3]. Social epidemiology aims at understanding the diseases' distribution in populations assuming that diseases are the product of interactions among social, individual and biological factors [4]. Some key findings of social epidemiology include that social inequalities in health are not entirely explained by measured behavioral risk factors [5] and access to healthcare [6] suggesting that others pathways are involved in particular social determinants of health which are "*the conditions in which people are born, grow, live, and work, and age, and the wider set of forces and systems shaping the conditions of daily life*" (WHO) [7]. Several theories that are to be viewed as complementary rather than mutually exclusive have been proposed and developed to gain new insights on the relationships between these living conditions and social inequalities in health. One of the most widely used models is Dahlgren and Whitehead's 1991 model [8]; more recently Krieger's 'ecosocial theory' [9] as well as other multilevel frameworks have proposed combining social and biological elements within a life course perspective to identify the determinants' distribution of disease within populations and better understand how social inequities in health arise.

Based notably on several theoretical works from different authors (Krieger [10], Hertzman [11] and Elder [12] in the early 2000s, and more recently by Blane *et al.* [13]), Kelly-Irving and Delpierre [14] proposed last year a framework for understanding health inequalities through the social-to-biological mechanisms. The social-to-biological transition refers to how the social environment can lead to biological alterations, literally "*how life gets under your skin*". Briefly, they defined two broad mains types of socially distributed initial mechanisms: the first are mechanisms of 'exogenous' origin whereby external entities or conditions either enter the body and trigger a physiological response (inert entities such as foodstuffs, asbestos or pollutants, or living entities such as viruses, bacteria, etc.) or result in physical damage (accidents, injuries) or physical effort (movements, actions). This

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concerns environmental exposures such as pesticides, pollution and work exposures as well as behaviors such as tobacco, alcohol and diet. Second is the mechanism of 'endogenous' origin wherein sensory interpretations of interactions with the surrounding environment induce responses from 'internal' molecules from the body mainly linked to stress perception and stress response systems, as well as psychological and cognitive functions. In terms of exposures this concerns especially psychosocial exposures such adversities during childhood (trauma, emotional or psychological abuse, sexual abuse, physical violence, neglect), occupational constraints, social support, social isolation and experiencing discrimination, whether related to age, gender, social class, skin colour, sexual orientation or disability. The two types of exposures may also interact and affect each other along the life course [14]. One important candidate of the social-to-biological transition that could explain how social inequalities are biologically embodied and further related to inequalities in health involved the stress response systems; the induce prolonged stimulation of the stress response and its consequence on hormones, inflammatory/immune, endocrine and nervous systems may ultimately lead to shorter lifespans and the onset of chronic conditions [15]. Additionally, all different organ systems are subjected to decline in their functional capacity and become dysregulated at multiple levels (anatomic, molecular and physiologic) with age. However, the decline rate may vary between systems within an individual and between individuals in relation to social environment. Research on aging incorporates the biological mechanisms contributing to aging itself and the environmental exposures along the life course including social conditions which can affect aging and the risk of age-related frailty, disability and disease [16]. In addition to chronological age, measures of biological aging at the individual level are being developed to identify, characterize and quantify the different decline rates over time according to adverse social exposures [17]. The commentary's aim is to illustrate how the social-to-biological transition can take place at the epigenome level – mainly through blood DNA methylation – especially because considering the complex interplay of these political, social, psychological and biological factors offers an important opportunity for prevention and intervention.

The epigenome (from Greek: 'epi' = over) refers to the DNA chemistry modifications that modify or mark the genome that can affect gene transcription and translation without change in the nucleotid sequence of DNA; different cell types have different epigenetic marks, which is essential for their pattern of gene expression and their functioning [18]. Epigenetics is the study of these modifications, through different mechanisms such as histone modifications, miRNA expression and DNA methylation, which can be reversible and closely interconnected, and can be altered by both environmental and genetics factors [19]. Epigenetic mechanisms begin in the gametes and zygote and continue to occur all along an organism's life course with the growth of the foetus, the birth and its development. Epigenetics processes are first involved in cell differentiation, which determines cells' fate during development, and they remain an integral element of cell processes throughout life.

Most of the studies have been centered on DNA methylation (the addition/deletion of a methyl group [CH_3] directly to a cytosine base in DNA), occurring most often in the context of a CpG site, which is a cytosine nucleotide located proximally to a guanidine nucleotide. DNA methylation happens when a methyl group is added to the fifth carbon of cytosine at a CpG site by DNA methyltransferase enzymes, while DNA demethylation arises when the methyl group is removed from the cytosine. Epidemiological studies mostly in adulthood have identified that several environmental factors including 'exogenous' mechanisms related to exposure (e.g., air pollution [20], pesticides [21], work exposure [22] and behaviors such as tobacco use [23], alcohol [24] and diet [25]) and 'endogenous' mechanisms related exposure (e.g., adverse childhood experiences [26], psychosocial stress [27,28], posttraumatic stress disorder [29] and social environment [30]) are associated with DNA methylation changes and/or aging using clocks (composites biological age predictors derived from mathematical techniques using a group of CpGs sites, also referred to as DNA methylation age: individuals aging more quickly should have a higher score compared with those aging more slowly [31]). However, few studies have investigated these factors in relation to histone modifications and miRNA expression. Furthermore, alteration in these mechanisms could mediate various pathophysiological conditions: metabolic disorders, neurological diseases and cancers [32]. Many of the above epidemiological studies are designed as observational studies, with the main limitation being confounding bias. Several statistical approaches have been proposed in the field of epidemiology which developed conceptual frameworks to deal with causality [33] to mitigate these confounding biases and consider intermediate variables on the path between exposure and outcome. Mediation, paths analyses or the counterfactual approach could be useful to dismantle and describe diverse pathways from exposure to outcome. However, in all cases, considerable thought must be given to define the relevant conceptual model, picking up the appropriate variables and statistical model, and carefully interpret the results.

There are different ways in which these epigenetic modifications are thought to contribute to the development of disease. One prevailing theory relates to the developmental origins of health and disease hypothesis in which environmental exposures during critical developmental stages, usually *in utero*, are thought to influence an organism's susceptibility to disease [34]. For instance, we performed epigenome-wide association studies of DNA methylation changes using data from a British birth cohort, at birth, in childhood (7.5 years on average) and in adolescence (15.5 years on average) in response to four early-life SEP indicators. We found that maternal education had the strongest effect on the methylome at birth and in adolescence, while the three other SEPs had a moderate effect on the methylome of the children [35] suggesting that maternal education may be embedded in the methylome of the offspring.

There are other situations where the lifestyle or exposures along the life course, in conjunction with this early programming, also contribute to the development of disease. The life course approach which arose in the social sciences in the 1980s has introduced the dimension of timing process and context to study the human experience [12]. The life course approach has found an echo in epidemiology because it offers a dynamic interpretation of the health state taking into account its temporal variation and the effect of social conditions during a person's lifetime and not because of shared risk factors but because of potentially linked causal chains or pathways [36].

Because the epigenome can respond to any type of environmental stressors in addition to being genetically regulated and because some changes are partially reversible or persistent, the epigenome can be seen as the mirror and the memory of the endogenous and exogenous environment along the life course [37]. As an example, when we investigated the dynamics of epigenetic modifications after quitting smoking in a sample of 745 women from two independent European cohorts with the genome-wide methylation profiles measured from blood samples, we observed two groups of CpG sites: sites whose methylation returns to levels of never-smokers, and sites that remain differentially methylated, even after smoking cessation for more than 35 years [38]. The number of epigenome-wide association studies has risen exponentially over the last decade due to the ability and the decreasing cost to study methylation at the genome-wide level together with the expansion of accessible bioinformatic pipelines. There are many sources of error in epidemiological studies including study designs, power and sample size consideration, population and selection bias, measurement errors and residual confounding, replication and/or validation analyses [39]. There are also many other limitations common to epigenomics studies, from data preprocessing, technical variations and statistical association testing to downstream analyses including methylation risk score, methylation quantitative trait loci analysis, estimating cell-type proportions (each tissue and cell type has unique DNA methylation profiles) and methylation age acceleration analysis [40,41]. Of note, most of the studies investigating the epigenome analyzed DNA methylation in blood as this is an easy fluid to collect. However, one can ask if the modifications of epigenome in organs would not be as or even more relevant when it comes to performing association with diseases. Thus, a key research challenge in epigenetic epidemiology is the cell/tissue specificity of epigenetic signatures (mostly from blood samples) and what can be extrapolated from blood as well as to what degree these epigenetic signatures may be extended to difficult-to-access tissues, such as the brain in studies investigating neurological disorders, for example. Another major limitation of epigenome-wide association study is the functional consequences of an observed DNA methylation change between two differentially exposed groups. Despite these limitations, the use of the epigenome is growing in epidemiology, including in the field of social epidemiology. One example is the emergence of human social genomics approaches that aim to help map key biological pathways in response to psychosocial conditions and an adverse social environment, and how these mechanisms influence disease development and progression [42]. Pathways of inflammation and immunity are especially noteworthy: changes in stress response have been shown to influence various biological mechanisms, in particular inflammatory and immune responses via the hypothalamic pituitary adrenal axis activation, and inflammation is a critical pathway involved in the risk and development of many chronic conditions. As an example, we recently proposed an integrative multiomics approach combining DNA methylation, gene expression and protein level in blood to define a functionally relevant inflammatory methylome and analyze this inflammatory methylome in response to SEP indicators along the life course in 178 participants from a European cohort study. We showed that participants with a disadvantaged SEP in young adulthood or in adulthood had a lower inflammatory methylome score later in life compared with participants with a more advantaged SEP independently of major health behaviors and BMI [43]. Key research challenges in epigenetic epidemiology are 1) cell and tissue specificity of epigenetic signatures and to what extent they are found in other cells and tissue, 2) the DNA sequence effect on DNA methylation, 3) population stratification and 4) functional consequences of DNA methylation changes [44]. Joint work from molecular and cellular biologists together with social epidemiologists may help to design the conceptual model and develop functional hypotheses to propose

longitudinal human studies in specific cell types, conducted in large and diverse samples, with multiple biological layer measurement to better understand the mechanisms of the social environment on molecular and cellular biology and how in turn they are involved in diseases' onset and development.

More controversially, the epigenome may also be involved in the intergenerational transmission of traits acquired in preceding generations. Substantial evidence derived from research with animal models suggest in fact that some epigenetic changes induced by environmental stressors can be transmitted and influence health outcomes over generations through a phenomenon called epigenetic inheritance [45]. Although mechanisms involved in the transmission of epigenetic marks across generations are complex and remain unclear, in theory two types of epigenetic inheritance can be distinguished (inter- and transgenerational) based on the studied generation, the timing of the exposure and whether the original exposure was transmitted from the mother or the father. An individual may experience epigenetic changes as a response to environmental exposures. This modification turns into a heritable epigenetic mark if it is transmitted to the following generation. 'Intergenerational inheritance' occurs when an epigenetic change is passed down to an individual's immediate offspring. In mice, this is equivalent to inheritance in the F1 generation for exposed male parents or in the F1 and F2 generations for exposed female parents. This is because not only the individual mouse was exposed, but also its germline and, in the case of the female, maybe the germline of her unborn progeny. In mammals, there are two waves of reprogramming and erasure of the epigenetic landscape 1) at the zygotic stage and 2) during germ cell differentiation [46]: in rare circumstances some regions have been shown to escape reprogramming and could thus persist from one generation to the other [47]. Almost all epigenetic changes are lost during the first few generations, and inheritance is stopped at the intergenerational level. However, in some rare circumstances, the epigenetic change is kept going through the further generations (F2/F3) and beyond. The epigenetic change is retained even in the absence of the initial environmental exposure, which is why epigenetic inheritance beyond this stage is referred to as 'transgenerational' [48,49].

One well-studied example of transgenerational inheritance is the transgenerational immune priming induced by pathogen infection that has recently been reviewed by Roth *et al.* [50]. Both vertebrates and invertebrates can pass on their immunological knowledge to their children, enhancing the offsprings' immune defense: epigenetic changes could be one mechanism involved in the transgenerational immune priming and deserves to be further investigated [50]. Molecular mechanisms involved in transgenerational inheritance have been recently reviewed by Fitz-James and Cavalli [51]; the authors illustrate well that the involved molecular mechanisms vary greatly among species but can share common principles with transmission occurring either directly *("signal is transmitted through meiosis in a similar manner to its mitotic maintenance")* or indirectly *("the primary epigenetic signals are erased but faithfully reconstructed in the progeny based on a secondary signal")* through signal reconstruction. They end by questioning the role of transgenerational inheritance in evolution and in human health. Along these lines, Peter Sarkies provides an interesting overview of transgenerational inheritance to evolution and adaptation by looking into the idea that epigenetic changes may help organisms to survive temporarily in a changing environment (adaptation) and that these epigenetic variations could encourage changes in DNA sequence which would lead to evolution [52]. Indeed, it has been shown that the methylation state of CpGs in response to environmental stressors could affect the mutation dynamics of neighboring nucleotides and thus potentially favour, under selection pressure, the occurrence and selection of favorable alleles, perhaps contributing to transgenerational inheritance [53].

Epigenetics and epigenetic inheritance can help to identify the biological response to the social environment and how this process in turn can affect the health of an individual and potentially their offspring. Identifying biological responses to the social environment will give the opportunity to identify direct, objective information on physiological mechanisms that eventually contributes to disease onset before its clinical diagnostics, which could in turn help to design preventive interventions (before disease development). Given the complexity and multidimensional nature of the social environment, the investigation of the relationship between the social environment and biology may also help to determine which components of the social environment are most detrimental to health, but also point to resilience and protective elements that buffer the detrimental consequences on the biology and health of disadvantaged social environments. Ultimately the social-to-biological transition research field may encourage action to improve social conditions to prevent disease, by contrast with treating already sick individuals. In the meantime, epigenetics and epigenetic inheritance raises many scientific questions, but also major social and ethical issues that are not only theoretical or abstract. It is therefore essential to give serious consideration and worry about potential misunderstandings, discrimination, determinism and stigmatization, calling for a need to move away from an individual perspective to a societal change.

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