Effets transgénérationnels des expositions reprotoxiques chez l'animal et l'Homme.

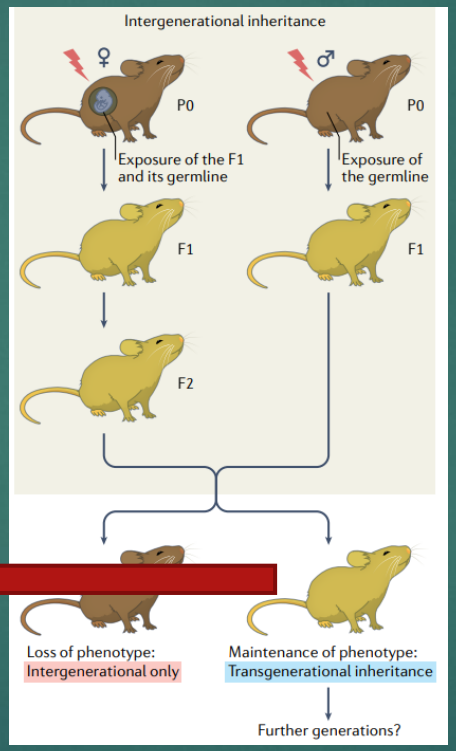
Pr. Roger Léandri

CHU de Toulouse

Effets transgénérationnels d'une exposition:

1°) si un phénotype ou un trait pathologique (ici reproductif) se transmet sur plusieurs générations **après que l'exposition ait cessé+++**

si transmission à la 3ème génération pour les expositions durant grossesse



Si transmission à la 2ème génération pour les expositions paternelles ou maternelles non gestantes

Fitz-James & Cavalli. *Nature Reviews Genetics* , 2022

Effets transgénérationnels d'une exposition:

2°) cette transmission passe obligatoirement par les gamètes donc par la méiose

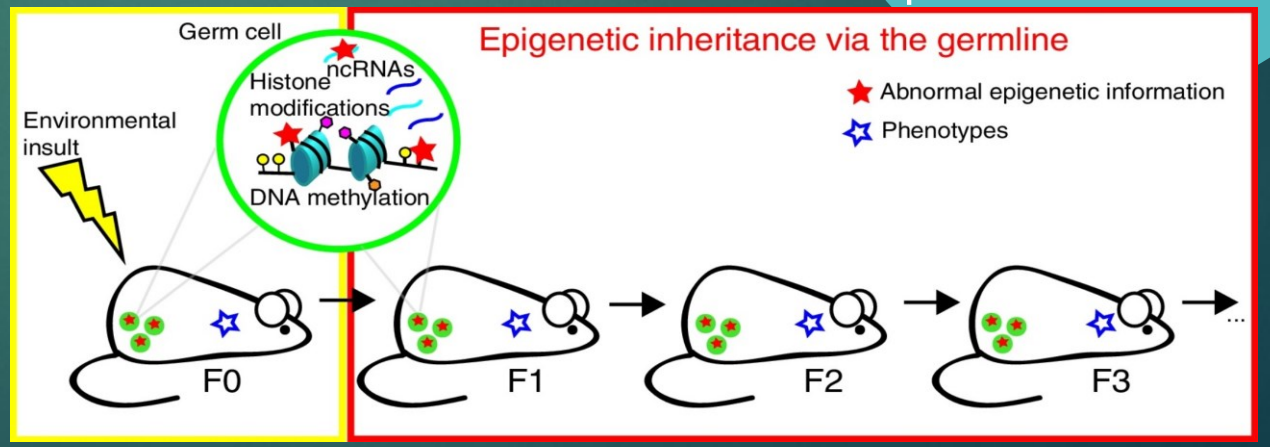
➔ on parle d'**hérédité transgénérationnelle épigénétique (TEI)**

3°) Liée à des **mécanismes épigénétiques**:

i.e une information héritée (par mitose ou méïose) qui influe sur l'expression d'un gène sans modification de la séquence

- Méthylation de l'ADN
- Modifications des histones
- Petits ARN non codants

➔ **Épimutation germinale**



Blake & Watson, *Curr Op Clin Biol*, 2016

Effets transgénérationnels d'une exposition:

La méthylation de l'ADN est reprogrammée 2 fois chez un individu:

1. Juste après la conception dans l'embryon préimplantatoire
2. Puis dans la lignée germinale de cet embryon-foetus

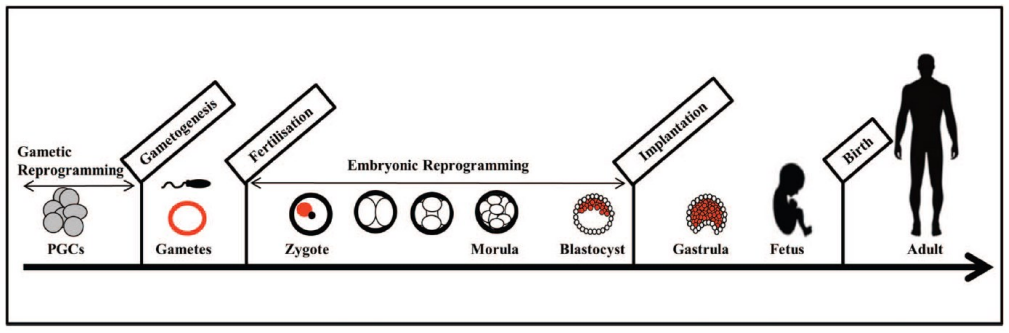
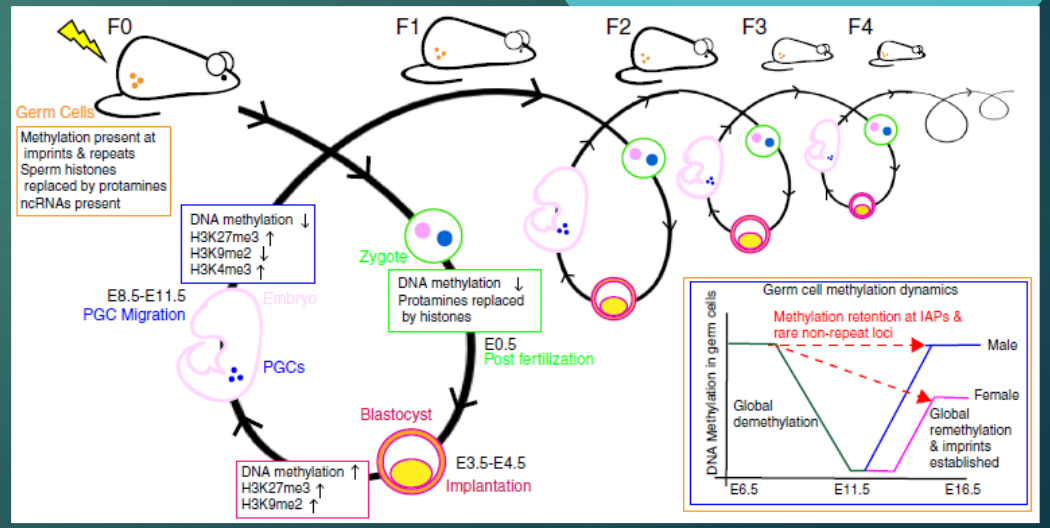


Figure 1 Epigenetic reprogramming cycles. During mammalian life, cells are submitted to two major genome-wide epigenetic reprogramming events. The Gametic Reprograming event takes place in PGCs of embryos during germline cell development, as PGCs migrate to the genital ridge. PGCs experience genome-wide DNA demethylation, removal and resetting of parental imprints, histone modifications and inactive-X-chromosome reactivation. The Embryonic Reprogramming event starts immediately after fertilization and lasts until the blastocyst stage of embryo development, when cells experience DNA demethylation, the removal and resetting of parental imprints and histone modifications.

Xavier et al., *Hum Reprod Upd*, 2019

➔ Une épimutation germinale liée à une exposition maternelle entrainant un effet transgénérationnel suppose une résistance à cette reprogrammation chez F1 et chez F2 (soit 4 reprogrammations)



Blake & Watson, *Curr Op Clin Biol*, 2016

Données chez l'animal

1ère démonstration:

Exposition à la vinclozoline (pesticide à action anti-androgénique) chez la ratte gestante

➔ Atteinte testiculaire **jusqu'à F4**

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

Matthew D. Anway, Andrea S. Cupp,* Mehmet Uzumcu,† Michael K. Skinner‡

Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F_1 generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F_1 to F_4). The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.

Anway et al., *Science*, 2005

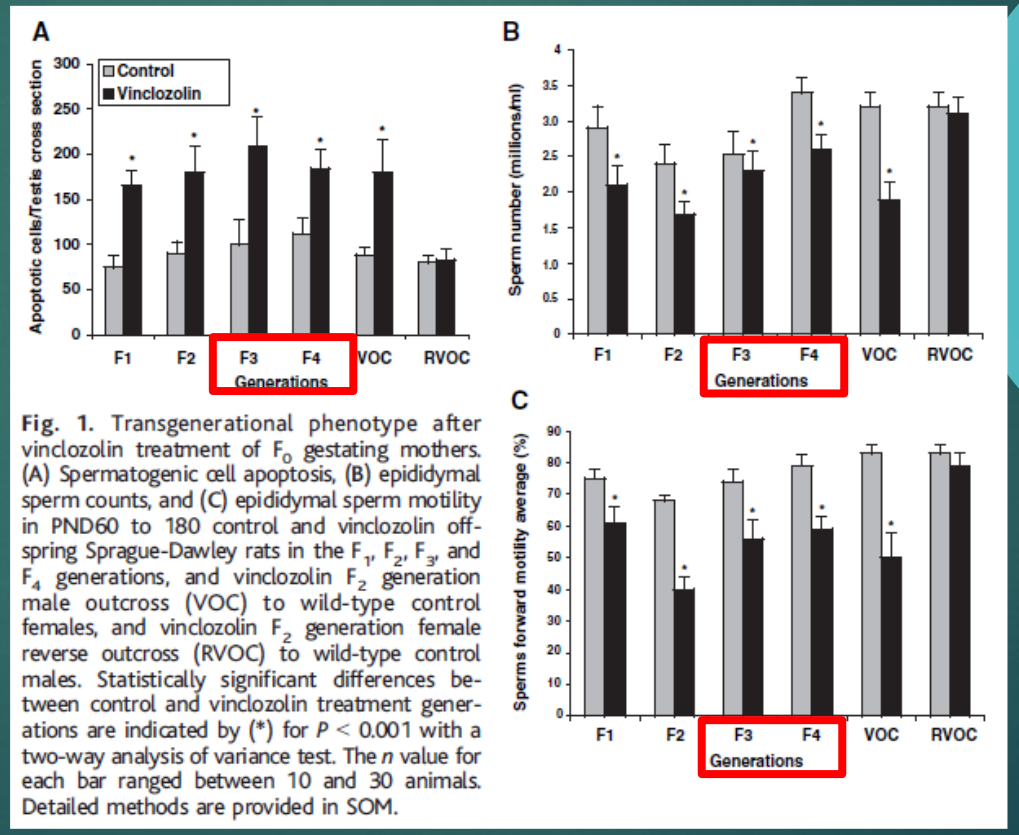


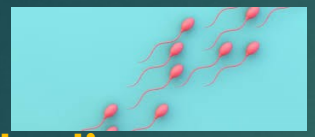
Fig. 1. Transgenerational phenotype after vinclozolin treatment of F_0 gestating mothers. (A) Spermatogenic cell apoptosis, (B) epididymal sperm counts, and (C) epididymal sperm motility in PND60 to 180 control and vinclozolin offspring Sprague-Dawley rats in the F_1, F_2, F_3, and F_4 generations, and vinclozolin F_2 generation male outcross (VOC) to wild-type control females, and vinclozolin F_2 generation female reverse outcross (RVOC) to wild-type control males. Statistically significant differences between control and vinclozolin treatment generations are indicated by (*) for $P < 0.001$ with a two-way analysis of variance test. The *n* value for each bar ranged between 10 and 30 animals. Detailed methods are provided in SOM.

Mécanismes:

DNA méthylation spermatique altérée (Guerrero-Bosagna et al. *Plos one*, 2010)

Small ncRNA spermatiques altérés (Schuster et al., *Environ Epigenet*, 2016)

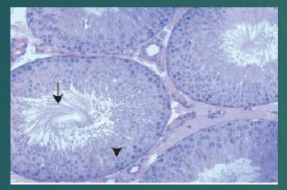
Effets reproductifs chez mâles F3 par TEI après exposition de femelles gestantes F0:



↘ Production spermatique
↘ Mobilité spermatique

Vinclozoline (Anway et al., *Science*, 2005)
DDT (Skinner et al., BMC Med, 2013)
BPA + Phtalates (Manikkam et al., Plos One, 2013)

Phtalates (Doyle et al, Biol Reprod, 2013)



↗ Apoptose testiculaire / anomalies histo des tubules seminifères

Vinclozoline (Anway et al., *Science*, 2005)
DDT (Skinner et al., BMC Med, 2013)
Perméthrine + DEET (Manikkam et al., Reprod Tox, 2012)
BPA + Phtalates (Manikkam et al., Plos One, 2013)

Dioxine (Bruner-Tran et al., Plos one, 2014)
Benzo(a)pyrène (Mohamed et al., Hum Reprod 2010)
Phtalates (Doyle et al, Biol Reprod, 2013)

Effets reproductifs chez mâles F3 par TEI après exposition de femelles gestantes F0:

Puberté retardée :

Phtalates (Doyle et al, Biol Reprod, 2013)

BPA + Phtalates (Manikkam et al., Plos One, 2013)
Perméthrine + DEET (Manikkam et al., Reprod Tox, 2012)
Dioxine (Manikkam et al., Plos One, 2012)

Effets reproductifs chez mâles F3 par TEI après exposition de femelles gestantes F0:

Travaux du groupe de Mickaël Skinner

Analyse de l'épigénome spermatique F3

➔ Régions différentiellement Méthylées / non exposés

1°) Ces DMR sont spécifiques des expositions

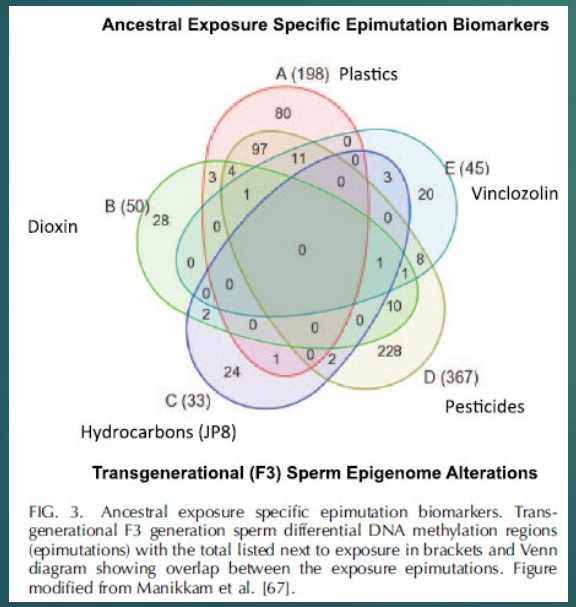
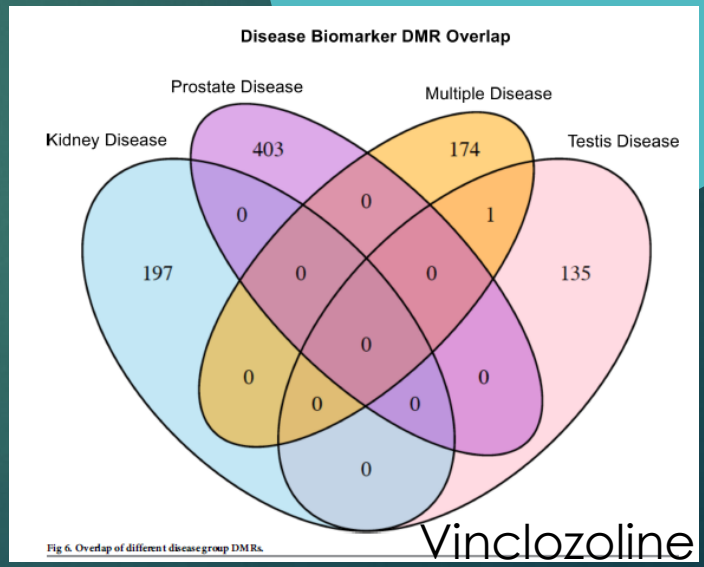


FIG. 3. Ancestral exposure specific epimutation biomarkers. Transgenerational F3 generation sperm differential DNA methylation regions (epimutations) with the total listed next to exposure in brackets and Venn diagram showing overlap between the exposure epimutations. Figure modified from Manikkam et al. [67].

Nilsson & Skinner, Biol. Reprod, 2015

DMR spermatiques: biomarqueurs d'une exposition ancestrale ?

2°) Pour 1 exposition: ces DMR sont spécifiques de l'effet induit

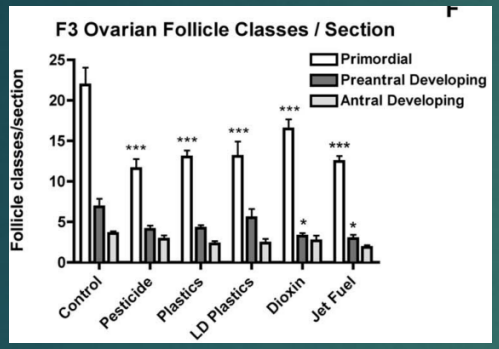


Vinclozoline

Nilsson et al., Plos One, 2018

Effets reproductifs chez femelles F3 par TEI après exposition de femelles gestantes F0:

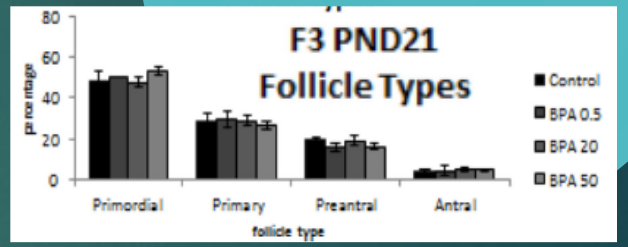
↘ Pool folliculaire ovarien



Manikkam et al., Plos One, 2012

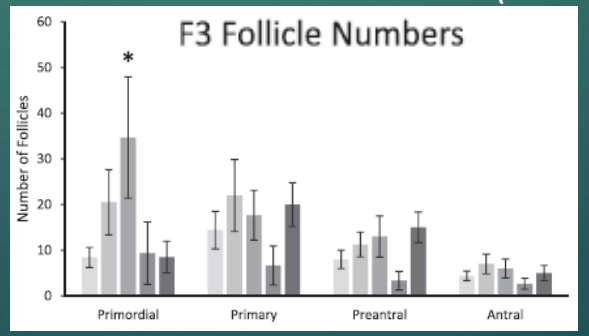
Vinclozoline (Nilsson et al., Plos One, 2012)
Perméthrine + DEET (Manikkam et al., Reprod Tox, 2012)
Dioxine (Manikkam et al., Plos One, 2012)
BPA + Phtalates (Manikkam et al., Plos One, 2013)

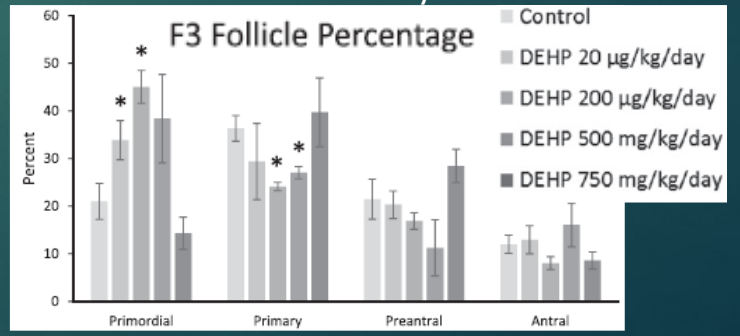
DEHP (Pocar et al., Toxicol. Appl. Pharm, 2017)
Pas d'effet du BPA (Berger et al., Reprod. Toxicol. 2016)



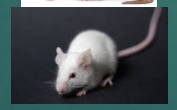
↗ Pool folliculaire ovarien (frein à l'initiation folliculogenèse

DEHP (Brehm et al., Endoc. 2018)





Effets reproductifs chez femelles F3 par TEI après exposition de femelles gestantes F0:

↗ kystes ovariens		Vinclozoline	(Nilsson et al., Plos One, 2012 Nilsson et al., Epigenetics, 2018 Guerrero-Bosagna et al., Reprod Tox. 2012)
		Perméthrine + DEET	(Manikkam et al., Reprod Tox, 2012)
		DDT	(Skinner et al., BMC Med , 2013 Nilsson et al., Epigenetics, 2018)
		Métoxychlore	(Manikkam et al., Plos One, 2014)
		Dioxine	(Manikkam et al., Plos One, 2012)
		BPA + Phtalates	(Manikkam et al., Plos One, 2013)
Troubles Pubertaires avancée		BPA + Phtalates	(Manikkam et al., Plos One, 2013)
		DEHP	(Rattan et al., Toxicol. Sci. 2018)
retardée		BPA	(Ziv-Gal et al., Toxicol. Appl. Pharmacol. 2015)

Effets reproductifs chez femelles F3 par TEI après exposition de femelles gestantes F0:

Troubles du cycle +  DEHP (Brehm et al., Endoc. 2018 Rattan et al., Toxicol. Sci. 2018)

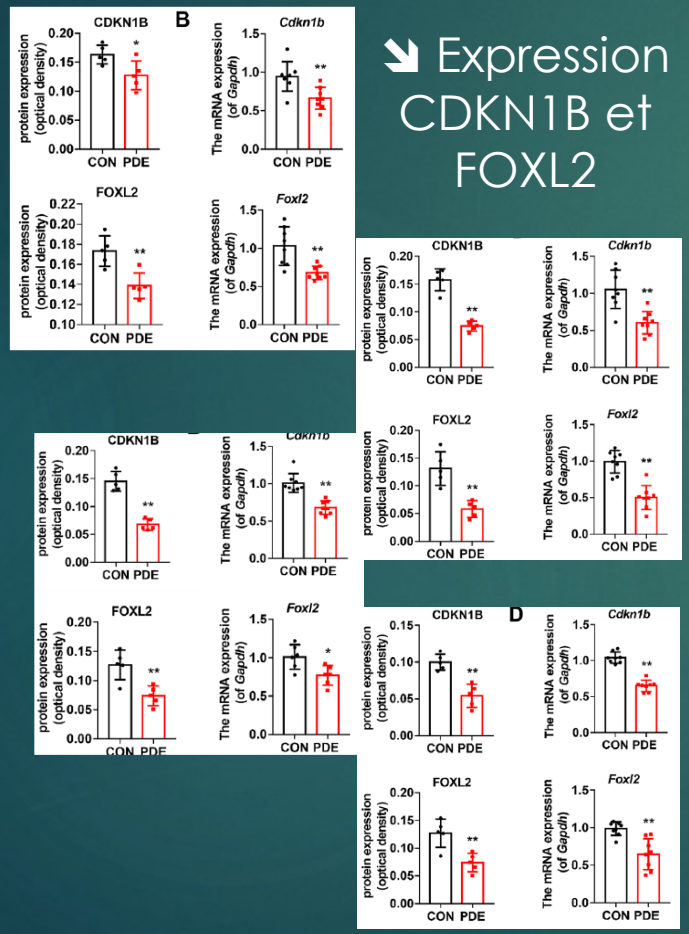
\- Mix Phtalates (Zou et al., Endoc, 2017)

Adénomyose  Dioxine (Bruner-Tran et al., Biol. Reprod., 2016)

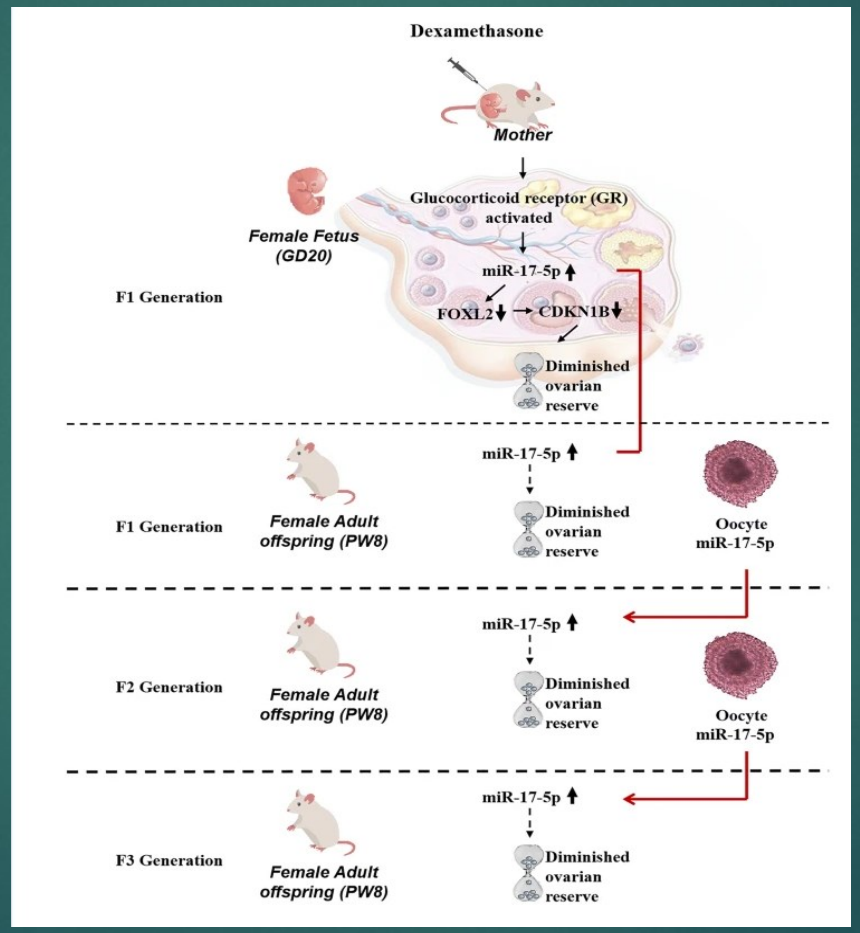
↘ fertilité  Mix Phtalates Dioxine (Zou et al., Endoc, 2017) (Bruner-Tran et al., Reprod. Tox. 2011)

Aucune étude moléculaire des ovocytes F3 à la recherche d'épimutation

Rare exemple de mécanisme déchiffré chez la femelle: Diminution transgénérationnelle de la réserve après exposition de femelles gestantes à la dexaméthasone



↘ Expression CDKN1B et FOXL2



Gong et al., Cell Biol Toxicol, 2023

Dexaméthasone induit ↗ expression miRNA 17-5p ovocytaire chez F1 et F2 , qui cible FOXL2

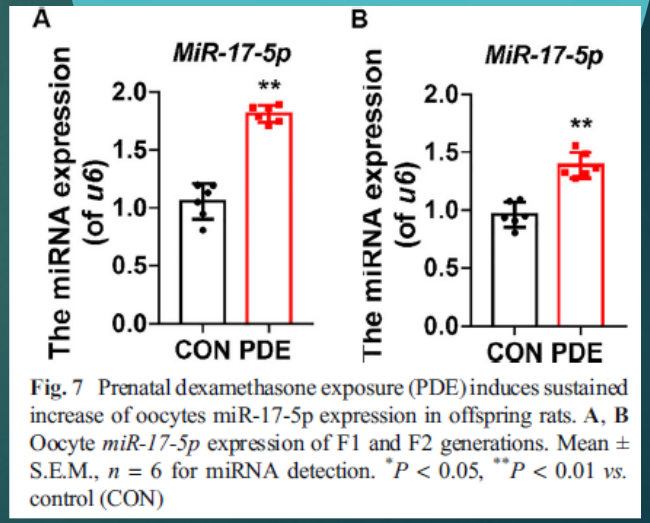
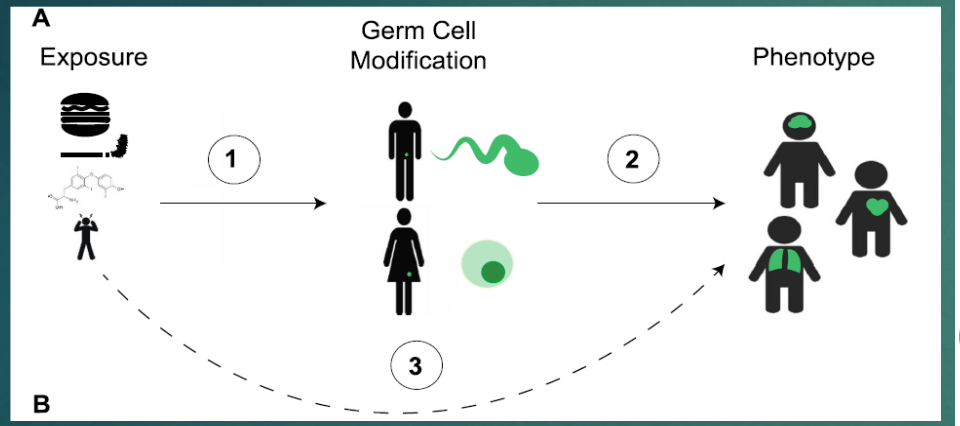


Fig. 7 Prenatal dexamethasone exposure (PDE) induces sustained increase of oocytes miR-17-5p expression in offspring rats. **A**, **B** Oocyte *miR-17-5p* expression of F1 and F2 generations. Mean ± S.E.M., $n = 6$ for miRNA detection. $^{*}P < 0.05$, $^{**}P < 0.01$ *vs.* control (CON)

Données chez l'Homme

Chez l'Homme

1°) Pas de preuves formelles d'effets de santé médié par TEI (via épimutations germinales)



Mais on trouve des associations entre 2 de ces 3 critères…

	EXPOSURE	GERM CELL MODIFICATION	PHENOTYPE/DISEASE	REFERENCE
1	Chemotherapy	DNA methylation of sperm		16#
	Exercise	DNA methylation and small RNA expression (piRNAs) of sperm		38#
	Bariatric surgery	DNA methylation of sperm		40#
	Childhood abuse	DNA methylation of sperm		52#
	Childhood stress	MicroRNA expression in sperm		53#
	Cigarette smoking	MicroRNA expression in sperm		60#
	Cannabis	DNA methylation of sperm		61**,$
	Agent Orange	DNA methylation of sperm		74#
	Flame retardants	DNA methylation of sperm		75#
	Mercury	DNA methylation of sperm		76#
	Polycyclic aromatic hydrocarbons	DNA methylation of sperm		77*,#
	Bisphenol A	DNA methylation of sperm		78*,**
2		DNA methylation in sperm	Autism in children	80#
3	Thyroid hormone in utero		Reduced Sensitivity to Thyroid Hormone in unexposed children and grandchildren	24**
	Food availability in pre-adolescence		Mortality in grandchildren	26-30**,$
	Famine in utero		Type II diabetes in children	31**,$
	Chewing betel nut		Metabolic syndrome in children	37**
	Holocaust		FKBP5 methylation in children; cortisol metabolism in children	43*#$, 44$
	World Trade Center collapse		Salivary cortisol in children	46$
	Cigarette smoking		Asthma in children and grandchildren; autism in grandchildren	54-58**,$
	Diethylstilbestrol		Genitourinary abnormalities in children	64-69**,$
	Agent Orange		Spina bifida in children	73**

Aucune étude sur ovocytes

Senaldi and Smith-Raska, Clinical Epigenetics (2020)

Chez l'Homme

2°) L'absence d'exposition sur plusieurs générations après l'exposition ancestrale n'est pas facile à affirmer (ex: effets socio-culturels)

- ➔ Facilite les études d'expositions médicamenteuses stoppées (DES), les accidents industriels (Dioxine, Sévéso), les crises sanitaires (famine hollandaise)
- ➔ Beaucoup plus difficile pour des polluants ubiquitaires et permanents

3°) La démonstration de la transmission d'une épimutation germinale entre les générations est très difficile !!! (disponibilité des échantillons sur plusieurs générations)

4°) De nombreux phénotypes/pathologies sont multifactoriels (obésité, CV…, RO, qualité du sperme) ➔ difficile à maitriser sur plusieurs générations

5°) Les arguments pour évoquer un effet médié par TEI concernent surtout des effets <u>autres que reproductifs</u>
Ex: Famine hollandaise ➔ obésité, hyperchol. chez descendants F1; ↗ IMC chez F2

➔ Effets TEI vrais ou simples effets de l'environnement in utero sur 2 générations ?

<u>Exposition in utero au DES:</u>
les individus de la 3ème génération …sont de la 2ème !

Publicité pour le desPlex®
(nom commercial du diéthylstilbestrol aux Etat-Unis)

➔ Aucune donnée humaine sur la génération F3 …
➔ Pas d'analyse d'épimutations ovocytaires

Car les femmes enceintes qui ont reçu le DES sont dites de la 1ère génération …et non pas F0 !

Menstrual outcomes in third generation women according to their mother's prenatal DES exposure status..

	Baseline			Follow-up		
	Mother's prenatal DES exposure status			Mother's prenatal DES exposure status		
Outcome	**Exposed (n = 796) No. (%)**	**Unexposed (n = 469) No. (%)**	**PR[a] (95% CI)**	**Exposed (n = 381) No. (%)**	**Unexposed (n = 280) No. (%)**	**PR[a] (95% CI)**
Menstrual cycles usually regular						
Yes	623 (78.9)	385 (83.0)		287 (75.3)	226 (80.7)	
No	167 (21.1)	79 (17.0)	1.22 (1.12,1.33)	94 (24.7)	54 (19.3)	1.32 (1.10, 1.60)
Amenorrhea in last 12 months						
No	661 (83.8)	405 (86.9)		314 (82.4)	238 (85.0)	
Yes	128 (16.2)	61 (13.1)	1.22 (0.85,1.75)	67 (17.6)	42 (15.0)	1.26 (1.06, 1.49)

Abbreviations: DES, diethylstilbestrol; PR, prevalence ratios; CI, confidence intervals.

[a]For outcomes prevalent at baseline and at follow-up, adjusted for age and cohort.

Titus et al., *Reprod Tox*, 2019

EN CONCLUSION

Chez l'animal, des effets reprotoxiques mâles et femelles, médiés par TEI, sont retrouvés après exposition maternelles in utero
Les effets femelles sont rarement étayés par la démonstration d'épimutation ovocytaire

Chez l'Homme, des phénotypes mâles et femelles altérés sur 2 générations existent après exposition maternelle ou paternelle.
La démonstration stricte de leur médiation par TEI n'est pas faite mais suspectée.

Des troubles reproductifs sur 2 générations post exposition sont très rarement rapportés.

Revues sur la question

BIOLOGY OF REPRODUCTION (2015) 93(6):145, 1–8
Published online before print 28 October 2015.
DOI 10.1095/biolreprod.115.134817

Minireview

Environmentally Induced Epigenetic Transge Disease[1]

Eric E. Nilsson and Michael K. Skinner[2]

Center for Reproductive Biology, School of Biological Scienc

ABSTRACT

Reproductive disease and fertility issues have dramatically increased in the human population over the last several decades, suggesting environmental impacts. Epigenetics provides a mechanistic link by which an organism can respond to environmental factors. Interestingly, environmentally induced epigenetic alterations in the germ line can promote aberrant gene expression and disease generationally. Environmental induced epigenetic transgenerational inheritance is defined as germ-line transmission of altered epigenetic information between generations in the absence of continued environmental exposures. This form of nongenetic inheritance has been shown to directly influence fertility and reproductive disease. This review describes the studies in a variety of species that indicate reproductive disease and abnormalities. Observations suggest serious attention be paid to the possibility that ancestral exposures to environmental insults promotes transgenerational inheritance of reproductive disease susceptibility. Environmentally induced epigenetic transgenerational inheritance appears to be an important contributing factor to reproductive disease in many organisms, including humans.

developmental biology, environment, epigenetics, genon

INTRODUCTION

Fertility issues have been increasing in human populations for decades. In men, there have been decreases in sperm [1–4], increases in testicular cancer [5], and increased abnormalities [6]. Fecundity rates in men and women in developing and industrial countries have dramatically increased in recent years [7, 8]. Although economic trends, and governmental policies certainly contribute, decreased birthrate, attention must be paid to environmental toxicants and other exposures in relation to reproductive disease [9–11]. Correlations have been found between environmental exposures and prostate disease [12, 13], semen quality [1, 14–16]

[1]Supported by an NIEHS grant to M.K.S.
[2]Correspondence: Michael K. Skinner, Center for Biology, School of Biological Sciences, Washington State University, Pullman, WA 99164-4236. E-mail: skinner@wsu.edu

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cells

Review

Multi- and Transgenera Toxicants on Mammalia

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Abstract: Environmental t
ment that contaminate food
into the organisms. In mam
their reproductive health thro
processes. In humans, direct e
across generations has been rec
ET reprotoxicity have only been
on laboratory model animals inv
persistent contaminants, on the n
multigenerational effects, where
tional effects in unexposed animals
methylation, histone tails and nonc
transmission of environmental infor

Keywords: environmental toxicant
multigenerational effect; transgenerat
epigenetic inheritance

1. Introduction

Since the beginning of the industr
been synthetized and used for many in
exponential employment and consequer
into the environment. They are highly an
water, air and soil [1] and, through the
at the beginning of the 1990s, the detrime
emerged worldwide, and their impact o
during the Wingspread Conference in 199
Exposure to environmental toxicants
production, maturation and quality of gam
and females and the delivery and pregnan
reproductive senescence (aging) [2].
During the past 30 years, declining huma
priority. Infertility affects nearly one in six co
the reproductive age), with a progressive incr

Cells **2022**, *11*, 3163. https://doi.org/10.3390/cells11193163 1

International Journal of Molecular Sciences

Review

Impact of Endocrine Disruptors upon N

Debbie Montjean [1,*], Anne-Sophie Neyroud [2], Marina G. Yefimova [3] Rosalie Cabry [4,5,6] and Célia Ravel [2,7,*]

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Abstract: Similar to environ
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Transgenerational Effects o Chemicals on Male and Fem

Emily Brehm[1] and Jodi A. Flaws[1]

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Endocrine-disrupting chemicals are known to inte
hormone signaling. Phthalates, bisphenol A, pestici
polychlorinated biphenyls and dioxins are known e
shown to negatively affect both male and female rep
on a daily basis owing to these compounds being f
pesticides. Recently, studies have shown that these c
on reproduction in both males and females. This is of
prenatally or during adult life can negatively impact t
This mini-review summarizes the endocrine-disrupting
daily basis and what is known about the transgeneratio
male and female reproduction. (*Endocrinology* **160**:

The Endocrine Society defines an endocrine-disrupting chemical (EDC) as "an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action" (1). EDCs are known to display non-monotonic dose-response curves because hormones interact with and activate their receptors in a nonlinear fashion and this leads to a U-shaped or inverted U-shaped curve (2–4). EDCs are found in many different products, including plasticizers, personal care products, and pesticides. Furthermore, EDCs such as polychlorinated biphenyls (PCBs) and dioxins are found in environmental contaminants. Humans are constantly exposed to EDCs on a daily basis by ingestion, inhalation, and dermal contact, and with this constant exposure has come detrimental effects on reproductive health. Specifically, EDCs are known to decrease fertility in both male and female animal models and they are associated with subfertility/infertility in humans (2, 5). These chemicals can affect the production of steroids (steroidogenesis), ovarian follicle development and growth (folliculogenesis), and development and maturation of sperm (spermatogenesis), leading to complications with reproduction (6–10).

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(14–16). In contrast
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Abbreviations: BPA, bisphenol A; dibutyl phthalate; DDE, dichloro chenmethane; DEHP, di(2-ethylhe phthalate; DINP, diisononyl ph methoxychlor; PCB, polychlorinat rachlorobenzo-p-dioxin.

Endocrinology, June 2019, 160(6):1421–1435 https://academic.oup.com/endo 1421

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https://doi.org/10.1186/s13148-020-00929-y

Clinical Epigenetics

REVIEW

Open Access

Evidence for germline non-genetic inheritance of human phenotypes and diseases

Liana Senaldi[1] and Matthew Smith-Raska[1,2*]

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Abstract

It is becoming increasingly apparent that certain phenotypes are inherited across generations independent of the information contained in the DNA sequence, by factors in germ cells that remain largely uncharacterized. As evidence for germline non-genetic inheritance of phenotypes and diseases continues to grow in model organisms, there are fewer reports of this phenomenon in humans, due to a variety of complications in evaluating this mechanism of inheritance in humans. This review summarizes the evidence for germline-based non-genetic inheritance in humans, as well as the significant challenges and important caveats that must be considered when evaluating this process in human populations. Most reports of this process evaluate the association of a lifetime exposure in ancestors with changes in DNA methylation or small RNA expression in germ cells, as well as the association between ancestral experiences and the inheritance of a phenotype in descendants, down to great-grandchildren in some cases. Collectively, these studies provide evidence that phenotypes can be inherited in a DNA-independent manner; the extent to which this process contributes to disease development, as well as the cellular and molecular regulation of this process, remain largely undefined.

Keywords: Human epigenetic inheritance, Human disease inheritance, Transgenerational epigenetic inheritance, Sperm DNA methylation, Sperm small RNAs, Thyroid hormone epigenetics, Reduced sensitivity to thyroid hormone, Överkalix study, Parent-of-origin

Introduction

The traditional Mendelian model of inheritance states that phenotypes are inherited based on the transmission of DNA sequences across generations, and diseases are inherited when these DNA sequences are abnormal. In model organisms, it is becoming increasingly apparent that phenotypes and disease risk can be inherited from sperm and oocytes in the absence of DNA mutations or variations. This non-genetic inheritance is based on the concept that non-DNA molecules in sperm and oocytes are inherited at fertilization and modify the phenotype of the offspring, sometimes across multiple generations. The central concept in this field is that an organism's exposures (diet, stress, chemicals, etc.) affect the composition of germline non-DNA molecules, and in this manner, these exposures can affect phenotypes in descendants. Localization of this phenomenon to the germ cells is proven by the use of in vitro fertilization with surrogate "mothers" carrying the fetus who never experienced the exposure [1]. While there are multiple examples of this phenomenon across a variety of model organisms [1–4], the role of this process in human inheritance is less well described, and the cellular and molecular mechanisms that drive the non-genetic inheritance of phenotypes across generations are similarly poorly characterized.

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Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations

Mohan Manikkam [1], Rebecca Tracey, Carlos Guerrero-Bosagna, Michael K Skinner

BPA 50 mg/kg BW/day
DEHP 750 mg/kg BW/day
DBP 66 mg/kg/BW/day)