Epigenetics Won't Do Miracles. Some Sobering Remarks in Response to Professor Johannes Huber

Konrad Oexle

Abstract In some quarters it is expected that epigenetics will translate desirable ethical attitudes into the biological disposition of a new human being that, thus, better fits into its fragile environment. Here, I confront such high flying expectations with the reality of research findings in epigenetics. This includes the fact that epigenetic reprogramming in each generation largely inhibits epigenetic information transmission so that true transgenerational epigenetic inheritance in mammals is an exception and, in fact, still not proven with sufficient evidence.

Keywords Epigenetics · Transgenerational inheritance · Germline · Reprogramming · Metastable epialleles

1 Huber's Expectations

Epigenetics is a promising field [5, 16]. As such, it has raised far-reaching expectations. The prominent Austrian gynecologist and endocrinologist Johannes Huber, for instance, provided a series of popular books, lectures, and interviews in which he addressed epigenetics and claimed that "love can be inherited." "Mothers and fathers have it far more in their hands than previously thought to influence a healthy and happy future for their offspring through a conscious life." "By epigenetics the training (of neurons) can be transmitted to the next generation," he states, and that "the child will inherit this further to its own children" so that epigenetics will allow us to create the new human being, the "homo sapiens sapiens," who will be sufficiently unselfish and "altruistic" in order to fit into the stressed environment of a crowded planet [9–11]. Even "the faith in God lies in the epigenome," according to Huber [11]. He proposes these and other speculative and partly esoteric theses with the attitude of a down-to-earth scientist, thus inspiring hopes in his audience that epigenetics might be the pathway on which mankind can overcome the ecological crisis.

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2 Review of Research Findings in Epigenetics

Huber's expectations touch on magical thinking. Here, I outline some basic concepts of epigenetics and review recent developments concerning transgenerational epigenetic inheritance in mammals including humans. As I will show, the developments suggest a rather sober and skeptical stance [1, 3, 8]. The following points will be emphasized.

(i) Epigenetics primarily means gene regulation.
(ii) Epigenetic mechanisms and their potential for adaptation to changing environments are encoded genetically.
(iii) In mammals and other animals, somatic cells which are subject to environmental influence do not turn into germ cells.
(iv) Moreover, epigenetic reprogramming in each generation largely inhibits epigenetic information transmission via the germline.
(v) Transgenerational epigenetic inheritance in mammals is an exception and still not proven with sufficient evidence.

Maintenance and directed modification of gene activity states underlie the stability and canalized plasticity, respectively, of cells and tissues. "Epigenetics" [16] is the science that examines these states. (As usual in the natural sciences, the discrimination between the science and its object is blurred so that "epigenetics" also is the name of the examined phenomenon.) Thus, epigenetics concerns the regulation of the orchestrated organismal development and of the many highly differentiated cell types according to the inherited genetic information. This regulation differs in time and space from cell type to cell type so that each cell type has its specific "epigenome." Characteristic aspects of the epigenome do not substantially change if the cell type is stable across cell divisions. Differentiation of cells into another type comes along with specific changes of their regulatory epigenetic states. Since the epigenetic regulation of permanence or differentiation of cells is largely determined genetically, epigenetics is the maid of genetics.

Organisms are disposed to react, to adapt, and to learn from environmental conditions. These conditions may affect the epigenetic states of cells. Therefore, epigenomes do integrate environmental information according to genetically determined schemes. Of note, this is not exceptional. Nearly any biochemical process in the organism integrates environmental information to some extent and via some more or less indirect mediation. Just consider an enzymatic turnover process, for instance, whose turnover rate adapts biochemically to the concentration of its environmental substrate.

The generational sequence of individual organisms is the upshot of a sequence of cells. Genetic information runs through this 'germline' from germ cell to germ cell (Fig. 1). On the germline 'stand' the mortal somata, i.e., the individual organisms that are necessary evolutionarily to help the germ cells from the spot, to survive, and to unite in case of sexual reproduction. Via the germline, epigenetic states may have a transgenerational impact as has been shown in plants, roundworms, and fruit

flies where epigenetic states may affect many consecutive generations. Since cellular epigenetic processes react to environmental influences, this amounts to the inheritance of acquired traits. Whether such transgenerational epigenetic inheritance also exists in mammals and humans, especially, has attracted considerable interest in recent years.

DNA methylation is the paradigmatic epigenetic modification. Contrary to a prevalent assumption, epigenetics is not limited to DNA methylation, however. There are other DNA modifications besides the typical methylation of cytosine, and there are various steering modifications of the DNA-packaging proteins ("histones"). Modifications of these histones may function, for instance, by influencing the access of regulating proteins ("transcription factors"). The direct binding of the transcription factors to DNA depends on DNA methylation, but they may also control methylation, thus being not only "readers" but also "writers" of epigenetic information. It would be erroneous, therefore, to reduce epigenetics to DNA methylation. In general, the key pathways in epigenetics include transcription factors, architecture, and modifications of the chromatin (= DNA plus packaging proteins), non-coding RNAs, and prions [3].

Environmental conditions during the lifetime of an organism are reflected in the epigenetic patterns of its cells. For example, overeating or the smoking habits of an individual leave traces in the DNA methylation profile of white blood cells. However, in animals such as mammals, flies, and roundworms, somatic cells do not enter the germline ("Weismann barrier", [19]) so that they cannot inherit their epigenetic information about environmental conditions to the next organismal generation via cell division. Thus, for transgenerational epigenetic inheritance to take place, either the environmental condition must reach the germ cells directly or the exposed somatic cells must release a messenger that modulates the germ cells' epigenomes.

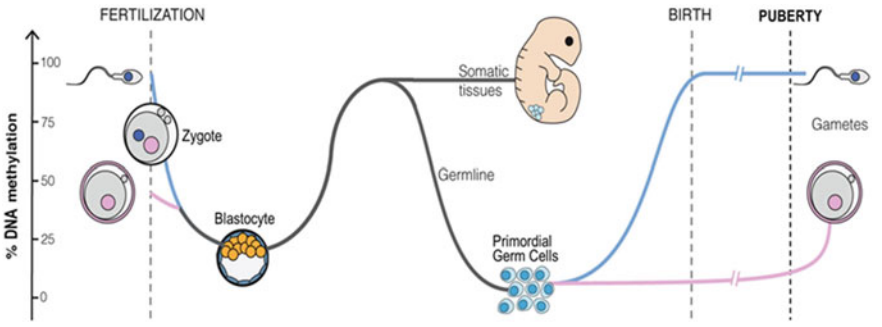

Fig. 1 Epigenetic reprogramming during prenatal development in mammals with two major steps of DNA methylation erasure. Soon after fertilization, the specific methylation patterns of the gametes (sperm and egg cell) are largely removed, except for some regions such as genes with parental imprinting. For the organogenesis in the embryo, specific methylation patterns are re-established thereafter. In primordial germ cells of the fetus, the DNA methylation is erased again to be re-established thereafter in the gametes according to the sex of the fetus (modified with simplification from [17])

In mammals, the corresponding hypothetical mechanisms still are largely unresolved [1, 3, 8].

Obviously, however, mammals do transmit information from one generation to the next, independent of the DNA sequence inherited via the germline. Transmission occurs by the shaping of the ecological niche or by cultural trends, for instance [5, 8]. Besides humans, many animal species exhibit some level of education and culture. Even flies display cultural copying [4]. Any such non-genetic transfer of information could be regarded as "epi"-genetic inheritance if a rather relaxed definition of the term was applied. However, the term would become inflationary thereby and thus lose its discriminatory power. Transgenerational epigenetic inheritance according to its prevailing definition requires non-genetic inheritance via the germline [1, 8].

The discrimination can get rather subtle, though, as evidenced by the process discussed in [5], for instance: In female pups of highly caring rat mothers the genes of sex hormone receptors in the brain show low levels of promoter DNA methylation, while female pups deprived of such care show high levels of methylation and silencing of these genes. Becoming mothers themselves, the pups with active sex hormone receptors will then also be caring mothers, while the pups of uncaring mothers will be uncaring mothers. This finding probably has triggered Huber's thesis that "love can be inherited" epigenetically [9, 10]. However, it is not a true instance of epigenetic inheritance because the epigenetic marks are not transmitted via the germline but are reinstalled in each generation as a consequence of the maternal behavior. The epigenetic marks (promotor methylation) do not themselves transmit the behavioral information to the next generation but are the molecular consequence of educational transmission, being reinstalled in each generation anew.

Various environmental exposures in early life (including nutritional factors, traumata, and "endocrine disruptors", that is, chemicals that interfere with hormonal systems) have been claimed to cause transgenerational responses in mouse and rat models. However, these studies still need to be confirmed [8]. And some have been challenged by others who showed that germ cell modifications are erased upon reprogramming in the next generation [2, 12, 18] or demonstrated that nutrition has a minor effect on the variance of DNA methylation in sperm cells [15]. Moreover, if the observed differences of germ cell DNA between exposed and unexposed animals are small, most of their germ cells must be identical at the epigenetic position in question because each germ cell carries only one genome which either has the epigenetic marker at that position or not. Then, however, it is difficult to explain a substantial difference in the phenotype (appearance, behavior) between the offspring of exposed and the offspring of unexposed because each offspring has been begotten by one germ cell [1].

Recently, Kazachenta et al. [13] systematically analyzed the mouse genome for the inheritance of local DNA methylation patterns, which qualify as "metastable epialleles," that is, as variants of a gene that are variably expressed in genetically identical individuals due to epigenetic modifications. They found that most of these patterns are reprogrammed in the offspring's organism and concluded that their "findings raise questions about the generalizability of non-genetic inheritance at metastable

epialleles and suggest that variable methylation can be reprogrammed and reconstructed across generations in the absence of a memory of parental state by a process that may depend on the genetic context of the variably modified locus."

Indeed, if parents and children share the same abnormal epigenetic pattern, this does not prove epigenetic inheritance. Co-segregation of a genetic mutation may generate that pattern as a "secondary epimutation" in each generation anew. Such constellations have been described in human genetic diseases including inborn errors of metabolism and familial colon cancer [6, 7]. To find the causative genetic mutation may be tricky since it may not reside in the same gene as the secondary epimutation. Instead, it may be located in a neighboring gene, for instance, where it generates aberrant read-through transcription. If the read-through transcription reaches the gene in question, it may affect the DNA methylation there, thus causing the secondary epimutation of that gene (ibd.). Even germ cells may show the secondary epimutation, making the differentiation from primary epigenetic variation rather difficult (ibd.).

Thus, transgenerational epigenetic inheritance in mammals is hard to prove. Horsthemke [8] recently proposed a roadmap to do so. Besides secondary epimutations, ecological or educational/cultural inheritance has to be excluded. Moreover, it is necessary to set apart prenatal exposure of the unborn ("fetal programming") and of the germ cells of the unborn ("intergenerational inheritance") which may affect the generation of the children and grandchildren, respectively. True transgenerational epigenetic inheritance can still be observed when the transmitting germ cells never could have been subject to the environmental exposure, that is, in the grandchildren of an exposed male or in the grand-grandchildren of an exposed pregnant female. Furthermore, the epigenetic factor (e.g., the specific DNA methylation) must be identified in the germ cells while contaminations by somatic cells need to be avoided. Finally, the proof must be completed by removing and re-adding the epigenetic factor to the germ cells while showing that the inherited phenotype disappears and re-appears, respectively.

Obviously, the last step of that roadmap can be taken in animal models only. There are reports on transgenerational epigenetic inheritance in humans, especially in connection with malnutrition (reviewed in [14]). However, the conditions of investigation are unreliable in comparison to the rodent model. Besides the limitations of experimental manipulation, the observation time is much longer due to the much higher reproductive age so that studies in humans usually can be retrospective only.

Important questions related to the molecular mechanisms of how the somatically acquired information should reach the germ cells and whether the corresponding factor is (or needs to be) translated there into (another) epigenetic code. It is assumed that non-coding RNA molecules are mediators that circulate in the blood and act on the germ cells in the gonads. However, the details are still unclear [1, 3, 8]. Moreover, the question arises as to how specific epigenetically inherited information would be: "How much information is transmitted by the germline—how coarse-grained is the representation of the world provided by parents to their children?" [3].

Acquired information that enters transgenerational epigenetic inheritance has to overcome epigenetic reprogramming in early embryogenesis and in germ cell development (see Fig. 1). Leading scientists [1, 8] remain skeptical as to the relevance

of transgenerational epigenetic inheritance in humans. In fact, in mammals whose generation time is long, epigenetic inheritance that extends over several generations is not to be expected from an evolutionist's point of view. If it comes up to its presumed evolutionary function, i.e., adaptation to changing environmental conditions, it should not last longer than the half-life of these conditions.

3 Conclusion

To summarize and to come back to Professor Huber, it is to be emphasized that the current state of knowledge in epigenetics does not support his claim that "mothers and fathers have it far more in their hands than previously thought to influence a healthy and happy future for their offspring through a conscious life." [9, 10] Instead of unwarranted speculations, he should realize that "at present there is no evidence for a direct effect of culture on the epigenome" [8].

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