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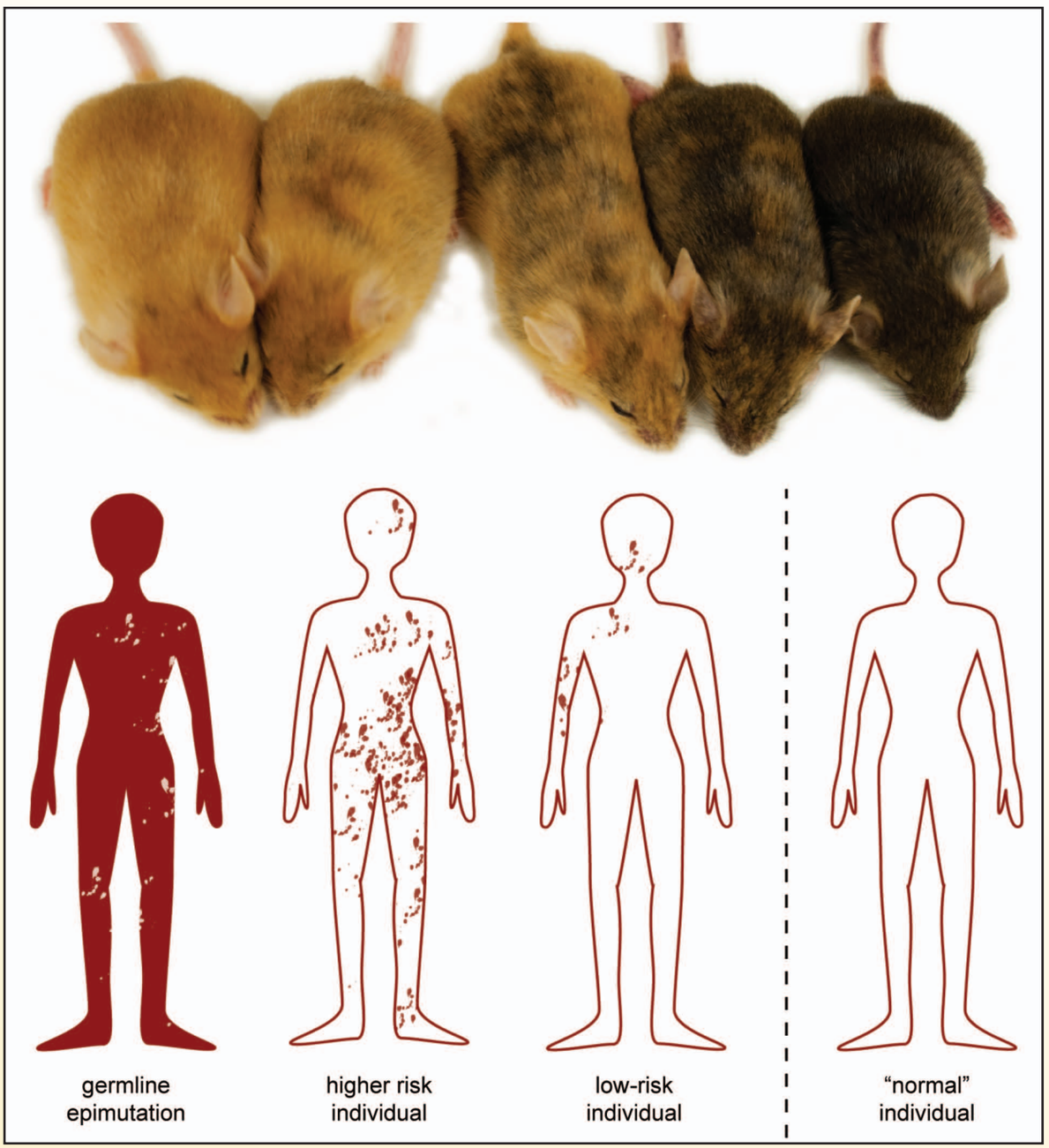

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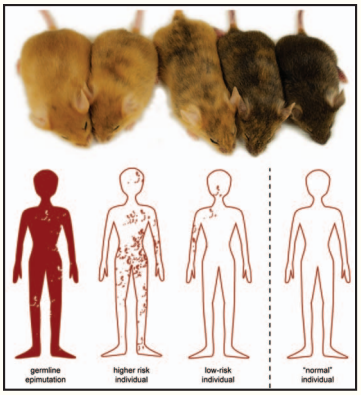

About the cover

Epigenetic mosaicism may modulate the risk and severity of epigenetic diseases. This is illustrated by the A^{vy} mouse (top). The range of coat colors of these isogenic littermates is caused by varying epigenetic mosaicism of the A^{vy} allele, which also leads to variable expressivity of the associated obese diabetic phenotype. In humans (bottom), the somatic burden of epimutation at disease-associated genes could impart a phenotype or disease risk relative to the proportion of cells affected.For more information, see Martin et al., pp. 843–8.

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Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability

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The majority of environmental factors can not modify DNA sequence, but can influence the epigenome. The mitotic stability of the epigenome and ability of environmental epigenetics to influence phenotypic variation and disease, suggests environmental epigenetics will have a critical role in disease etiology and biological areas such as evolutionary biology. The current review presents the molecular basis of how environment can promote stable epigenomes and modified phenotypes, and distinguishes the difference between epigenetic transgenerational inheritance through the germ line versus somatic cell mitotic stability.

Key words: epigenetic, transgenerational, inheritance, mitotic, environmental, toxicants, evolution, disease etiology

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Role of Environmental Epigenetics in Development and Biology

A highly differentiated adult cell type or biological phenotype has been generated through a complex cascade of developmental processes. The stem cell populations of the embryo or selected tissues undergo a cascade of genetic steps through cell fate determinations, development of differentiated cell types, organogenesis, specified physiological states and phenotypes. This genetic process includes classic transitions in transcriptional control to lead to a cascade of specific transcriptomes at each stage of development. This programmed developmental process is hardwired and follows classic genetic processing. The genetic control of developmental biology is stable and integrated into the overall physiology and phenotype of the organism. In contrast to the genetic control of cellular activity, the epigenetic cascade of events is responsive to environmental factors and can directly impact the genetic cascade of events. Just as there is a cascade of genetic steps during development, a cascade of epigenetic steps also exists and impacts the transcriptional stages of cellular differentiation and development (**Fig. 1**). Environmental epigenetics provides a direct molecular mechanism for environmental factors or toxicants to influence the genetic cascade of events involved in development, such that the environment can directly impact biology. An interesting element of these integrated molecular events for developmental biology[1] is the fact that critical windows of susceptibility exist[2] where the environmental factors have a more dramatic ability to modify and impact important stages of development (**Fig. 1**). These critical windows generally are very early in development, such as the fetal or early postnatal periods, when the organ systems are rapidly developing and sensitive to subtle shifts in the epigenome.[3] These critical exposure windows allow an environmental factor or toxicant to permanently modify an epigenome that then continues throughout development to impact genetic programming and result in a modified adult epigenome and genome activity (transcriptome). This promotes a susceptibility to develop disease or creates an increased biological variation in phenotype that will facilitate an adaptation event and influence natural selection (**Fig. 1**).

The stages or cascade of steps in both the genetics and epigenetics are highly integrated and influence each other during the developmental process. Therefore, environmental epigenetics and genetics

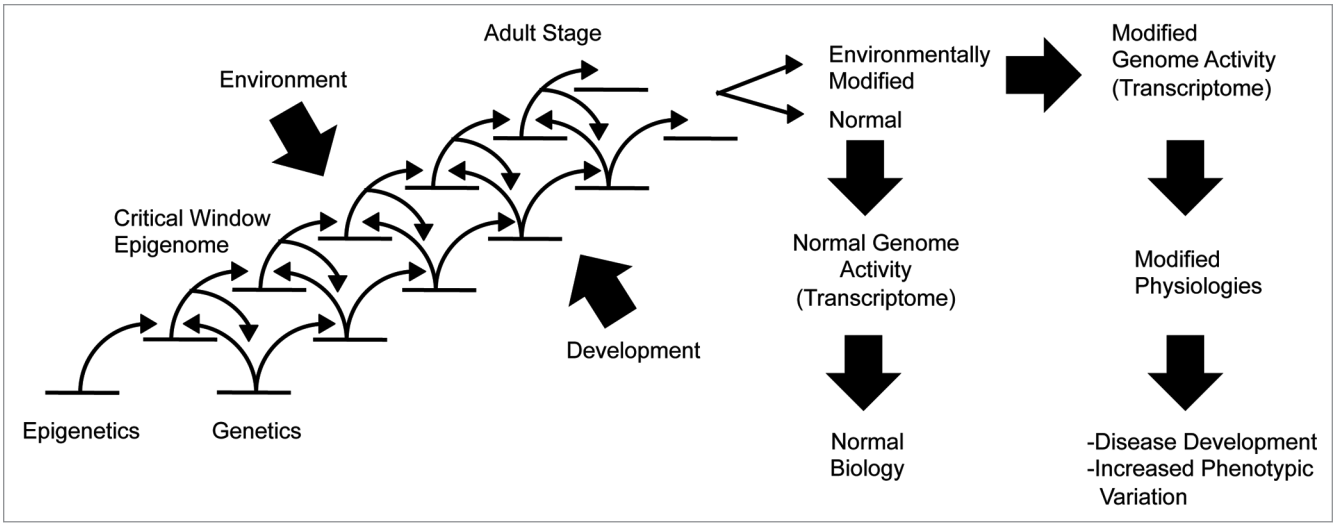

Figure 1. Integration epigenetics and genetics in development.

should not be considered mutually exclusive, but instead highly integrated and dependent on each other. The genome DNA sequence provides the stable nature of an organism that is hardwired and programmed. The epigenome provides a more plastic molecular process[4-6] that is responsive to the environment to impact biology, disease etiology and evolutionary biology. Epigenetics and genetics should be considered cooperative and together provide a more complex and integrated molecular mechanism for the control of development and biology.

Environmental Epigenetic Transgenerational Inheritance

Epigenetic transgenerational inheritance requires germ line transmission of epigenetic information between generations in the absence of direct environmental exposures. During a critical window of germ cell development, embryonic gonadal sex determination in mammals, environmental factors or toxicants have been shown to influence epigenetic programming in the male germ line (sperm), which becomes permanently programmed (imprinted),[7] and then allows the transgenerational transmission of adult onset disease phenotypes.[8,9] The general mechanism for this epigenetic transgenerational inheritance in mammals involves exposure of a gestating female during the period of gonadal sex determination when the primordial germ cell is being reprogrammed at the DNA methylation level.[10] The environmental toxicant alters the DNA methylation to generate new imprinted-like sites that then are transmitted to subsequent generations through the germ line (sperm) (**Fig. 2**). All the somatic cells derived from this germ line will have a baseline shift in their epigenome and, as the cells differentiate, a corresponding shift in genome activity and transcriptomes that in some tissues will promote disease states or phenotypic variation (**Fig. 2**).[11] The transmission of any genetic or epigenetic molecular information between generations requires germ line transmission and permanent alterations in DNA sequence or the epigenome.[11] Due to the reprogramming of the epigenome (DNA methylation) at fertilization,[10,11] the modified epigenetic sites will need to be imprinted-like to escape the demethylation process.[3,8,11,12] The suggestion that an altered epigenome may increase genomic instability and allow genetic mutations to develop in subsequent generations[12] remains a possibility that needs to be investigated further.[7]

A number of environmental factors and toxicants have now been shown to promote epigenetic transgenerational inheritance of disease states or phenotypic variation including the fungicide vinclozolin,[8] plastic compound bisphenol A (BPA),[13] toxicant dioxin,[14] stress responses[15] and nutrition.[16] A critical factor in epigenetic transgenerational inheritance is that the disease states or phenotype be transmitted through the germ line in the absence of direct exposure.[11] If direct exposure of the environmental factor is involved then this would simply be direct exposure toxicology. An example is exposure of a gestating female that has the F0 female, F1 fetus and germ line within the fetus that will generate the F2 generation directly exposed.[17] Therefore, an F3 generation is required to assess a potential transgenerational phenotype from a gestating female exposure.[17] In the event an adult male or female is exposed, the F0 generation adult and the germ line that will generate the F1 generation are directly exposed, such that an F2 generation is required to obtain an epigenetic transgenerational phenotype.[18] Although previous literature has suggested transgenerational phenotypes in F1 or F2 generations, these studies often had direct exposures involved so can not be considered epigenetic transgenerational inheritance phenotypes, but direct exposure toxicology. Epigenetic transgenerational inheritance phenotypes require the lack of direct exposure to be considered transgenerational.

Environmentally induced epigenetic transgenerational inheritance has significant impacts in the areas of disease etiology, inheritance of phenotypic variation and evolutionary biology. This phenomenon provides an alternate to genetic Mendelian inheritance that can provide a molecular mechanism for how the

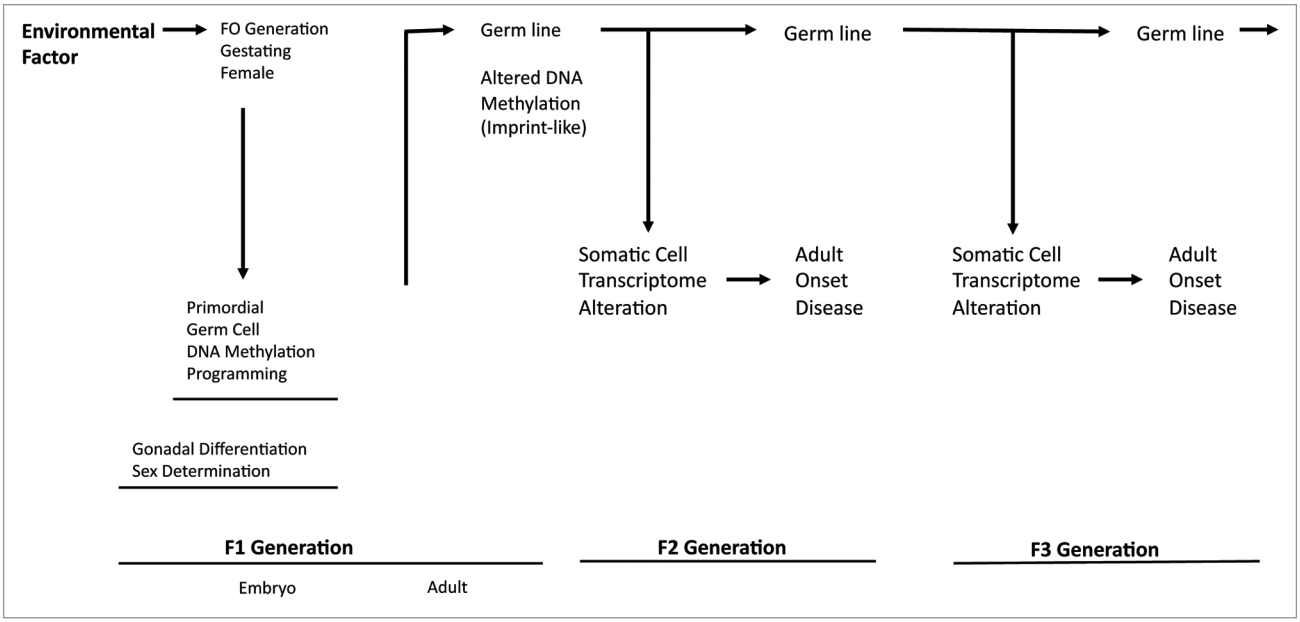

Figure 2. Scheme for epigenetic transgenerational inheritance.

environment can influence disease etiology and general biological phenotypes. In regards to disease etiology, the familial transmission or non-Mendelian characteristics of a variety of disease states can be explained. In regards to evolutionary biology, the ability to acquire an increased biological variation in phenotype following an ancestral environmental exposure will facilitate a potential adaptation event to allow the natural selection process. Environmental epigenetic transgenerational inheritance may provide a molecular process to explain rapid evolutionary events and how environment can influence evolution.

Somatic Epigenetic Mitotic Stability

In the 1940s, when Conrad Waddington described environment-gene interactions as epigenetics, he discussed the stable nature of epigenetics,[4] but had no idea of the molecular aspects of the phenomena. It was not until the 1970's that DNA methylation was described by Robin Holliday[5] and Art Riggs.[6] Riggs discussed the stable nature of the epigenetics as epigenetic inheritance following cell proliferation or mitosis.[19] Unfortunately, this nomenclature of 'inheritance' is not accurate and misleading to suggest generational events. The definition of "inheritance" is transmission of information between generations of an organism, and is accepted by the public and general scientific community as such. The ability of the epigenome to be replicated and transmitted upon cellular proliferation through the mitotic process is distinct and should be considered "mitotic stability" not "inheritance". The use of the term epigenetic inheritance has confused the scientific community and public to consider germline-mediated transgenerational phenomena, rather than simply replication of the epigenome during mitosis. Therefore, the proposal is made to define the replication of the epigenome during mitosis as "Mitotic Stability" and not refer to this as epigenetic inheritance. The definition of epigenetics would be as previously described in reference 11, "molecular factors or processes around DNA that regulate genome activity independent of DNA sequence and that are mitotically stable."

The insight of Art Riggs to suggest the critical need for epigenetic marks to be replicated and stable during mitosis[6,12] was very significant and indeed allows epigenetics to have a profound biological impact. In the event the epigenome was not replicated during mitosis, epigenetics would only impact the immediate cell and not have a long-term impact on the cell population or associated physiology. The ability to maintain a specific epigenome after mitosis is in part how different cell types maintain distinct differentiated states and facilitate a normal developmental process.

The mechanisms involved in the replication of the epigenome during mitosis are understood for DNA methylation and small RNAs, but limited information exists for histone modifications and chromatin structure. The DNA methylation marks are identified on the parental DNA strand during S phase DNA synthesis by DNA methyltransferase (DNMT), which then methylates the newly synthesized strand of DNA to replicate the DNA methylation pattern of the parental cell. Therefore, the DNA methylation marks are replicated during mitosis to maintain the methylome. The non-coding RNAs that act independent of DNA or RNA sequences act as epigenetic components to alter gene expression. The non-coding RNA islands of DNA sequence are replicated through normal DNA synthesis to have mitotic stability of these non-coding RNAs. The histone modifications appear to be replicated following mitosis but the molecular mechanism for replicating the histone code is not known at present.[20] Similarly, replication of the chromatin structure is known to occur, but the

basic replication molecular mechanism remain to be elucidated.[21] Therefore, further research is needed to clarify the basic molecular mechanisms involved in epigenetic mitotic stability.

Although the germ cell is critical for transmission of genetic and epigenetic information between generations, the somatic cells of organism (non-germ cell types) are essential for the basic developmental biology and physiology of an organism. Somatic cells are not capable of transmitting information between generations, but have a critical role in the physiology and disease states of the individual. The reason epigenetic mitotic stability is critical relates to the somatic cell differentiation and function. In the event, as shown in **Figure 1**, an environmental factor modified the epigenome of a somatic cell during a critical window of development, the somatic epigenetic mitotic stability would replicate this epigenome and permanently influence the somatic cell differentiation and function throughout life. Therefore, long after an early life exposure, the modified epigenome will continue to alter gene expression and that cell population. This provides a mechanism for the developmental origins of disease to explain how a transient exposure early in life can promote a susceptibility for disease later in life. The most critical molecular factor involved in this phenomenon is the somatic epigenetic mitotic stability. As previously discussed, the integration of the epigenome to genome activity and the mitotic stability of the epigenome on somatic cells provides a molecular mechanism for environment to influence disease etiology and phenotypic variation associated with evolution.

Summary

Epigenetics provides a molecular mechanism for environmental factors (for example, nutrition) and toxicants to influence biology and disease. The integrated nature of the epigenetics and genetics indicates a highly cooperative interaction to control development and biology (**Fig. 1**). A large number of previous observations have suggested the environment has a major impact on biology, but genetics alone could not explain the phenomena involved. The inclusion of epigenetics in our consideration of basic developmental processes and physiology significantly expands our ability to understand the systems biology of the organism. The ability of the epigenome to be replicated during somatic cell mitosis also can explain how early life exposures can program later life physiology and adult onset disease. This is a new paradigm for disease etiology that needs to be considered. Somatic cell epigenetic mitotic stability provides a somewhat permanent shift in the epigenome following an exposure during a critical window of development, such that later life physiology and disease can be linked (**Fig. 1**).

These somatic cell effects are likely more common and critical for the individual exposed than epigenetic transgenerational inheritance of exposure phenotypes. However, the germ line transmission of a permanent shift in the epigenome will potentially impact all subsequent generations to promote a phenotypic variation and/or disease state (**Fig. 2**). Since all the somatic cells generated from the germ line involved will have a shift in their epigenomes and genome activity, the environmental epigenetic transgenerational inheritance has a profound effect on biology and disease. In the case of disease etiology this can explain non-Mendelian inheritance of disease, environmentally induced increases in disease frequency and regional differences in disease frequencies. Clearly epigenetics will have a critical role in disease etiology and the amount of adult onset disease associated with epigenetic transgenerational inheritance will need to be established.

In regards to environmentally induced epigenetic transgenerational inheritance of biological or phenotypic variation, a significant impact on evolutionary biology needs to be considered.[11] An environmental factor such as nutrition promoting a modification of germ line epigenetic programming that becomes permanently programmed (**Fig. 2**) will have a role in the epigenetic transgenerational inheritance of phenotypic variation. This variation may subsequently impact an adaptation process to facilitate natural selection. An increase in phenotypic variation induced by environmental epigenetics that is heritable will be a molecular mechanism to consider in evolutionary biology. Previously, we have demonstrated an environmental toxicant exposure during fetal gonadal sex determination can promote epigenetic transgenerational inheritance of altered sexual selection phenotypes.[22] Since sexual selection is a major determinant for natural selection, this experiment provides direct evidence that environmental epigenetic transgenerational inheritance may have a role in evolution. This does provide a "neo-Lamarckian influence to facilitate Darwinian evolution" concept for evolutionary biology.

The reviewed environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability will both have significant roles in development, physiology, disease and evolution. These molecular mechanisms and an integration with classic genetics are now required to more fully understand the systems biology of development, physiology and disease, as well as areas of biology such as evolution.

References

1. Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. Birth Defects Res C Embryo Today 2011; 93:51-5.
2. Barker DJ. The developmental origins of adult disease. J Am Coll Nutr 2004; 23:588-95.
3. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet 2007; 8:253-62.
4. Waddington CH. The epigenotype. Endeavour 1942; 1:18-20.
5. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. Science 1975; 187:226-32.
6. Singer J, Roberts-Ems J, Riggs AD. Methylation of mouse liver DNA studied by means of the restriction enzymes msp I and hpa II. Science 1979; 203:1019-21.
7. Guerrero-Bosagna C, Settles M, Lucker BJ, Skinner MK. Epigenetic transgenerational actions of vinclozolin on promoter regions of the sperm epigenome. PLoS One 2010; 5:13100.
8. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005; 308:1466-9.
9. Anway MD, Leathers C, Skinner MK. Endocrine disruptor vinclozolin induced epigenetic transgenerational adult-onset disease. Endocrinology 2006; 147:5515-23.
10. Feng S, Jacobsen SE, Reik W. Epigenetic reprogramming in plant and animal development. Science 2010; 330:622-7.
11. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of environmental factors in disease etiology. Trends Endocrinol Metab 2010; 21:214-22.
12. Whitelaw NC, Whitelaw E. How lifetimes shape epigenotype within and across generations. Hum Mol Genet 2006; 15:131-7.
13. Salian S, Doshi T, Vanage G. Impairment in protein expression profile of testicular steroid receptor coregulators in male rat offspring perinatally exposed to Bisphenol A. Life Sci 2009;85: 11-8.

14. Bruner-Tran KL, Osteen KG. Developmental exposure to TCDD reduces fertility and negatively affects pregnancy outcomes across multiple generations. Reprod Toxicol 2011; 31:344-50.
15. Matthews SG, Phillips DI. Transgenerational inheritance of stress pathology. Exp Neurol 2011; In press.
16. Burdge GC, Slater-Jefferies J, Torrens C, Phillips ES, Hanson MA, Lillycrop KA. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. Br J Nutr 2007; 97:435-9.
17. Skinner MK. What is an epigenetic transgenerational phenotype? F3 or F2. Reprod Toxicol 2008; 25:2-6.
18. Skinner MK. Metabolic disorders: Fathers' nutritional legacy. Nature 2010; 467:922-3.
19. Chen ZX, Riggs AD. Maintenance and regulation of DNA methylation patterns in mammals. Biochem Cell Biol 2005; 83:438-48.
20. Turner BM. Histone acetylation and an epigenetic code. Bioessays 2000; 22:836-45.
21. Georgatos SD, Markaki Y, Christogianni A, Politou AS. Chromatin remodeling during mitosis: a structure-based code? Front Biosci 2009; 14:2017-27.
22. Crews D, Gore AC, Hsu TS, Dangleben NL, Spinetta M, Schallert T, et al. Transgenerational epigenetic imprints on mate preference. Proc Natl Acad Sci USA 2007; 104:5942-6.