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Review

Intergenerational epigenetic inheritance in models of developmental programming of adult disease

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ABSTRACT

It is now well established that the environment to which we are exposed during fetal and neonatal life can have a long-term impact on our health. This has been termed the developmental origins of health and disease. Factors known to have such programming effects include intrauterine nutrient availability (determined by maternal nutrition and placental function), endocrine disruptors, toxins and infectious agents. Epigenetic processes have emerged as a key mechanism by which the early environment can permanently influence cell function and metabolism after multiple rounds of cell division. More recently it has been suggested that programmed effects can be observed beyond the first generation and that therefore epigenetic mechanisms could form the basis of transmission of phenotype from parent to child to grandchild and beyond. Here we review the evidence for such processes.

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1. Introduction: early life programming of future disease risk

Among both scientists and laypersons, the notion that a human being is a product of both our genes and our environment is now well accepted. It follows that a person's health is not necessarily limited to what their DNA permits, but can be modified by lifestyle and environment. In recent years fetal and neonatal life have been highlighted as particularly critical periods of development when the environment can interact with our genotype to have a permanent effect on our phenotype. A strong case for this has been shown recently in a study by Rosenquist et al. [1], which found that the impact of the FTO gene variant which has been linked to obesity is largely affected by the year of birth, such that there was no correlation in participants born prior to 1942, whereas there was a far stronger correlation for those born post-1942 (post-World War II). This study was preceded by a number of epidemiological studies showing the effects of historical cases of hunger or malnutrition resulting from wars or natural famine not only immediate effects on the contemporary population, but also that of individuals who were in-utero at the time of these events. The Dutch Hunger Winter [2,3] and the Leningrad Siege [4] were catastrophic periods of hunger and malnutrition during which rations were strictly imposed on all sections of the population including pregnant and nursing mothers. A large number of studies have focused on the malnutrition experienced during these periods of famine and starvation and uncovered associations with chronic adult disease such as cardiovascular disease and metabolic disease in individuals born around the affected periods. As well as long term detrimental effects of under-nutrition in utero, there is now also a wealth of evidence that maternal over nutrition or obesity is also associated with offspring cardio-metabolic disease. This is particularly relevant in Western Societies where a combination of a reduction in physical activity and increased ease of access to highly palatable foods has tilted the balance of energy homeostasis, in favor of energy intake over expenditure, leading to an epidemic of obesity. Studies in animal models have shown that this is a causal relationship between maternal under-nutrition and over-nutrition on offspring metabolic and cardiovascular health that is independent of genotype. Such studies have also highlighted the importance of the pre- and early postnatal environment in growth and development, and that the timing of an insult or deviation from the norm is as important as the insult itself in determining (a) the organ systems affected and (b) the timing of onset and severity of disease outcome. Information on precise mechanisms through which such events in early life program a permanent effect on tissue structure and function, even after numerous rounds of cellular replication during early development and constitutive growth and differentiation, are less well characterized. However, growing evidence to indicate that the programmed phenotype brought about by early environmental insults such toxicants and pollutants, maternal under or over nutrition or parental obesity may extend through more than one generation has led to great interest in the role of epigenetic mechanisms [5,6].

2. Epigenetics and chromatin

The term "epigenetics" was first coined by Waddington [7] to define the "interactions of genes with their environment which bring the phenotype into being". It is now used, but not without a great deal of controversy [8], to refer to covalent modifications of DNA and core histones that are heritable and affect genome function without altering the DNA nucleotide sequence. It is however clear that epigenetic information is transmitted from parental cells to daughter cells, and potentially inherited across generations, through the stable perpetuation of chromatin states.

2.1. Chromatin

The genome of eukaryotic cells is packaged into "chromatin", a structure that comprises the complex of histone proteins and DNA. The nucleosome is the basic unit of chromatin; it contains an octamer of two each of histones H2A, H2B, H3 and H4, or some variant of these canonical core histones, wrapped inside ~147 base pairs (bp) of DNA. Additionally, histone H1 is involved in the compaction of chromatin, functioning as an internucleosome linker. Research over the past decades revealed that chromatin not only provides the scaffold for the packaging of the entire genome, but also plays key roles in both transcriptional regulation and the maintenance of genomic stability.

2.1.1. Chromatin marks

Covalent post-translational modifications of DNA and histone proteins, defined here as "chromatin marks", can alter the organization and function of chromatin, with implications for the regulation of DNA-based processes, such as DNA repair, replication and transcription. These modifications, or marks, are laid down and removed in a dynamic fashion by specialized enzymes. The characterization of such chromatin-modifying enzymes represented major breakthroughs, as it provided a first handle on how to control the modifications and established the principle of a dynamic system that can respond to cellular stimuli and environmental cues.

Table 1 shows an overview of key (selected) chromatin marks, with information related to proposed function, association with genomic location and annotation of corresponding writers, readers, and erasers of the modification.

2.1.2. Histone marks

Histone marks occur in the N-terminal tail domains of the core histones that protrude out from the nucleosome, but also in the core histone domains and in newly synthesized histones. Histone tails contain an extraordinary number of sites that can be subjected to post-translational modifications. Some of these modifications, such as acetylation and phosphorylation, can alter the charge of the tails and, thus, have the potential to influence chromatin through electrostatic mechanisms. However, the primary mechanism by which tail modifications act seems to be through their function as "docking" sites for chromatin "readers" that specifically recognize these modifications, and in turn recruit additional chromatin modifiers and remodeling enzymes. Chromatin readers