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Environmentally-Mediated Epigenetic Effects: Uncovering the Fertile Soil in the Development of Pediatric Cancer

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Abstract: Environmentally-induced epigenetic changes of gene regulation could result from chronic, lifelong exposure, to low doses of environmental toxicants, such as chemicals including, tobacco smoking and endocrine disrupting compounds, or to other environmental factors such as nutritional changes, and lifestyle-related conditions. These environmentally-acquired epigenetic marks may influence the control of gene regulation through DNA methylation, histone modification, or through a large set of non-coding RNAs (ncRNAs). These epigenetic effects might be passed on to the developing embryo and child as inheritable non-genetic marks, which recapitulate previous lifelong history of exposure to environmental influences that start from the stage of primordial germ cell, passing through the maturing germ cell, and ending by the zygote stage. This involves the paternally transmitted information on the sperm that contribute to modulating embryogenesis functions and later childhood development, in concert with, the maternally transmitted information encountered by the exposure to a large milieu of environmental factors either periconceptionally or during lactation period.

Keywords: Pediatric Oncology, Childhood Cancer, Epigenetics, Environmental Exposures, Epigenetic Inheritance & Evolution, Pediatric Cancer Susceptibility

1. Epigenetics: the Role in Embryogenesis & Development

As all cells in living organism contain the same genetic blueprint, epigenetics allows for cells to adopt different phenotypes and maintain them upon cell replication. As such, during the life cycle, there are moments in which the epigenetic information needs to be reset for the initiation of a new organism. [1]

In at least two stages of the life cycle of mammals, epigenetic stability is globally perturbed: when gametes fuse to form the zygote and when gamete precursors (primordial germ cells; PGCs) develop and migrate in the embryo. That is what is called *in vivo* 'reprogramming' of the epigenetic landscape that points to the reacquisition of totipotency in the zygote and the formation of the next generation through PGCs. [2]

At fertilization, two specialized cell types (gametes) merge into the zygote to generate the first cell of the developing embryo. Initially, the gamete genomes remain physically separate in the zygote, where they are subject to different chromatin changes while under the effect of a common set of maternally inherited factors. In the early zygote, the acquisition of a hyperacetylated and hypomethylated chromatin state may increase the accessibility of the paternal genome and allow additional remodeling to occur. [2] For this reason, sperm require a myriad of chromatin structural changes, not only to serve a protective role to DNA throughout spermatogenesis and future delivery to the egg, but also, it seems, to contribute to the developmental program of the future embryo. [3]

Histone modifications, which include, but not limited to, phosphorylation, ubiquitylation, sumoylation, acetylation and methylation could have different consequences on chromatin

condensation, and therefore regulate chromatin accessibility to different transcription factors and regulators, thus result in diverse effects on gene expression. In fact, growing evidence suggests that mature sperm provide appropriate epigenetic marks that drive specific genes toward activation and contribute to the totipotent state of the embryonic cells. [4]

These epigenetic factors may reveal the historical record of spermatogenesis, foresee future functions in embryogenesis, and help explain the mechanism of pluripotency. In contrast to the once held dogma regarding the importance of the paternal epigenome, the unique epigenetic landscape in sperm appears to serve more than the gamete itself and is likely influential in the developing embryo. [5] Also, the asymmetric program in the zygote is probably a consequence of inheriting gametes from the previous generation that had widely different epigenetic profiles. However, its functional importance still remains unclear. [2]

2. Evolutionary Epigenetic Remodeling through Trans-Generational Inheritance

Epigenetics, or regulation of gene expression independent of DNA sequence[6], is the missing link between genotype and phenotype. Epigenetic memory, mediated by histone and DNA modifications, is controlled by a set of specialized enzymes, metabolite availability, and signaling pathways. [7]

A largely unstudied theme is how sub-toxic exposure to different xenobiotics during specific developmental stages can alter the epigenome and contribute to the development of disease phenotypes later in life. Furthermore, it has been shown that exposure to low-dose xenobiotics could result in further epigenetic remodeling in the germ line and contribute to increase disease risk in the next generation. [7] These heritable non-genetic marks that passed on from parents, by multi- or trans-generational mechanisms, to their descendants might reprogram critical developmental pathways during the early embryonic life. Aberrant reprogramming of these pathways would impact the health of the offspring and influence their susceptibility to develop diseases later on in life.

A recent study done by Skinner et al., on rats exposed to an environmental toxicant such as vinclozolin revealed that, negligible copy number variants (CNV) in the rat sperm were identified in the first (F1) generation following exposure; however, in the transgenerational F3 generation, a significant increase in CNV was observed in the sperm. The study emphasized that the environmental toxicant vinclozolin could promote an epigenetic reprogramming of the germline in the first generation that induced increased genomic instability and genetic mutations transgenerationally that clearly appeared in The F3 generation. [8]

In addition, the study provides an example of the ability of epigenetic mechanisms to drive genetic change and sheds the light on the role of environmental epigenetics that may be the major molecular mechanism involved in environment-gene interactions and emergence of genetic variation. This study also argues against the predominant current view for the origin and evolution of disease that considers genetic mutations as the primary molecular mechanism involved. Furthermore, it gives insights on how the environment may have direct impact on disease etiology and on the origins of phenotypic and genotypic variation in evolutionary processes. [8]

3. Environmentally-Mediated Epigenetic Effects: the Developmental Window of Pediatric Cancer Susceptibility

The old adage that you are what you eat highlights the interconnected relationship between humans and their environment. [9] A recent study examined the maternal diet and metabolism and their impact on fetal development, has demonstrated that circulating maternal lipids are associated with developmental epigenetic programming, which in turn may impact lifelong health and disease risk. [10] In addition, it was found that maternal plasma folate impacts differential DNA methylation in an epigenome-wide meta-analysis of newborns. [11]

Also, there is overall consistency in literature about negative effects of fetal and postnatal exposure to parental tobacco smoking on several outcomes: preterm birth, fetal growth restriction, low birth weight, sudden infant death syndrome, neurodevelopmental and behavioral problems, obesity, hypertension, type 2 diabetes, impaired lung function, asthma and wheezing. While maternal smoking during pregnancy plays a major role on adverse postnatal outcomes, it may also cumulate negatively with smoking during lactation and with second-hand smoking exposure. [12]

Recently published results of pooled analysis from two French national population-based case-control studies (ESCALE and ESTELLE) have shown positive associations between neuroblastoma diagnosis on the one hand, with being born either small or large for gestational age, or having a congenital malformation, on the other hand. In addition, the study has shown protective effects of breastfeeding and preconception use of supplements containing folic acid, vitamins or minerals. [13]

However, an infectious etiology and a role of immunological modifiers in neuroblastoma development have not been prominent hypotheses as reported in pediatric leukemia. [14] Epigenetic mechanisms have been suggested based on the contribution of some human milk compounds to metabolic and differentiation processes, and to the development of the infant's immune system. [13, 15] Epigenetic mechanisms have rapidly and controversially emerged as silent modulators of host defenses that can lead to a more prominent immune response and shape the course of inflammation in the host. Thus, the epigenetics can both drive the production of specific inflammatory mediators and control the magnitude of the host response. [16]

DNA methylation was identified as a potential mediator of environmental risks in the development of childhood acute

lymphoblastic leukemia[17], which is the commonest pediatric cancer. Differentially altered DNA methylation profiles have been observed between acute lymphoblastic leukemia (ALL) cells and nonleukemic bone marrow, and also within ALL subtypes, as a result of established environmental exposures that are linked to ALL risk, especially smoking [18-20], folic acid [21, 22] and infection. [17, 23] There is also evidence, although weaker for other exposures associated with ALL risk, such as iron, caffeine, pesticides/herbicides, paints and chemicals. [17, 24-32]

In an Australian population-based case–control study, it was found that both maternal and paternal exposures to diesel exhaust before the child's birth were (independently) associated with an increased risk of childhood brain tumors [33], which is the most common solid tumor in children with cancer and the leading cause of death in these patients. It is estimated that 5% of human cancers are caused by viruses, 5% by radiation, and the remaining 90% by chemicals. Of these, an estimated 30% are caused by the use of tobacco products and the rest by chemicals associated with diet, lifestyle, and the environment. [34]

4. Aberrant Reprogramming: the Potential Link between Developmental Malformations & Childhood Cancer

The findings described in the previous section from the pooled analysis of the ESCALE and ESTELLE French studies support the hypotheses that fetal growth anomalies and congenital malformations are related to neuroblastoma [13], which is the commonest extracranial pediatric solid tumor. This emphasizes the notion that pediatric solid tumors are developmental disorders. [35]

Association of childhood tumors with congenital abnormalities suggests that disruption of normal developmental processes may be linked with oncogenesis. [36] Environmental influences through aberrant reprogramming could disrupt critical epigenetic processes during development, thus affecting gene-related signaling pathways and cellular function.

Indeed, the process of cell reprogramming toward a pluripotent state shares many characteristics with cancer development, although the process is not accompanied by the genetic alterations that are believed to be the causative abnormalities in most cancers. In addition, recent *in vivo* reprogramming studies provided some clues to understanding the role of reprogramming-related epigenetic regulation in cancer development. It was shown that premature termination of the *in vivo* reprogramming result in the development of tumors that resemble pediatric cancers. [37]

Differentiation and development are normally unidirectional processes in which progenitor/stem cells differentiate into more mature cells. Transformation of adult cells into cancer cells is accompanied in many cases by dedifferentiation of the adult cell, while differentiation failure of progenitor cells can result in development of pediatric cancer. [38] Considering the fundamental role of epigenetic regulation in cell fate maintenance and conversion, it is expected that the failed reprogramming is attributable to the incomplete/unsuccessful reorganization of the epigenetic modifications. [37]

It is noteworthy that failed reprogramming-associated cancers have a number of shared characteristics with pediatric cancers. Intriguingly, failed reprogramming-associated cancers in the kidney resembled Wilms' tumors, the most common pediatric kidney cancer. [39] The study done by Urbach et al., showed that overexpression of *Lin28*, a gene encoding an RNA-binding protein that regulates gene expression during kidney development in mice, markedly expands nephrogenic progenitors by blocking their final wave of differentiation, ultimately resulting in a pathology highly reminiscent of Wilms tumor. They also observed Wilms tumor only when *Lin28* is aberrantly expressed in multiple derivatives of the intermediate mesoderm, implicating the cell of origin as a multipotential renal progenitor. Surprisingly, they found that withdrawal of *Lin28* expression reverts tumorigenesis and markedly expands the numbers of glomerulus-like structures. [40] Additionally, failed reprogramming-associated cancers of the liver and the pancreas showed similarities to those of hepatoblastomas and pancreatoblastomas, respectively. [39]

Furthermore, epigenetics-related diseases such as imprinting disorders, in particular, Beckwith–Wiedemann syndrome that has been associated with pediatric embryonal tumors (most commonly Wilms tumor) [41, 42]. These findings provided a further connection between failed reprogramming-induced epigenetic regulations and pediatric blastomas development, [39] and give an explanation about the association of pediatric cancer with dysmorphic developmental anomalies such as congenital malformations & fetal growth anomalies.

5. Remaining Questions & Concluding Remarks

Many questions still remain to be answered; some of these questions are outlined hereafter:

1. Could the multi- & trans-generational epigenetic inheritance explain why pediatric cancer has a shorter latency to develop, as unusual, when compared to the long latency required for the development of adult cancer?
2. Could the longstanding lifelong parental exposure to low-doses of environmental influences behave as promoters for carcinogenesis by modulating embryogenesis by aberrant reprogramming through epigenetic effects?
3. Could the environmentally-mediated epigenetic effects [43-45] that transgenerationally [46, 47] passed on from the parents to their offspring be the fertile soil for oncogenesis, through global epigenetic changes [48-51] that precede the initial genetic mutations (hits) [50, 51],

or even could drive their formation by the development of epigenetically-induced genetic variants [52, 53] through successive generations?

4. Does the epigenetic progenitor origin model for human cancer [54] fit well in explaining pediatric cancer pathogenesis?

It seems that the epigenetic origin model for human cancer explain many of the unique criteria of pediatric cancer. Aberrant reprogramming through environmentally-mediated disruption of critical epigenetic processes during development could alter cellular state and fate of progenitor cells that finally emerge as developmental disorders or cancer in children.

Plasticity in developmental programming [55-57] that involves epigenetic adaptation to environmental changes may explain the regression of some pediatric tumors[58, 59]. In addition, the intra and inter-tumor heterogeneity [56, 57] encountered in pediatric cancer could be explained on the basis of inheriting gametes from the previous generations that known to have widely diverse epigenetic profiles. This epigenetic heterogeneity recapitulates previous lifelong history of exposure to environmental influences.

To uncover many of unanswered questions, more focused research should be carried out through longitudinal studies that address the effects of various environmental influences involving successive generations using integrated genetic & epigenetic approaches to gain insights & accumulate further evidence about the interplay between genetics, epigenetics & exposure, and its possible role in initiation, promotion & progression of different pediatric tumors.

Author Contributions

A. M. Morsy is primarily responsible for this review's conception, design and drafting of the manuscript. All authors provided evaluation and revision of the manuscript, and have given final approval of the manuscript.

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