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Current Opinion in Genetics & Development

Environmentally induced epigenetic transgenerational inheritance of male infertility

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Decreasing male fertility has been observed for the past fifty years. Examples of affected reproductive parameters include decreases in sperm count and sperm quality and increases in testicular cancer, cryptorchidism and hypospadias. Exposures to environmental toxicants during fetal development and early postnatal life have been shown to promote infertility. Environmental exposures inducing epigenetic changes related to male infertility range from life style, occupational exposures, environmental toxicants and nutrition. Exposures during fetal gonadal sex determination have been shown to alter the epigenetic programming of the germline that then can transmit this altered epigenetic information to subsequent generations in the absence of any exposures. This environmentally induced epigenetic transgenerational inheritance of disease will be a component of the etiology of male infertility.

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Current Opinion in Genetics & Development 2014, **26**:79–88

This review comes from a themed issue on **Molecular and genetic bases of disease**

Edited by **Cynthia T McMurray** and **Jan Vijg**

For a complete overview see the Issue and the Editorial

Available online 11th August 2014

http://dx.doi.org/10.1016/j.gde.2014.06.005

Introduction

Trends have been observed in human populations showing decreasing male fertility for decades [1,2••,3,4]. Examples of the reproductive parameters affected are decreases in sperm count and quality [2••], increases in testicular cancer [3] and increases in cryptorchidism or hypospadias [1]. Data of particular interest include several meta-analysis suggesting a strong decline in sperm quality from the 1940s to present [5–8]. Similar to the phenotypes associated with the metabolic disease syndrome [9], it has been postulated that these male reproductive disorders have a common developmental origin and are physiologically linked, leading to a complex disease trait of 'Testicular Dysgenesis Syndrome' (TDS) [10,11•,12]. The syndrome describes these male reproductive disorders as sharing the same patho-physiological etiology and as being caused by disrupted testicular development in the early fetus [12,13]. Interestingly, one of the key studies that documented the recent decrease in sperm quality in men [5] concludes that '*Such remarkable changes in semen quality and the occurrence of genitourinary abnormalities over a relative short period is more probably due to environmental rather than genetic factors*', an opinion that is supported by more recent publications [2••,11•,13]. This highlights the importance that environmental exposures have on the development of phenotypes associated with fertility in human populations. The vast majority of environmental exposures do not have the capacity to alter the DNA sequence such that classic genetics has difficulty providing a molecular mechanism for the early life exposure effects on later life male fertility [14]. Environmental epigenetics appears to be the molecular mechanism involved [14]. The current review will describe epigenetic mechanisms for the etiology of male infertility that can be dramatically influenced by the environment [15]. The roles of epigenetics versus genetics in environmentally induced male infertility will be reviewed, as well as the generational impacts of environmental epigenetics. Therefore, one of the primary questions addressed is the potential role of epigenetics versus genetics in the etiology of male infertility (Table 1).

Recent studies demonstrate that exposure to environmental factors such as toxicants, stress or dietary compounds early during development have a significant impact on human health [16••,17,18••]. In particular, the male reproductive system appears to be especially sensitive to environmental exposures [13]. It is becoming obvious that phenotypes associated with TDS are related to early developmental environmental exposures [2••,11•,13] and particularly to exposure to endocrine disrupting chemicals [13,19]. Early developmental exposures that are reported to be associated with impairment in reproductive function in men include pesticides [20,21], phthalates [22,23], analgesics [24], smoking [25,26] and alcohol [27]. In addition to these common exposures, industrial exposures of men to toxicants have also been reported. For example, in Taiwan accidental *in utero* exposures of men to the synthetic organic pollutants polychlorinated biphenyl (PCB) and PCDF were reported to produce a marked effect in semen quality and motility later in adulthood [28,29]. Other examples exist in which agro-workers were exposed to high amounts of the nematicide 1,2-Dibromo-3-chloropropane

Table 1

Categorization of the causes of impaired fertility

Causes	Description	Examples	Refs
Genetic	Genetic abnormalities that associate with impaired fertility parameters	Aneuploidies of the sex chromosome; Mutations (e.g. genes *Cftr*, *Fsh beta*, *Nr5a1*, *Art3*, *Ddr1*, *Usp8*, *Prmt6*, *Pex10*, *Sox5* *Slc6a14*, *Insr*, *Or3w3*); deletions (e.g. *Azfc* region, genes *Fkbp6*, *Ppp1cc2*)	[34,36–42,44•]
Epigenetic	Environmental exposures anytime during the life of the individual that are associated with epigenetic alterations and impaired fertility parameters	Adult exposures to butyl-paraben or methoxychlor; neonatal exposure to BPA; Prenatal exposure to ethanol	[72,73,76,77]
Epigenetic Transgenerational Inheritance	Impaired fertility parameters are triggered by germ line epimutations produced as result of ancestral environmental exposures	Early developmental exposure to environmental toxicants (e.g. vinclozolin, BPA, phthalates, DDT or methoxychlor) that produce alterations in sperm DNA methylation	[73,74••,78••,79, 90,92,93]
Life style practices/ occupational exposures	Chronic adult daily practices or exposures that are detrimental to reproductive parameters but potentially reversible	Constant scrotum overheating (e.g. hot baths); obesity; smoking; use of marihuana or cocaine; exposure to insecticides, pesticides or organic pollutants	[2••,11•]

(DBCP) and produced induced sterilization in California during the 1970s [30] and in Costa Rica from early 1960s to 1984 [31].

Fertility rates in both developing and industrialized countries have shown progressive reductions in recent years [32••]. Although this trend is certainly partially attributed to government policies together with social, economic and cultural changes, the impact environmental exposures have on impairments in the male reproductive system will be significant. The increasing association of environmental exposures with the incidence of disease [33] support the assumption that human fertility problems are strongly impacted by environmental exposures.

Recently, several studies have described genetic abnormalities associated with decreases in male reproductive parameters. A study found specific genetic abnormalities in 24% of men with oligozoospermia and azoospermia [34]. Genetic abnormalities related to infertility or subfertility include sex chromosomal aneuploidies, mutations in the cystic fibrosis transmembrane receptor (*Cftr*) gene or deletion of the AZFc region of the Y chromosome [34,35]. Several gene polymorphisms have also been described to date that associate with reduced male reproductive parameters. A polymorphism in the FSH beta subunit promoter region was shown to be associated with low FSH levels, sperm counts and testis volume [36]. In both mice and rats the deletion of *Fkbp6* (FK506 binding protein 6, 36 kDa), which is involved in meiotic pairing of homologous chromosomes, is implicated in sterility in male animals [37]. Recent conditional knock out experiments in mice have shown that adequate levels of PPP1CC2 (protein phosphatase 1, catalytic subunit, gamma isoform 2) are required for normal spermatogenesis and male fertility [38]. Mutations in *Nr5a1* (nuclear receptor subfamily 5, group A, member 1), which are associated with impaired transactivational activity of this steroidogenic gene have been observed in 4% of men with severe spermatogenic failure [39]. After initial genome-wide expression screening comparing testis specimens from azoospermic versus normal men, it was found that small nucleotide polymorphisms (SNPs) in the gene *Art3* (ADP-ribosyltransferase 3) were associated with both gene expression changes and testosterone levels in patients with azoospermia [40]. A recent genome-wide association study on humans concluded that SNPs associated with candidate genes that correlated with impaired male reproductive parameters [41]. These genes include *Ddr1* (dopamine receptor D1), *Usp8* (ubiquitin specific peptidase 8) and some genes associated with immune processes such as *Ubd* (ubiquitin D), *Epsti1* (epithelial stromal interaction 1) and *Lrrc32* (leucine rich repeat containing 32) [41].

Another recent GWAS study assessing loci correlations to non-obstructive azoospermia also found SNPs associated to some genes. These genes correspond to *Prmt6* (protein arginine methyltransferase 6), *Pex10* (peroxisomal biogenesis factor 10), *Sox5* (SRY sex determining region Y-box 5) and *Sirpa-Sirpg* (signal-regulatory protein alpha and gamma) [42]. The first genome-wide association study for idiopathic male fertility [43] and a follow up study from the same group have identified several SNPs with significant associations to azoospermia and oligozoospermia in men [44•]. The most significant associations identified correspond to SNP related to the genes *Slc6a14* (solute carrier family 6 (amino acid transporter), member 14), *Insr* (insulin receptor), *Or3w3* (odorant receptor 3), *Tas2r38* (taste receptor, type 2, member 38), *Tex15* (testis expressed 15), *Faslg* (Fas ligand), *Brdt* (bromodomain, testis-specific) and *Jmjd1a* (Protein JMJD) [44•]. Although these SNPs have been identified, the correlation with male fertility in the diseased population

of specific SNPs is generally less than 1% of the diseased population. Genetic mutations will be important, but observations suggest other mechanisms will be involved.

Infertility and epigenetics

The genetic background is essentially static in populations where increases in male disorders are occurring. Therefore, ancestral and/or early life exposures to environmental toxicants through environmental epigenetics [14] may be fundamental for the etiology of the disease [45]. In contrast to the low DNA sequence variation observed between humans, extensive natural sperm epigenome variation exists between healthy men [46]. Therefore, correlation of environmental exposures with epigenetic variation in germ cells is critical in order to address fertility issues in humans [47]. Several studies have documented epigenetic disruption related to the incidence of different types of germ cell tumors [48] or related to impaired fertility and spermatogenesis [49]. Indeed, sperm DNA of infertile men display abnormal histone marks (e.g. H3K4me and H3K27me) [50,51] and also abnormal DNA methylation at imprinted and developmental loci [50–55]. Genome-wide changes in histone marks during spermiogenesis would alter chromatin packaging of the sperm DNA and generate poor reproductive outcomes [50,56]. For DNA methylation the changes associated with infertility also appear to be widespread in the sperm genome, including alterations in imprinted and non-imprinted genes [57•]. Moreover, it is speculated that altered DNA methylation patterns in imprinted genes would generate imprinting abnormalities in the offspring when this sperm is used in Assisted Reproductive Technologies (ART) [52,53].

Epigenetic modifications in the germline of either humans or rodents that are associated with infertility include DNA methylation changes in the *Mthfr* (methylenetetrahydrofolate reductase) promoter region [58], hypomethylation in regions of the imprinted IGF2-H19 locus [53–55,59], hypermethylation in the imprinted genes *Mest* [51,54], *Lit1* (Protein LIT-1), *Snrpn* (small nuclear ribonucleoprotein N), *Peg3* (paternally expressed 3) and *Zac* (ADP-ribosylation factor GTPase-activating protein AGD12) [51], and altered methylation in several other imprinted and non-imprinted genes such as *Hras* (Harvey rat sarcoma viral oncogene homolog), *Nt3* (3′-nucleotidase), *Mt1a* (metallothionein 1A), *Pax8* (paired box 8), *Diras3* (DIRAS family, GTP-binding RAS-like 3), *Plagl1*(pleiomorphic adenoma gene-like 1), *Sfn* (stratifin) and *Sat2chrm1* (spermidine/spermine N1-acetyltransferase family member 2) [57•]. Histone modifications in the sperm DNA associated with infertility include increased H3K9 acetylation and H3K27 tri-methylation in exons of the *Brdt* gene (bromodomain, testis-specific) leading to reduction in its expression [60], reduced H4 acetylation in spermatids of infertile man with either qualitatively normal or abnormal spermatogenesis [61], loss of de-methylation activity on H3K9 that reduces expression of genes required for histone replacement in spermiogenesis TNP1 (transition protein 1) and PRM1 (protamine 1) [62], and aberrant acetylation of histones (e.g. H4K12ac) in promoters of developmentally important genes that leads to an insufficient sperm chromatin compaction that persist in the zygote [56].

In addition to the importance of epigenetic mechanisms in the germline, epigenetic marks in somatic cells supporting germ cells are also fundamental for fertility. For example, repeat elements such as B1 SINEs (small interspaced repeat element) have been proposed to have a role in transcriptional regulation of testis-specific genes [63]. Genes involved in the pathway of PIWI associated small RNAs (piRNAs), such as *Piwil2* (piwi-like RNA-mediated gene silencing 2) and *Tdrd1* (tudor domain containing 1), are hypermethylated in the testicular tissue of males with different forms of fertility problems [64]. In Sertoli cells *Rhox5* (reproductive homeobox 5) gene deletion associates with repression of DNA methylation in two promoters increasing germ-cell apoptosis and decreasing sperm count and motility [65]. Sertoli cell microRNAs have been shown to be involved in the spermiation failure induced by androgen and FSH (follicle stimulating hormone) suppression [66]. Ablation of *Dicer* (an RNase III endonuclease essential for microRNA processing) in Sertoli cells leads to infertility with a complete absence of spermatozoa and testis degeneration [67]. *Dicer* is also essential in the testis for the haploid differentiation of the germ cells [68].

The importance of the role of epigenetic mechanisms for infertility is related to the fact that many environmental insults can induce epigenetic alterations. Several examples of environmentally induced developmental effects associated with decreased fertility parameters exist. For example, *in utero* exposure to phthalates induces a variety of abnormalities in the reproductive tract of adult males which resemble the pathophysiological features of Testis Dysgenesis Syndrome [69]. Similar effects are reported with *in utero* exposures to vinclozolin [18••,70], bisphenol A (BPA) and diethylstilbestrol [71]. Although the majority of these examples do not include assessment of modifications in epigenetic mechanisms, the persistence throughout life of the effects induced during development suggests that epigenetic mechanisms are involved.

In addition to these developmentally induced effects, examples of epigenetic modifications that are environmentally induced and associate with male infertility exist. For instance, exposure of adult male rats to different doses of butyl-paraben [72] and exposure of adult male mice to methoxychlor [73,74••] have been shown to alter DNA methylation in sperm. Neonatal exposure to BPA is detrimental to spermatogenesis and has been shown to alter DNA methylation of the IGF2-H19 imprinting

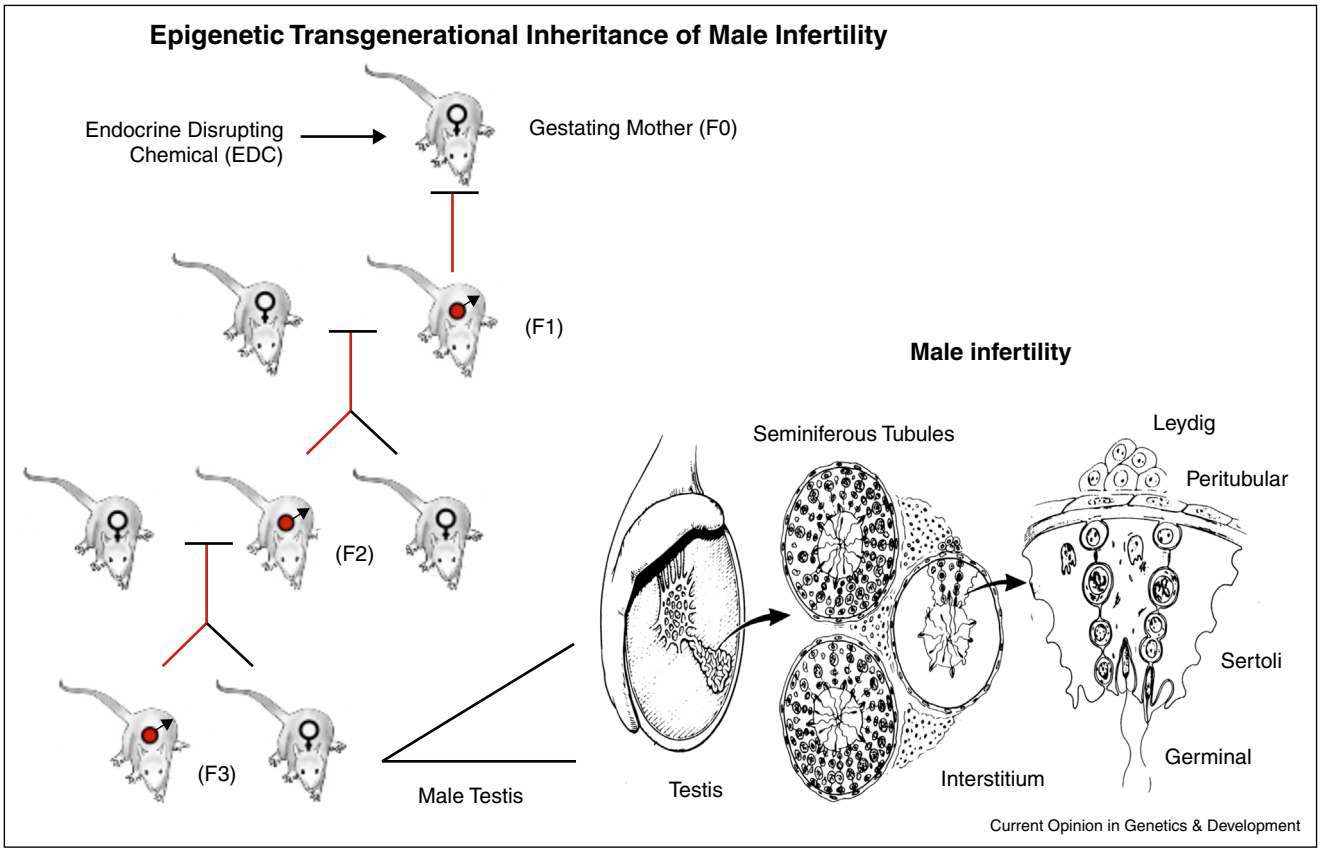
control region in sperm [75] and of the estrogen receptors alpha and beta in testis [76]. Prenatal exposure to ethanol has been shown to induce decreased spermatogenesis and sperm DNA methylation changes in imprinted genes [77]. Different laboratories have shown that an early developmental exposure to the fungicide vinclozolin increases spermatogenic cell apoptosis and alters sperm DNA methylation [74••,78••,79–81]. Interestingly, vinclozolin-induced effects are observed to be transgenerationally transmitted [74••,78••,79,81–83] through a process known as epigenetic transgenerational inheritance, which will be discussed next in more depth. The germ line consequences of environmental exposure might not only stay at the epigenetic level but is able to induce genomic rearrangements [84].

In spite of these interesting epigenetic effects observed in the germline, the majority of environmentally induced epigenetic changes related to infertility are described in somatic cells supporting spermatogenesis, such as Sertoli and Leydig cells (Figure 1). Changes in DNA methylation have been observed in mouse Leydig TM3 cell line cultures following exposure to either low or high doses of arsenic [3]. Exposure of these cells to cadmium leads to reduced expression of DNA methyltransferase 1 [85]. *In utero* exposure to di-(2-ethylhexyl)phthalate (DEHP) has been shown to produce postnatal alteration in demethylation in several nuclear receptor genes in Leydig cells, among them the estrogen receptor beta, thyroid receptor beta, peroxisome proliferator activated receptor alpha (*Ppar*-alpha) and the mineralocorticoid receptor [69]. Not only environmental insults but also natural hormones have the ability to induce epigenetic changes. For example, epigenetic changes are produced in the proximal promoter of the *Faah* gene (reduced DNA and histone H3 methylation) in response to estradiol in mouse Sertoli cell cultures [86] and treatment of Leydig cells with luteinizing hormone causes hypomethylation [87]. This hormonal regulation of DNA methylation suggests that epigenetic effects in testicular cells derived from environmental exposures are mediated by hormone actions [87].

Male fertility and epigenetic transgenerational inheritance

Environmentally induced epigenetic transgenerational inheritance is defined as early developmental exposures

Figure 1



Epigenetic transgenerational inheritance of male infertility. The environmental actions on an F0 generation gestating female reprograms the germline epigenome to promote a transgenerational event through the male germline in the absence of exposure for four (F4) generations. The testis morphology shown demonstrates the cooperation of somatic cells and spermatogenic cells in the process.

that promote altered epigenetic programming in the germline that then transmits altered epigenetic marks to subsequent generations in the absence of environmental exposures [14,18••]. These epigenetic germline alterations will subsequently affect gene expression and epigenetic programming patterns in somatic tissues [15,88]. This alteration in gene expression contributes to an altered phenotype that is observed generation after generation in a lineage [14,18••] (Figure 1). The first example of an environmentally induced epigenetic transgenerational inheritance process was described in 2005 using an early developmental exposure to the endocrine disruptor vinclozolin [74••]. Vinclozolin is an agricultural fungicide with anti-androgenic activity widely used in fruit and vegetable crops around the world [89]. A developmental exposure to vinclozolin produced increased apoptosis in spermatogenic cells in rats, which was observed four generations after this initial exposure [74••,82,83] (Figure 1). The mechanism involved in the transgenerational transmission of these altered phenotypes was an induced alteration in the sperm epigenome, which was observed three generations after the developmental exposure to vinclozolin [74••,78••,79]. Transgenerational DNA methylation alterations in imprinted genes in sperm have also been reported due to a developmental exposure to vinclozolin [81]. Early developmental exposure to di-(2-ethylhexyl)phthalate has also been shown to induce transgenerational effects related to impairment of male fertility, including disruption of testicular germ cell association, reduced sperm count and decreased sperm motility [90]. Other studies have focused on exposures after birth. Perinatal exposure to BPA impairs fertility and spermatogenesis [91] and induces transgenerational alterations in the expression of steroid receptors and their co-regulators in testis [92]. Exposure of 6-week old mice to oral administrations of benzo(a)pyrene induced impairment in several parameters associated with male fertility up to the F2 generation, including testicular malformations, reduced number of seminiferous tubes with elongated spermatids and decreased sperm count [93].

In addition to increased apoptosis in spermatogenic cells, other phenotypes are transmitted through the process of epigenetic transgenerational inheritance. These phenotypes include obesity [94–98], abnormalities of the female reproductive system [78••,88,97–103], kidney diseases [82,100,103], prostate diseases [82], pubertal abnormalities [97,101–103] and increased incidence of tumors [82].

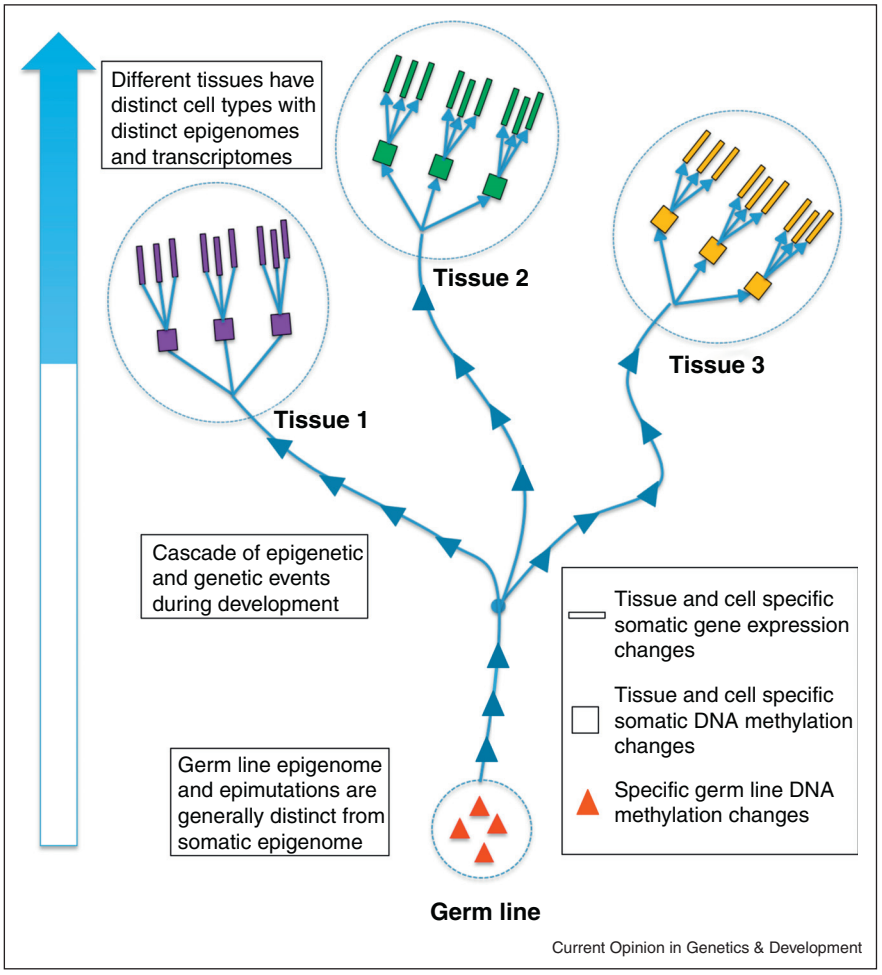
Environmentally induced epigenetic transgenerational inheritance of disease and sperm altered DNA methylation (epimutations) have been observed with plastic compounds (BPA and phthalates) [97], hydrocarbons (jet fuel JP8) [98], dioxin [99,103], pesticides (permethrin and DEET) [102], DDT [95], tributyltin [104], and nutrition abnormalities [94,96]. Epigenetic transgenerational inheritance has also been observed in plants [105], flies [106], worms [107], rodents [74••] and humans [108]. Therefore, the epigenetic transgenerational inheritance of disease and male testis abnormalities has been observed with a number of environmental exposures and species [18••,101].

Physiological and molecular mechanisms involved in epigenetic transgenerational inheritance

In order for a transgenerational effect to be produced it is fundamental that the germline epigenome is altered, because it is the germline epigenome that will be transmitted to future generations [18••]. The most sensitive period when the germline epigenome can be affected is a major event of epigenetic reprogramming that occurs during primordial germ cell development and initiation of the sex specific germline development. In this period a DNA methylation erasure occurs followed by the initiation of re-establishment of DNA methylation patterns [109,110••]. The erasure of DNA methylation occurs when primordial germ cells migrate to the genital ridge and gonads. Re-methylation is initiated during the first events of sex determination [111,112]. This period in germ cell development and epigenetic programming represents a window of sensitivity to environmental factors [18••,113]. Exposure to environmental compounds induces an altered epigenetic programming during these early developmental stages and the altered epigenome can be perpetuated across generations [18••,74••,79]. Experimental evidence of this window of sensitivity involving the sex determination period exists for vinclozolin and a number of other exposures. For example, the pattern of gene expression is altered in the rat embryonic testis after a maternal exposure to vinclozolin while the embryo is undergoing sex determination [114,115]. Interestingly, embryonic testis gene expression is consistently altered in the next generations [116]. Further analysis of vinclozolin-induced transgenerational transcriptome and epigenomic alterations in primordial germ cells in rats (E13 and E16) have been performed [117]. Although the vinclozolin-induced epigenetic and gene expression alterations in primordial germ cells are distinct between these two stages, the cellular processes affected seem to be the same and the effects are more pronounced in E13 (period of maximum erasure of DNA methylation) than in E16 [117].

Environmentally induced reprogramming of the germline epigenome will induce epigenomic changes in somatic cells [18••], as seen in granulosa cells [88] and Sertoli cells [15] using the transgenerational vinclozolin model. Sertoli cells in F3 generation vinclozolin lineage males were found to have a transgenerational epigenome and transcriptome that correlated with the spermatogenic cell apoptosis phenotype observed [15]. Analysis of the transgenerational transcriptome revealed a large number of differentially regulated and reduced gene expression was

Figure 2



Schematic representation of environmentally induced germline epigenome modifications and further epigenomic and transcriptomic effects in somatic cells that are distinct between tissues and cell types.

in the pyruvate synthesis and degradation pathway [15]. Since pyruvate is an essential energy metabolite provided by Sertoli cells and required for spermatogenic cells, the transgenerational testis phenotype appears to be in part due to abnormal Sertoli cell function [15] (Figure 1).

A general misconception exists that the epigenome changes observed in the germline should be the same as the ones observed in somatic cells. Although the environmentally induced epigenetic changes will influence the developing epigenomes seen in somatic cells, *they are not* necessarily the same due to the dramatic epigenetic programming required for somatic cell differentiation [14]. In the same line, the derived epigenomic somatic changes will influence gene expression changes in that tissue but not necessarily in the same genes (Figure 2). What has been observed using the vinclozolin model is that transgenerational environmentally induced epigenome changes in somatic tissues will affect the gene expression of many genes in a tissue and cell specific manner [15,88]. This phenomenon can be due to long distance regulation of clusters of gene expression through epigenetic control regions [101,118].

Conclusion

Epigenetic transgenerational inheritance is a phenomenon to be considered in disease etiology, reproduction and human fertility. Clearly, considering only genetic mutations cannot completely explain disease etiology. Environmental exposures and related epigenetic changes are equally important for consideration. Interestingly, these environmental exposures can influence the future generations' susceptibility for disease, particularly disease related to reproduction. Future studies will need to focus on identifying these epigenetic alterations and epigenetic biomarkers to understand the epigenetic mechanisms that mediate environmental exposures and impairment of fertility. These investigations will provide important

information to develop novel diagnostics and therapeutics for the treatment of male infertility.

In considering the relative roles of epigenetics and genetics in the etiology of male infertility, as well as nearly all disease, environmental epigenetics is a critical factor to consider. However, epigenetics does not act in isolation and depends on the genetic background. The epigenetics works through altering genome activity. Therefore genetics and epigenetics are integrated to a point that few epigenetic only events and genetic only events will exist. These two integrated processes directly influence the etiology of disease. What epigenetics provides is a conduit for the environment to alter directly genome activity and provides a mechanism for early life or ancestral exposures to impact adult onset disease such as male infertility.

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