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# The secret language of destiny: stress imprinting and transgenerational origins of disease

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Epigenetic regulation modulates gene expression without altering the DNA sequence to facilitate rapid adjustments to dynamically changing environmental conditions. The formation of an epigenetic memory allows passing on this information to subsequent generations. Here we propose that epigenetic memories formed by adverse environmental conditions and stress represent a critical determinant of health and disease in the F3 generation and beyond. Transgenerational programming of epigenetic regulation may represent a key to understand adult-onset complex disease pathogenesis and cumulative effects of life span and familial disease etiology. Ultimately, the mechanisms of generating an epigenetic memory may become of potentially promising diagnostic and therapeutic relevance due to their reversible nature. Exploring the role of environmental factors, such as stress, in causing variations in epigenetic profiles may lead to new avenues of personalized, preventive medicine based on epigenetic signatures and interventions.

**Keywords: epigenetics, microRNA, methylation, histone, programming by perinatal stress, adverse experience, neurological and psychiatric diseases, metabolic diseases**

## INTRODUCTION AND SCOPE

It is well established that the risk of many human complex diseases is determined by a heritable component. Recent evidence suggests that non-genomic and epigenetic processes participate in the heritable origins of disease with effects that extend beyond a single generation. The evolutionary conservation of these mechanisms is central to produce viable and apt offspring. Since the dynamic formation of a heritable memory may persist through multiple generations it may also poorly prepare the offspring to a dynamically changing environment, thus contributing to disease and compromising longevity. Therefore, programming by transgenerational inheritance represents a central mechanism by which environmental conditions may influence disease risk across multiple generations.

The concept of transgenerational inheritance refers to three main mechanisms. Aside from altered maternal endocrine responses and postnatal parental behavior, transmission of modifications in the epigenome appears to be a major component of transgenerational programming of disease (Jablonka and Lamb, 1989; Gluckman et al., 2007). Epigenetic transgenerational inheritance refers to the passage of epigenetic marks to the next generation without being altered or erased (Reik and Walter, 2001). Epigenetic processes readily respond to environmental conditions and so allow rapid modifications to an adverse environment, such as stress. Here we argue that human complex diseases, including psychiatric and metabolic disorders, are related to transgenerational epigenetic inheritance of maladaptive responses to environmental stress (**Figure 1**).

The main hypothesis of this review is that an adverse environment affects disease predisposition and outcome beyond a single life span to create a heritable or familial contribution to disease. According to Skinner (2008), we propose that epimutations need to propagate to at least three generations in order to represent genuine epigenetic inheritance. Very few studies have in fact investigated transgenerational inheritance of parental experience through three subsequent generations. We will first review the basic concepts of epigenetic regulation of gene expression and transgenerational programming. We will then discuss the role of environmental adversity, such as stress, in shaping the predisposition to future disease within a single lifespan and across generations. We will provide evidence supporting the conclusion that health and disease are programmed across multiple generations via epigenetic mechanisms.

## UNRAVELING THE SECRET LANGUAGE OF DESTINY: BASIC CONCEPTS OF EPIGENETIC PROGRAMMING

Epigenetic regulation can "program" the genetic information and cell fate and thus largely determine the functionality of an organ including the brain. These mechanisms may facilitate an adaptive response to a changing environment to optimize the chances of survival and reproductive success. Epigenetic programming, or re-programming by changing experience, permits reversible and heritable modulation of gene expression without altering the DNA sequence to rapidly adjust cellular processes to constantly changing environmental conditions (Champagne and Meaney, 2006, 2007; Champagne et al., 2008; Migicovsky and Kovalchuk, 2011; Skinner, 2011; Skinner et al., 2011; Babenko et al., 2012a,b).

Epigenetic changes are mitotically stable mechanisms responsible for gene expression modulation and/or their inheritance by molecular adjustments. The major epigenetic events include DNA cytosine methylation, histone modifications, transcriptional, and posttranscriptional control of gene expression

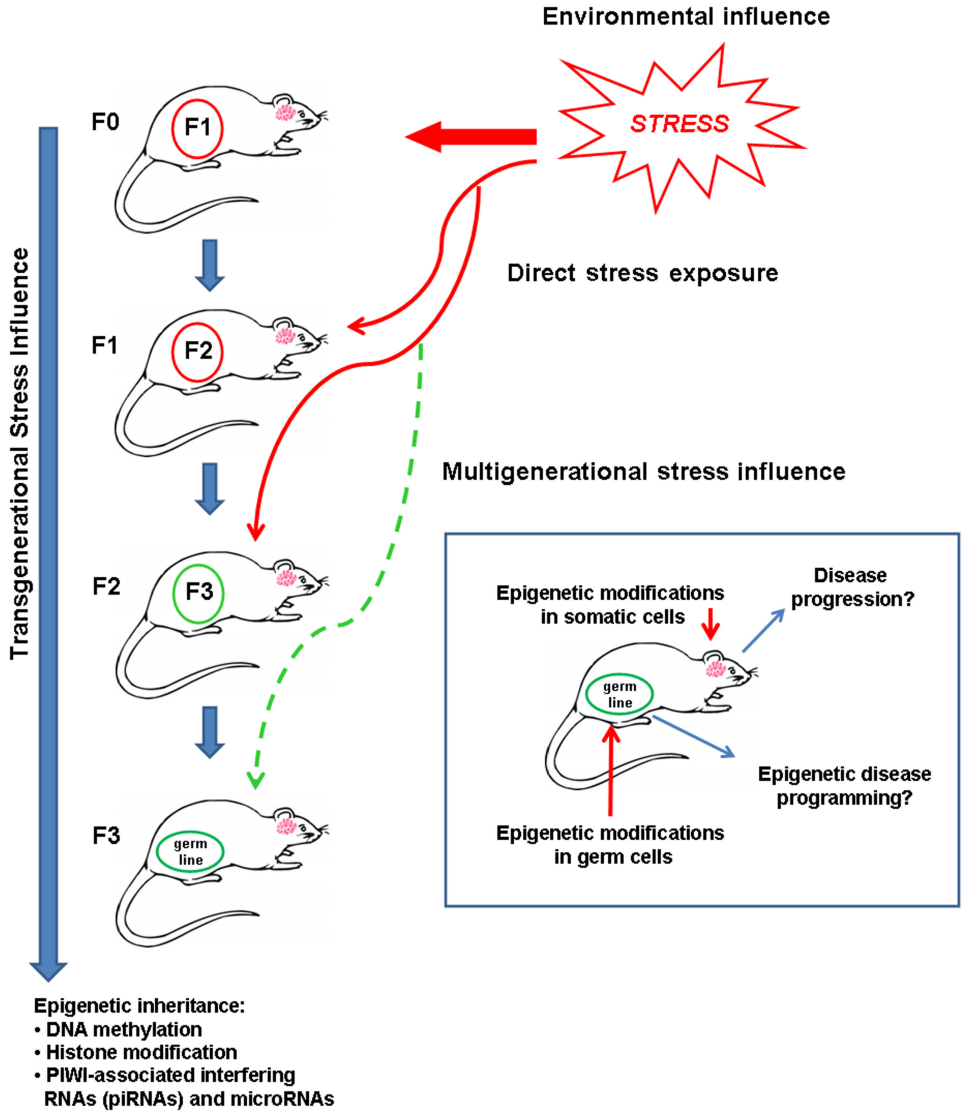


**FIGURE 1 | Inheritance of an epigenetic memory caused by an adverse environment, such as stressful experiences, produce phenotypes in next generations that may influence disease risk.** Solid red arrow indicates direct exposure to stress in an animal; thin red arrows indicate direct stress exposure leading to intergenerational stress influence in F1 and F2 generations; dashed thin green arrow indicates possible transgenerational inheritance of a multigenerational stress phenotype in the F3 generation. To prove genuine epigenetic programming, it is necessary to determine phenotype transmission to the third generation (F3).

through PIWI-interacting RNA (piRNA), microRNA (miRNA), and heterochromatin gene silencing (**Figure 2**; Ilnytskyy et al., 2008; Yauk et al., 2008; Filkowski et al., 2010; Migicovsky and Kovalchuk, 2011). Recent studies have recognized the importance of differential expression of miRNA-regulated pathways in complex epigenetic selfregulation (Bartel, 2004). For instance, miR-184, a brain-specific miRNA suspected in the etiology of autism spectrum disorder, is upregulated by the release of the methyl-CpG-binding protein 2 (MeCP2) from paternal allele-specific expression (Nomura et al., 2008). While MeCP2 is integral to the function of mature neurons, the presence of a methyl-CpG-binding domain and interaction with miR-184 provides a link between epigenetic pathways involving small regulatory RNAs and DNA methylation. These pathways may synergistically affect transgenerational programming of disease via genomic imprinting.

Genomic imprinting refers to a process that involves chromatin modifications to achieve monoallelic gene expression (Reik and Walter, 2001). One of the first evidences of genomic imprinting was derived from an observation linking Angelman syndrome, a brain developmental disorder including speech and motor deficits (Angelman, 1965), to Prader–Willi syndrome, a congenital condition that is characterized by insatiable appetite and delayed motor maturation (Curfs and Fryns, 1992). These two very distinct human phenotypes are both linked to loss of function of the ubiquitin *UBE3A* pathway, encoded by a nucleotide sequence on chromosome 15 (Magenis et al., 1987; Adams, 2008). Usually the

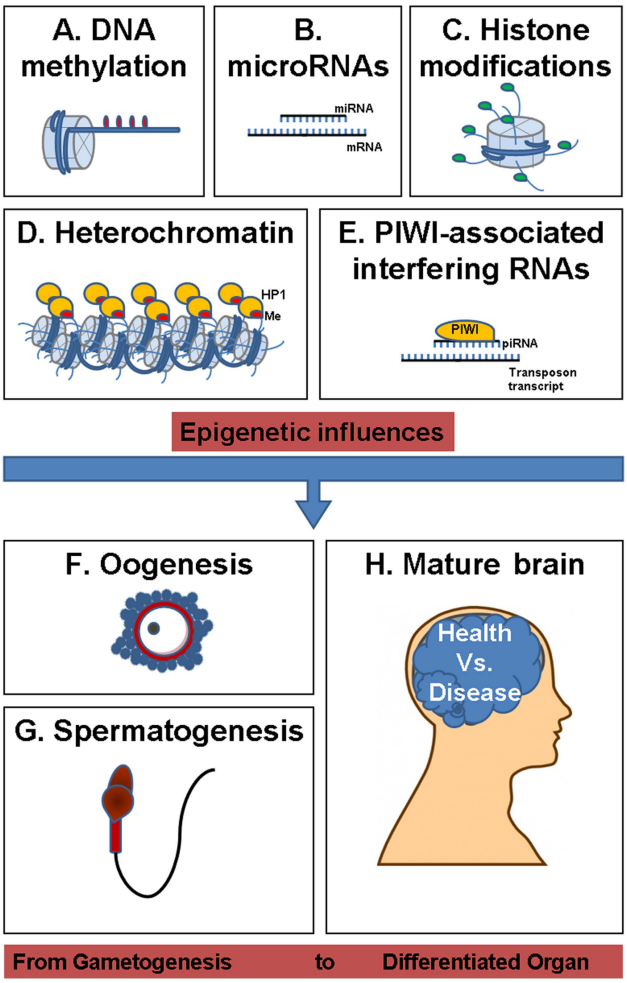


**FIGURE 2 | Overview of epigenetic influences shaping health and disease from gametogenesis to differentiated organ. (A)** DNA methylation (DNA containing methyl groups, which is packed in a nucleosome core histone complex). **(B)** microRNAs (microRNA–mRNA complex). **(C)** Histone modifications (histone tail acetylation, methylation, ubiquitination, sumoylation, or phosphorylation). **(D)** Heterochromatin (containing hypoacetylated, methylated H3K9 histone tail). **(E)**, PIWI-associated interfering RNAs (PIWI protein and piRNA guide forming a complex with transposon transcript). **(F)** Oogenesis (ovulum). **(G)** Spermatogenesis (spermatozoid). **(H)** Mature brain.

sequence derived from the mother encodes function of this pathway while the paternal contribution is silenced. Thus, the paternal gene is unable to compensate for the loss of the maternal gene in Angelman syndrome, leading to this characteristic phenotype (Jiang et al., 1998; Rougeulle et al., 1998). In Prader–Willi syndrome, however, the neighboring region *SNRPN* on chromosome 15, encoding a pathway for mRNA splicing, shows the opposite pattern of gene imprinting. Here, the paternal contribution of the gene is normally being transcribed and the maternal contribution is silenced. If function of the paternal gene becomes lost, the methylated maternal gene is unable to correct for this loss and the phenotype of Prader–Willi syndrome may occur (Cassidy et al., 2012). While this kind of inherent genomic imprinting is a potent influence on future health and disease, the epigenome, in particular methylation patterns, readily respond to changes in life style.

Methylation has been the most widely investigated mechanism of genomic imprinting in health and disease. Based on the observation that alleles may be expressed from only one of the two parental chromosomes (Reik and Walter, 2001; Wilkins and Haig, 2003), recent studies suggested that DNA methylation may represent a central mechanism to facilitate phenotypic variation of complex traits (Itier et al., 1998; Wilkinson et al., 2007; Wang et al., 2010). Methylation patterns are highly responsive to parental life style and environment. For instance, prenatal exposure to maternal tobacco smoking may elevate DNA methylation of the gene encoding brain-derived neurotrophic factor (BDNF; Toledo-Rodriguez et al., 2010), a vital growth factor in brain development, plasticity, and psychiatric disease (Balaratnasingam and Janca, 2012). Methylation of the BDNF-6 exon causes reduction in BDNF expression and possibly facilitates variations in brain development in the fetus exposed to maternal smoking (Toledo-Rodriguez et al., 2010). Thus, one may argue that transgenerational variation in BDNF expression may contribute to the programming of psychiatric diseases. Aside from substance use, the maternal psychological state may also determine the psychiatric health of the offspring through altered DNA methylation status. For example, maternal depressed mood during pregnancy was found to be related to methylation of the SLC6A promoter, which encodes a transmembrane serotonin transporter, in both mother and infant (Devlin et al., 2010). The authors of this study showed that maternal depressed mood in the second trimester was associated with reduced maternal and newborn SLC6A4 methylation status (Devlin et al., 2010), which represents a risk factor for greater vulnerability to post-traumatic stress disorder (Koenen et al., 2011). These findings suggest that maternal mood and wellbeing can have profound consequences on offspring health.

## EPIGENETIC MECHANISMS AS AN INTERFACE BETWEEN STRESS AND DISEASE ACROSS ALL AGES

Epigenetic mechanisms represent a critical interface between a stressful environment and the genome. The term stress refers to perturbation of homeostasis by an adverse experience or environmental threats that activate the hypothalamic–pituitary–adrenal (HPA) axis and associated neuroendocrine changes (Seckl, 2008). The onset of the stress response results in the release of primary stress hormones, such as cortisol in primates, which bind to glucocorticoid receptors in the cytoplasm. As a hormone–receptor complex, cortisol then translocates to the nucleus to regulate gene expression and protein synthesis (Zucchi et al., 2010). The genomic response to stress mediates a set of complex neural, metabolic, and endocrine adaptations that may have long-term consequences (Drake et al., 2005). Above and beyond these regulatory activities, stress may also leave an epigenomic imprint to affect health and disease (Babenko et al., 2012a,b). A particularly sensitive time window to programming of long-term physiology and health through epigenetic marks is the perinatal period.

Perinatal programming refers to the priming of long-term physical and psychological health outcomes during critical periods

in early development. Excessive glucocorticoid levels caused by severe maternal stress during pregnancy may saturate the protective placental enzyme barrier, 11-beta-hydroxysteroid dehydrogenase (11beta-HSD), to reach the fetus (Miller and Chernoff, 1995; Welberg et al., 2000; Brummelte et al., 2010) and permanently modulate fetal HPA axis activity (Drake et al., 2005) and behavior. For example, perinatal stress influences anxiety- and depression-like behaviors and cognitive abilities (Champagne et al., 2003, 2008; Richards and Sacker, 2003; Gatt et al., 2009; Kinsella and Monk, 2009; Rokyta et al., 2008) as well as central dopaminergic system function to modulate rewarding behavior in later life (McArthur et al., 2007; Mueller and Bale, 2008). Many of the behavioral effects of stress likely include an epigenetic component (Colvis et al., 2005; Champagne et al., 2006) that facilitates robust perinatal programming. A striking example of this link was proposed by studies of maternal care. Variations in maternal care may program individual differences in stress reactivity across generations by epigenetic mechanisms, including DNA methylation (Francis et al., 1999; Champagne et al., 2003; Weaver et al., 2004). This early life experience has long-lasting effects on the progeny and is transmitted to the next generation (Francis et al., 1999; Caldji et al., 2003).

Prenatal glucocorticoid exposure and postnatal care by a stressed mother not only program the response to recurrent stress in later life, but may also affect the predisposition to disease in adulthood. The concept that vulnerability to disease is acquired in the perinatal period was developed more than 30 years ago (e.g., Dörner et al., 1984). Studies by David Barker's group in the 1990s have first associated adverse perinatal environment with higher incidence of obesity and cardiovascular disease in the aged offspring (Law et al., 1992; Barker, 2007). Experience during gestation and/or early postnatal life may prime the susceptibility for disease in later life, including metabolic (e.g., type 2 diabetes mellitus, obesity), neurological (Mabandla et al., 2009; Mabandla and Russell, 2010; Babenko et al., 2012b), and cardiovascular disease (Newnham, 2001; Zambrano et al., 2005; Cottrell and Seckl, 2009; Zambrano, 2009; Singhal, 2010; Thompson and Einstein, 2010). Thus, while the information given to the developing fetus may support immediate adaptation to the postnatal environment, it may not support successful aging because these endocrine adjustments to an adverse environment come at a high metabolic expense (**Figure 3**).

Later in life, stress-induced changes in epigenetic regulation are suspected to contribute to the enhanced susceptibility to neurological and psychiatric disease through regulation of components of the HPA axis activation, such as corticotrophin-releasing factor (Sterrenburg et al., 2011). Moreover, prenatal stress causes region-specific changes in miRNA expression resulting in dysmasculinization of the male brain (Morgan and Bale, 2011). During critical periods of sexual differentiation, methylation patterns change regardless to neonatal hormone exposure and are dynamically regulated throughout the life span (Schwarz et al., 2010). Accordingly, evidence suggests that risk factors for cardiovascular disease, including stress and an unbalanced diet, are associated with modified epigenetic markers (Ordovás and Smith, 2010). Possible epigenetic correlates of elevated cardiovascular risk were reported to include global DNA hypermethylation (Stenvinkel et al., 2007) and miRNA-29b (miR-29b)-induced regulation of genes that influence atherosclerosis risk (Chen et al., 2011). The latter study showed that miR-29b upregulation results in DNMT3b down-regulation in human aortic smooth muscle cells and altered MMP-2/MMP-9 gene expression involved in cell migration (Chen et al., 2011). Moreover, central genomic and epigenomic responses to psychological stress or associated endocrine changes involve DNA methylation (Mychasiuk et al., 2011; Sterrenburg et al., 2011) and miRNA regulation (Babenko et al., 2012a). Interestingly, age-related epigenetic re-programming may also be responsible for a positive relationship between advanced maternal or grandmaternal age at the time of birth and an increased risk of psychiatric conditions, such as autism spectrum disorder (Golding et al., 2010) or memory impairments (Burns and Mery, 2010) in the offspring. These studies concur that epigenetic activity closely influences brain development and neurological functions (**Figure 2**).

Aside from perinatal programming, the cumulative effects of life-long adverse stimuli may also modify the risk of functional decline and disease in adulthood and old age (Mora et al., 2007; Miller and O'Callaghan, 2008; Merrett et al., 2010; Schreier et al., 2011). Epigenetic signatures are central to adult-onset complex diseases including psychiatric and neurological (Glaser et al., 2010; Ronald et al., 2010; Babenko et al., 2012b), cardiovascular (Stenvinkel et al., 2007; Kaneda et al., 2009; Chen et al., 2011; Stein et al., 2011), and metabolic conditions (Ling et al., 2008; Begum et al., 2012; Volkmar et al., 2012). It may be the cumulative experience to stress throughout life that, through epigenetic regulation, precipitates or accelerates pathological processes that promote neurodegenerative events (Babenko et al., 2012b). Accordingly, methylation patterns in the brain are correlated with chronological age (Hernandez et al., 2011) and with life style (Kaliman et al., 2011). Notably, the aging of the brain and age-related decline in motor and cognitive functions corresponds to a global reduction in gene expression (Lu et al., 2004) and a diminished capacity for epigenetic memory in chromatin of oligodendrocytes (Shen et al., 2008). The age-associated loss of the epigenetic memory may significantly alter cellular function over time.

Central targets of epigenetic programming in the brain at any age are neurotrophic molecules, which are highly sensitive to the effects of stress and other environmental factors (Kobilo et al., 2011; Taliaz et al., 2011; Johansen et al., 2012). Neurotrophic and growth factors that are modulated by epigenetic regulation include glial cell line-derived neurotrophic factor (GDNF; Uchida et al., 2011), BDNF (Fuchikami et al., 2010; Zeng et al., 2011), and nerve growth factor (NGF; Sen and Snyder, 2011). Epigenetic regulation of histones mediates neurotrophin actions with histone acetylation enhancing cAMP response element-binding (CREB)-associated transcription elicited by BDNF and NGF (Sen and Snyder, 2011). BDNF activates neuronal nitric oxide synthase with the nitrosylated GAPDH/seven in absentia homolog (Siah) complex translocating to the nucleus. Degradation of the histone–lysine *N*-methyltransferase SUV39H1 by Siah facilitates histone H3K9 acetylation, CREB binding to DNA, and enhances expression of CREB-regulated genes and neurite outgrowth (Sen and Snyder, 2011). Histone deacetylases are the first identified

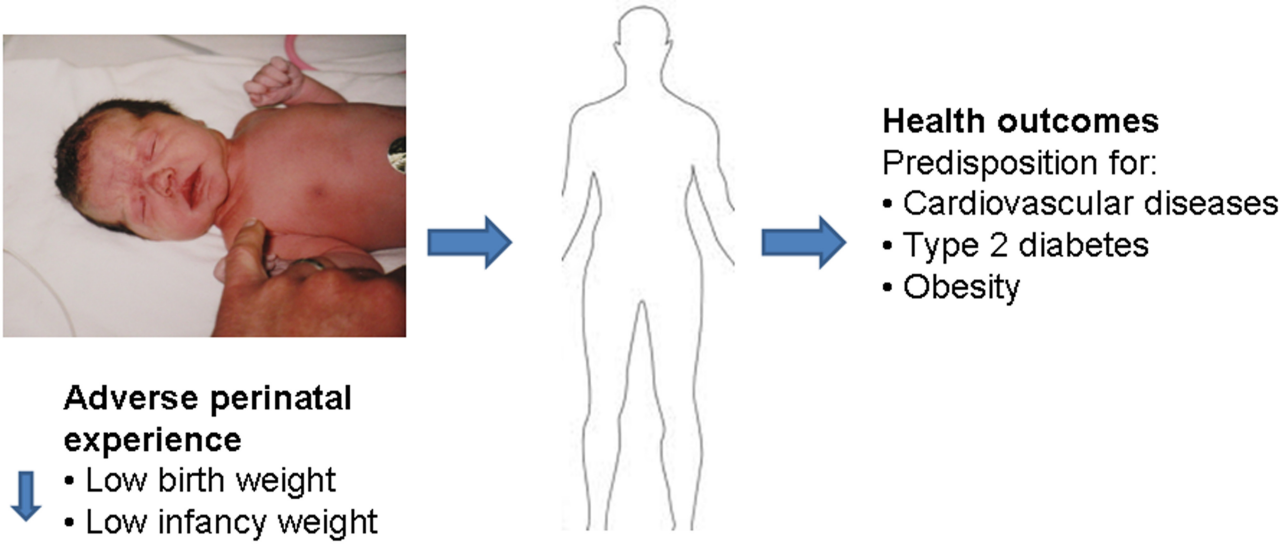


**FIGURE 3 | Adverse perinatal experiences may influence the risk of cardiovascular and metabolic diseases in adulthood.** Low birth weight and low infancy weight (first year) has been correlated with a predisposition of adult onset diseases, such as high blood pressure and risk of cardiovascular disease, insulin resistance and risk of diabetes, and adulthood obesity.

intranuclear targets of nitric oxide, but, due to its highly diffusible nature, it is likely that many other nuclear factors are directly regulated by nitric oxide (Nott and Riccio, 2009).

Dysregulation of neurotrophic molecules is a central component in the pathogenesis of major psychiatric and neurologic disorders, such as schizophrenia, obsessive-compulsive disorder, Alzheimer's and Huntington diseases (Mattson, 2008). The cumulative adverse effects of stressful experiences throughout life may accelerate age-related decline through loss of neurotrophic factors and neuroplasticity (Pham et al., 2002; Gatt et al., 2009), reduced gene expression (Bishop et al., 2010), and altered epigenetic status (Siegmund et al., 2007). Interestingly, susceptibility and adaptation to adverse environments during a lifetime may be closely linked to the epigenetic status of the GDNF gene (Uchida et al., 2011). Importantly, epigenetic signatures of neurotrophic factors may be passed on to the fetus (Toledo-Rodriguez et al., 2010) and propagate to subsequent generations.

## FORMING AN EPIGENETIC MEMORY ACROSS GENERATIONS

Epigenetic memory refers to transgenerationally stable, yet dynamic re-programming of the germline epigenome that will transfer epigenetic information from one generation to the next in the absence of DNA sequence mutations (Zambrano, 2009; Migicovsky and Kovalchuk, 2011). A pioneering example of an epigenetic memory was generated by studies focusing on the *agouti* locus in mice that controls coat color (Morgan et al., 1999). In mice expressing the viable yellow (*Avy*) allele the coat color is determined by the epigenetic status of intra-cisternal A particle (IAP) retrotransposons. Without methylation, the transcription of an IAP retrotransposon inserted upstream of the agouti gene will initiate the expression of agouti protein, resulting in yellow fur along with abnormal metabolic responses and predisposition to tumors (Morgan et al., 1999). In the hypermethylated state, however, silencing of the promoter in the IAP I will result in a black coat and mice become indistinguishable from wild-type (*A/A*) mice (Morgan et al., 1999). Such profiles may persist to subsequent generations to form an epigenetic memory. Epigenetic modifications may propagate to the offspring by means of two different processes and at different stages in a mammal's lifecycle: programming of somatic cells and the germline, as illustrated in **Figure 1**.

Programming of somatic cells, including the brain, may mediate transgenerational inheritance. Environmental conditions may impact the organization of brain organogenesis and phenotype through epigenetic reprogramming rendering the individual susceptible to adult-onset neurological disease. These acquired memories may lead to organ- or tissue-specific metabolic imbalance or disease predisposition. The mechanisms also include behavioral and physiological modifications in response to the environment that shape intergenerational transmission (Champagne and Meaney, 2006). Thus, a behavioral phenotype may perpetuate across generations via changes in chromatin. For example, a behavioral trait such as a certain type of maternal care may be passed on to the subsequent generation. Rats raised by a mother displaying poor maternal care, such as low levels of licking and grooming toward her pups, also are more likely to exhibit poor maternal care toward their own offspring (Weaver et al., 2004, 2007; Cameron, 2011). This behavioral phenotype is linked to hypermethylation of the BDNF gene and consequently low expression of BDNF in the prefrontal cortex of offspring (Roth et al., 2009). Transgenerational behavioral traits of maternal care may also determine survival in other ways. In the biparental burying beetle *Nicrophorus vespilloides*, grandparents and parents of both sexes cumulatively influence offspring development (Lock, 2012). In the biparental condition, females spend most of their time caring for the larvae, while males

spend most time with indirect care by maintaining the carcass in which the larvae lives. The existence of an intergenerational influence from F0 to F2 generations provide a selection pressure for the division of parental investment in biparental species across different taxa, which seems to enhance survival of this species (Lock, 2012).

The second mechanism of transgenerational programming by stress may be mediated through the germline. These modifications may be passed on to future generations without direct exposure (Chong and Whitelaw, 2004). The germline-mediated epigenetic transgenerational inheritance is based on marks in the chromatin that influence the gonadal development and reproductive success of the affected individual (Whitelaw and Whitelaw, 2008). Usually, DNA methylation sites are selectively erased during gonadal sex determination in embryogenesis. Some DNA marks will survive this critical time window, however, and persist throughout development and maturation (Migicovsky and Kovalchuk, 2011). The methylated DNA then may integrate in the gametes and be passed on to the embryo of the next generation. These genes "imprinted" with a pattern of DNA methylation may propagate stress-induced modifications to the subsequent generations (Skinner et al., 2008). An example of germline transmission is represented by the effects of environmental toxins, such as the endocrine disruptor bisphenol-A (BPA), which resembles the actions of reproductive hormones and thus influences the reproductive success of females in the next generation (Dolinoy et al., 2007). The hypothesis that diseases might be programmed by transgenerational influences, such as stress through epigenetic mechanisms seems reasonable in this framework, considering that the environment shapes current (somatic cells) and future (germ cells) generations.

Transgenerational epigenetic inheritance may be defined as a phenotype that is transmitted to more than one generation by means other than Mendelian genetics (Whitelaw and Whitelaw, 2008; Migicovsky and Kovalchuk, 2011; Daxinger and Whitelaw, 2012). Thus, physiological and/or environmental factors affecting the parent (F0 generation) can have consequences for the next, unexposed generation (F1 generation) and possibly for further subsequent generations (F2, F3) as well. A recent concept argues that only epigenetic alterations persisting to the F3 generation may be considered truly heritable when pregnant females are concerned (Skinner, 2008). Skinner (2008) defined transgenerational epigenetic inheritance as changes in unexposed generations (F3 and beyond). This concept excludes F0 generation exposure to a given environmental factor during pregnancy that directly also affects the phenotype of the F1 embryo and F2 primordial germ cells. Therefore, as illustrated in **Figure 1**, the interpretation of genuine transgenerational effects requires analysis of the F3 phenotype. In this context, transgenerational phenotypes are defined as traits acquired from an initial exposure, persistently transmitted to the next generation in the absence of continued exposure in any of the successive generations (Skinner, 2011). An intergenerational phenotype refers to transmission to the F1 and F2 generations that are not (yet) known to persistently alter the F3 phenotype. By contrast, multigenerational phenotypes are characterized by direct exposure of multiple generations to an environmental factor or toxin (Skinner, 2011). For instance, endocrine disrupting agents and pesticides induce gene imprinting (F1–F4; Anway et al., 2005; Jirtle and Skinner, 2007; Manikkam et al., 2012), anxiety-like behavior (Skinner et al., 2008), and adult-onset disease (Anway et al., 2006) in a genuine transgenerational pattern. According to these studies, the present review will consider the definition of transgenerational inheritance to the F3 generation, and our hypothesis is that disease is programmed by epigenetic inheritance across three successive generations.

An epigenetic transgenerational phenotype will ultimately affect gene expression, molecular adjustments, cellular function, physiological parameters, and behavioral profiles. These processes may perturb the integrity of somatic and/or germ cells in the offspring later in life, leading to compromised health. The short-term adaptation that results from epigenetic modifications may facilitate rapid adaptation to adverse environmental conditions and immediate survival of an individual. In the long-term, however, acquired physiological and epigenetic profiles, such as those in response to stress, may produce a mismatch to later-life challenges and enhance the vulnerability to disease.

## LIFE-TIME VERSUS TRANSGENERATIONAL EPIGENETIC PROGRAMMING

Epigenetic programming represents a major mechanism to allow passing on the effects of experience to subsequent generations. This process generates an epigenetic memory that is now recognized as a central component in the transmission of information about early experience, environmental conditions, and life style factors to the progeny (Boyko et al., 2010; Boyko and Kovalchuk, 2010; Migicovsky and Kovalchuk, 2011). For example, in the womb epigenetic re-programming seems to occur rapidly to facilitate adaptation of the fetus to current environmental conditions (Breton et al., 2009; Guerrero-Preston et al., 2010; Toledo-Rodriguez et al., 2010). While initially a beneficial response to prime developmental plasticity (Mousseau and Fox, 1998; Cropley et al., 2012), transgenerational transmission of epigenetic alterations in the long-term may have maladaptive consequences that compromise overall health and successful aging. Thus, epigenetic programming may represent a key to understand diseases processes, propagation through generations, and cumulative effects of life span and familial disease etiology.

Epigenetic programming might direct evolution through inheritance of certain epimutations across generations. Experience throughout life, however, can modify the imprints of perinatal programming and disease risk. Accordingly, positive experiences such as education, physical activity, and social environment can ameliorate maladaptive programming and disease vulnerability (Wirdefeldt et al., 2005; Carlson et al., 2008; James et al., 2011). Moreover, positive experience in rats, including exposure to an enriched environment, can diminish consequences of neurodegenerative influences and age-related functional decline (Escorihuela et al., 1994; Mattson et al., 2001; Laviola et al., 2004; Jadavji et al., 2006; Paban et al., 2009; Segovia et al., 2009). Accordingly, the sum of cumulative favorable and adverse experiences creates age-associated epigenetic drift, which was shown in animals (Bennett-Baker et al., 2003) and in monozygotic twins (Fraga et al., 2005; Martin, 2005; Poulsen et al., 2007). Fraga et al. (2005) demonstrated that advancing age leads to greater global and

locus-specific differences in DNA methylation and histone H3 and H4 acetylation in peripheral blood lymphocytes, buccal mucosal epithelial cells, skeletal muscle biopsies, and adipose tissue of identical twins. Different epigenetic patterns were found in almost all telomeres and certain gene-rich regions of chromosomes (Fraga et al., 2005). These findings illustrate that epigenetic modifications in somatic cells may perpetuate throughout the life span (Siegmund et al., 2007; Hernandez et al., 2011; Uchida et al., 2011) likely by stable mitosis (in cell lines, tissues, or organs) to facilitate adaptation to ongoing environmental conditions (Skinner, 2011).

The effects of parental exposure to environmental factors may persist to the F2 generation and enhance vulnerability to adult-onset disease across multiple generations (Gluckman et al., 2007; Zambrano, 2009; Nolan et al., 2011; Feil and Fraga, 2012). For example, a recent collaboration between Swedish and British scientists provided evidence of sex-specific programming of longevity in humans. A transgenerational correlation was found between the nutritional status during early life of the paternal grandparents and the grandchild's chances of longevity, including associations with cardiovascular and diabetic disease (Pembrey, 2010). A prominent case of intergenerational programming of disease stems from a systematic study of the Dutch Famine Birth Cohort. Exposure to poor nutrition during pregnancy in the Dutch winter 1944/45 led to smaller babies (Stein and Lumey, 2000), who developed an increased risk of insulin resistance in adulthood (Painter et al., 2005). Furthermore, granddaughters of women pregnant during the famine were smaller, more prone to neonatal adipositas and poor health in later life (Painter et al., 2008). These findings confirm that consequences of prenatal adverse experience may reach down across several generations.

Another link to intergenerational HPA axis programming is illustrated by lower cortisol levels in offspring of Holocaust survivors with post-traumatic stress disorder (Yehuda et al., 2007). HPA axis changes may also be involved in the observation that grandchildren of Holocaust survivors present with higher rates of psychiatric illness (Sigal et al., 1988), elevated levels of fear, neurotic behavior, and aggression (Scharf, 2007) and depression (Felsen and Erlich, 1990). On the other hand, adaptive changes may reflect in improved coping skills (Sigal and Weinfeld, 2001). Thus, ancestral programming may result in both beneficial and detrimental physiological and behavioral outcomes.

In rat and guinea pig models, intergenerational stress-induced changes lasting to the F2 generation have been shown for caloric restriction (Benyshek et al., 2006; Bertram et al., 2008; Pinheiro et al., 2008) or overfeeding (Pentinat et al., 2010). A protein-restricted diet in the parental generation led to reduced birth and brain weight and altered glucose metabolism in the unexposed F2 generation (Zamenhof et al., 1971; Benyshek et al., 2006). Altered glucose metabolism in these studies is usually characterized by high blood sugar, increased blood insulin, and insulin resistance, which may be indicative of diabetes (**Figure 3**; Pinheiro et al., 2008). Various mechanisms may participate in the perinatal programming of these phenotypes, including altered gestational endocrine milieu and maternal behavior, as well as gene imprinting by epigenetic factors (Migicovsky and Kovalchuk, 2011; Matthews and Phillips, 2012). An epigenetic component to intergenerational programming was demonstrated for depressive-like behaviors induced by maternal separation stress in mice (Franklin et al., 2010). These behavioral changes were accompanied by altered DNA methylation profiles in the germline and brains of the offspring of stressed males (Franklin et al., 2010).

Support for the notion that stress-induced intergenerational long-term adaptations are epigenetically programmed originates from a recent longitudinal study in children. Essex et al. (2011) showed that maternal stress in infancy and paternal stress in preschool years are predictive of permanent differences in DNA methylation patterns in adolescent school children. The association between adversity in early childhood and the DNA methylation profiles in adolescents suggests that early experience creates a lasting imprint on the epigenomic status. The neonatal environment may be a particularly important determinant of the onset of age-related complications. Although life-long experience may change these patterns, the stability of DNA methylation patterns through development and adolescence suggests that parentally programmed or inherited epigenetic profiles create an epigenetic blueprint that persists into adulthood and potentially into old age.

Although the importance of transgenerational programming of disease has been recognized, a limited number of reports have investigated the F3 generation and beyond. Transgenerational inheritance refers to the ability of environmental factors to promote an intergenerational phenotype or disease state beyond the exposed mother, her female offspring and grandoffspring (Skinner et al., 2008). Truly transgenerational effects were shown for factors such as nutrition (Benyshek et al., 2006; Dunn and Bale, 2011), physiological disturbance (Aerts and van Assche, 1979), and endocrine disruptors (Blatt et al., 2003; Anway et al., 2005; Brouwers et al., 2006; Nilsson et al., 2008; Skinner et al., 2008; Guerrero-Bosagna et al., 2010). By contrast, if a phenotype was caused by a direct effect of experience on the germline and somatic cells without lasting heritable genomic imprints, these effects are expected to disappear by the F3 generation. For example, Drake et al. (2005) observed that prenatal treatment with the synthetic steroid dexamethasone in rats resulted in low birth weight and metabolic markers for elevated diabetes risk, such as hyperglycemia, hyperinsulinemia, and increased activity of gluconeogenic enzyme phosphoenolpyruvate carboxykinase, in the progeny. These changes, however, were resolved by the third generation (Drake et al., 2005). This observation indicates that perinatal programming by steroid hormones may be caused by direct effects on the primordial germ line rather than stable epigenetic imprinting. Similarly, *Avy* hypermethylation induced by maternal methyl supplementation to induce the agouti phenotype in mice is also not inherited transgenerationally from F0 to F3 generations (Waterland et al., 2007). However, transgenerational inheritance of stress responses and associated epigenetic correlates are well established in plant models (Boyko et al., 2010; Boyko and Kovalchuk, 2011; Bilichak et al., 2012). Information about the causative mechanisms of transgenerational inheritance in mammals is still extremely limited, however, selective breeding experiments may offer a welcome venue for such studies.

Studies of selective breeding during domestication support the notion of lasting transgenerational traits, although a possible epigenetic component still remains to be determined. For instance, long-term multigenerational selection for traits of docility and tolerance toward human company of the silver fox (*Vulpes vulpes*) resulted in complex feature changes including attenuated HPA axis activity (Trut et al., 2009). This selection was accompanied by a change in 3% of the transcriptome in the fox prefrontal cortex (Kukekova et al., 2011). Aside from selection for genetic variants epigenetic regulation may have largely contributed to the changes in gene expression associated with the domestication of this species. Another interesting insight provides a multigenerational study of breeding 11 generations of mice selected for anxiety traits (Filiou et al., 2011). Anxiety-like behaviors were linked to altered proteomic status and metabolic pathway function, along with substantial differences in the transcriptome (Czibere et al., 2011; Filiou et al., 2011).

Although the above criteria of transgenerational programming do not apply to invertebrates, a recent study showed intriguing evidence of multigenerational programming of longevity. An example of epigenetic transmission of an adaptive parental trait to future generations was recently described in the nematode *Caenorhabditis elegans* (Greer et al., 2011). In this study, deficiency in the chromatin modifying histone H3 lysine 4 trimethylation complex, which regulates *C. elegans* lifespan, can be passed on to three subsequent generations to extend their lifespan (Greer et al., 2011). Through methylation-induced gene silencing, RNA or protein inheritance a histone modification involving H3K4me3, a regulatory complex associated with longevity, was shown to persist to the F4 generation of a *C. elegans* population (Greer et al., 2011). In this study, however, epigenetic inheritance of longevity disappeared in the F5 generation. The mechanisms involved in developing transgenerational behavioral, physiological, and metabolic traits remain to be elucidated.

The findings discussed above suggest widespread and drastic phenotypic changes after transgenerational pre- or postnatal adverse environment with an emphasis on epigenetic regulation. A growing body of evidence provides examples of transgenerational stability of epigenetic changes, such as DNA methylation patterns and miRNA expression (Zambrano, 2009; Boyko et al., 2010; Matthews and Phillips, 2010, 2012) and alterations associated with aging processes (Fraga et al., 2005; Rodríguez-Rodero et al., 2010). Transgenerational differences and the effects of age on miRNA expression are robust (Jukic et al., 2010). The specific mechanisms of transgenerational transmission are not entirely known, but DNA methylation and miRNA expression changes are likely involved (Boyko et al., 2007, 2010; Skinner and Guerrero-Bosagna, 2009) and these may offer an exciting potential to identify epigenetic signatures of prognostic significance for disease. Interestingly, recent findings support the potential to obtain predictive epigenetic markers of disease through blood samples or placenta (Tsui et al., 2010; Du et al., 2011; Hahn et al., 2011), which bears important therapeutic potential.

## IMPLICATIONS AND CONCLUSION

While life-long experience constantly modulates epigenomic patterns, ancestral programming sets the stage for responses to stress, disease, and aging across the lifespan. In this review, we proposed that epigenetic imprints of environmental information may persist through multiple generations. Such epigenetic memories may represent a unifying component to phenotypic plasticity to influence development, performance, and disease (Petronis, 2010). Most mechanistic studies of epigenetic inheritance have focused on F0–F1 transmission. Fewer reports of transgenerational phenotypes and epigenotypes including and beyond the F3 generation exist, however, transgenerational programming of brain and developmental plasticity, metabolic, neurological and psychiatric functions is a critical and rewarding field of investigation.

Transgenerational programming of disease risk may explain the general difficulty to identify the causes of complex adult-onset diseases. Understanding the possibly substantial contribution of ancestors to disease risk in an individual may significantly advance prognostic medicine. The impact of transgenerational programming versus life-long experience on health and disease is a central issue for personalized medicine and disease prevention.

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