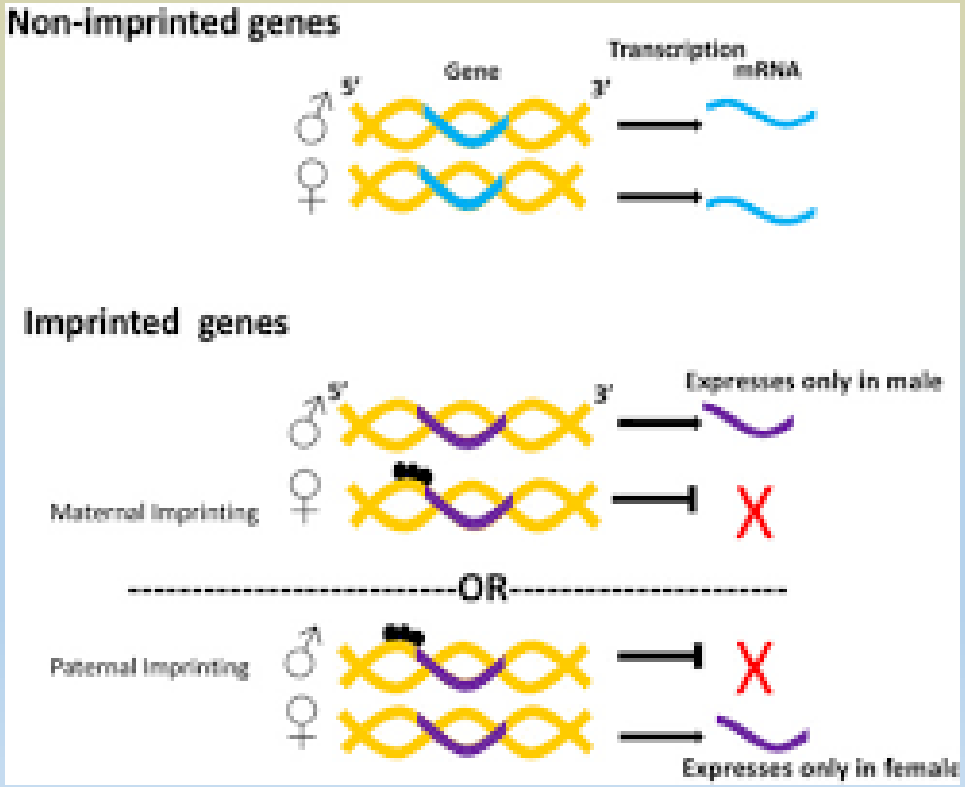
Gene (Genomic) Imprinting (GI)



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February 2024

Definition

- Two alleles are inherited from mother and father in higher eukaryotes including humans. Both alleles are usually functional for the majority of the genes. However, one of them is sometimes switched off or “stamped”. So, this allele, or a separate gene is defined as imprinted in offspring. Imprinting is the gene silencing in the offspring though the same gene obtained from the other parent remains expressed.

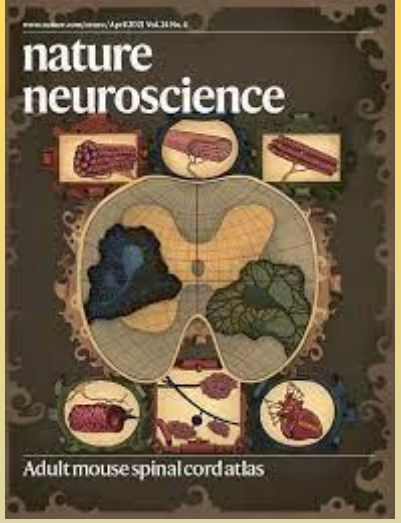
Key words

genomic imprinting (GI), epigenetic inheritance, gene, DNA methylation

Background

- GI is the inheritance lying beyond the Mendelian borders. A range of inherited diseases and human development features violate the Mendelian law of inheritance, and therefore, this way of inheriting is studied by **epigenetics**.

Overview on GI as a whole

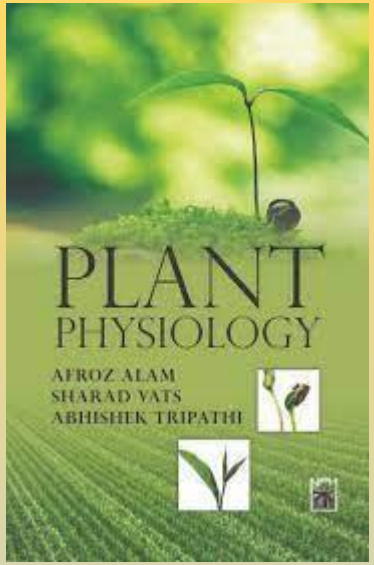


- Epigenetics shows that gene expression can change in more complex way than modifications of the DNA sequence. Epigenetics considers the environmental impact on the gametes prior to fertilization.
- The GI mechanisms are not still completely clear. GI involves epigenetic modifications (EMs) which are erased and then reset during the egg and sperm formation. GI is a process of the gene silencing reached through DNA methylation.

Overview on GI as a whole (cond.)

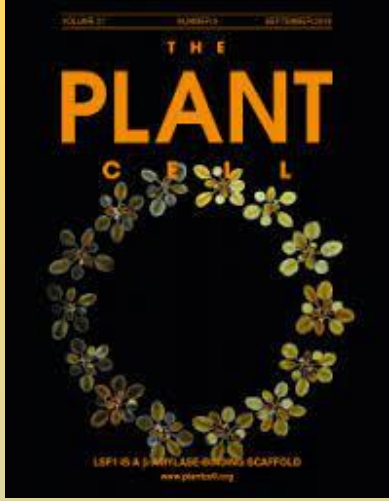
- The repressed allele is methylated, whereas the active allele remains unmethylated. The most well-studied conditions belong to a Prader-Willi syndrome, and an Angelman syndrome. These two syndromes are supposed to rise from GI or other gene-related errors involving the long arm genes of chromosome 15.

The life cycle of imprints



Genomic imprints change in a regular way during the life cycle of the organism. Imprints are set up during the development of gametes (germ cells) into sperm or eggs. After fertilization, they are ‘maintained’ as duplicated but separate chromosomes in the developing organism. In the haploid gametes (germ cells) of the new organism, imprints are ‘erased’ at an early stage. Then they are re-established at a later stage of the gamete development to finish the GI cycle. In diploid somatic cells, imprints are maintained and modified during development, too.

The life cycle of imprints (cond.)



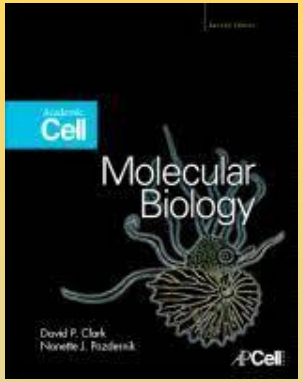
The imprints that are introduced in the parental eggs and sperm (germlines) remain in the early embryo and fully matured zygote during differentiation, these imprints control the genome. Their reading means that genes are expressed differently due to the chromatin methylation. In result of GI, the allelic expression is differential. It prefers the expression from one parental locus over the other.

Scattering CpG islets (dyads) in the early-cleavage embryo point to a continuous partial loss of methylation. It is then repaid by selective de novo methylation. A combination of passive and active demethylation events counteracted by de novo methylation are involved in the distinct reprogramming dynamics of DNA methylomes in the zygote, the early embryo, and primordial germ cells (primary eggs and sperm, PGCs) .

GI-related neurodevelopmental disorders

- Prader-Willi syndrome (PWS) is characterized by abnormal feeding and appetite, and learning disability. PWS patients may also develop a severe affective psychotic illness similar to bipolar disorder. This includes loss of antisense transcripts which represses the expression of UBE3A, which encodes E6-AP (E6-associated protein) ubiquitin ligase from the paternal chromosome. So, the paternal copy of this gene, which is normally expressed from the maternal chromosome, becomes reactivated leading to increased dosage.

- Angelmann Syndrome (AS) is a neurodevelopmental disorder characterized by severe cognitive disability, motor dysfunction, speech impairment, hyperactive behavior, and frequent seizures. AS is caused by disruption of the maternally expressed and paternally imprinted UBE3A, which encodes an E3 ubiquitin ligase.

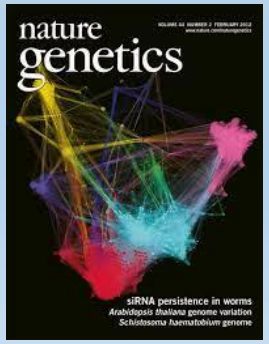


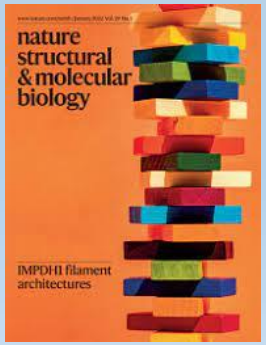
GI-related disorders (cond.)

- Alike AS and PWS, the 15q11–q13 imprinting chromatin region has also been linked to other non-syndromic neuropsychiatric illnesses. For instance, maternal duplication of this interval is associated with the incidence of autism.

GI regulation in plants

- Throughout the years, extensive efforts have been made to characterize the epigenetic marks underlying GI imprinting in animals and plants. The data collected to date stress that GI cannot be solely explained by DNA methylation/demethylation for the imprinting of all genes. At present, new models explaining GI regulation in plants, are advanced as functioning independent of parental DNA methylation asymmetries in the GI setting.





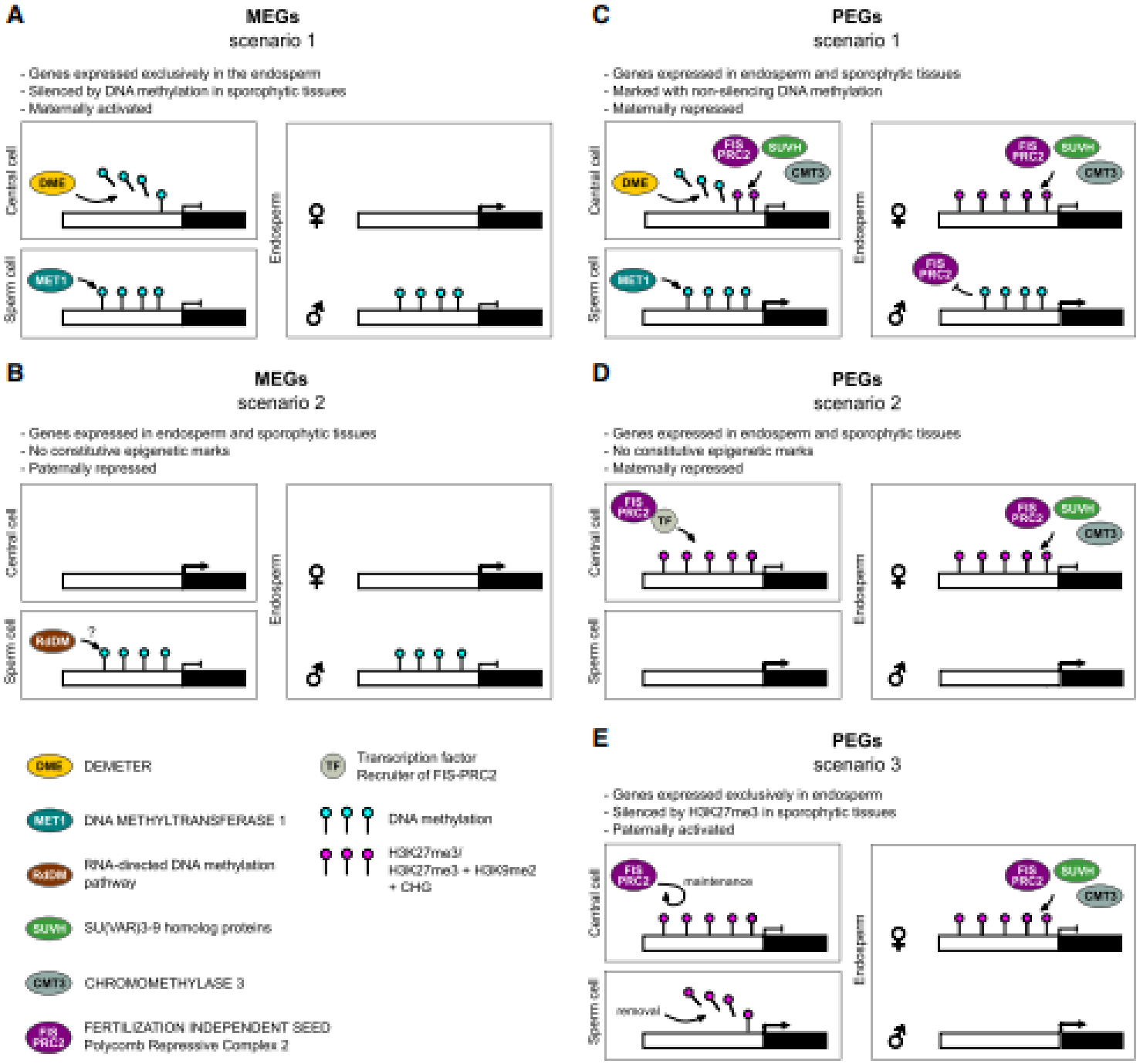
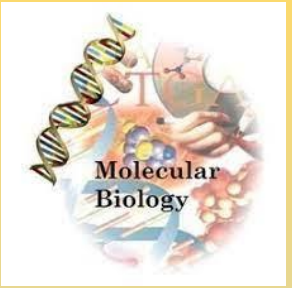

A
MEGs
scenario 1
- Genes expressed exclusively in the endosperm
- Silenced by DNA methylation in sporophytic tissues
- Maternally activated
Central cell
Sperm cell
Endosperm
DME
MET1
B
MEGs
scenario 2
- Genes expressed in endosperm and sporophytic tissues
- No constitutive epigenetic marks
- Paternally repressed
RdDM
?
C
PEGs
scenario 1
- Genes expressed in endosperm and sporophytic tissues
- Marked with non-silencing DNA methylation
- Maternally repressed
FIS PRC2
SUVH
CMT3
D
PEGs
scenario 2
- Genes expressed in endosperm and sporophytic tissues
- No constitutive epigenetic marks
- Maternally repressed
TF
E
PEGs
scenario 3
- Genes expressed exclusively in endosperm
- Silenced by H3K27me3 in sporophytic tissues
- Paternally activated
maintenance
removal
DME DEMETER
MET1 DNA METHYLTRANSFERASE 1
RdDM RNA-directed DNA methylation pathway
SUVH SU(VAR)3-9 homolog proteins
CMT3 CHROMOMETHYLASE 3
FIS PRC2 FERTILIZATION INDEPENDENT SEED Polycomb Repressive Complex 2
TF Transcription factor Recruiter of FIS-PRC2
DNA methylation
H3K27me3/ H3K27me3 + H3K9me2 + CHG

Figure 2. Models of imprinted gene regulation in plants (by Batista& Kohler, 2020)

- Different models for the epigenetic regulation of MEGs (A,B) and PEGs (C–E). Models represent the epigenetic status of maternal and paternal alleles in the central cell, sperm cell, and endosperm. The estimated proportion of genes regulated by each of these scenarios is reported in Supplemental Table 1. (A) In this scenario, MEGs are constitutively marked with DNA methylation and are therefore silenced in sporophytic tissues. Maternal expression in the endosperm requires the removal of maternal DNA methylation, as well as maintenance of paternal methylation, which is achieved by DME and MET1, respectively. (B) MEGs that are expressed both in the endosperm and in sporophytic tissues do not carry any constitutive marks. In this scenario, maternal-specific expression is achieved through silencing of the paternal allele, a process that could possibly be mediated by RdDM activity in pollen. (C) These PEGs are constitutively marked with DNA methylation; however, this mark does not lead to transcriptional silencing, but rather prevents the deposition of H3K27me3 by FIS–PRC2. Maternal-specific demethylation mediated by DME allows deposition of H3K27me3 in these alleles, leading to their transcriptional inactivation in the endosperm. The presence of DNA methylation in paternal alleles prevents deposition of H3K27me3, allowing for the transcription of this allele. (D) PEGs in this scenario do not show any constitutive epigenetic marks and are expressed in the endosperm as well as in sporophytic tissues. Paternal-specific expression in the endosperm can be achieved through silencing of the maternal alleles in the central cell, mediated by FIS–PRC2 and central cell-specific transcription factors. (E) In this scenario, PEGs show constitutive H3K27me3 and are transcriptionally inactive in sporophytic tissues. This silencing mark is faithfully maintained during female sexual lineage differentiation. On the other hand, decreased activity of the PRC2 in sperm cells causes removal of H3K27me3, leading to transcriptional activation of paternal alleles

Conclusion



- GI is important process of inheritance that plays significant role in future genetic and epigenetic studies.
- It is a complex process the core of which is based on DNA metylation in alleles of chromosomes.
- Numerous external factors influence DNA methylation, which may cause the disease onset or its progression, namely in offspring neurodevelopment and autism spectrum disorder.
- GI is a rather rare phenomenon in humans. The majority of genes isn't imprinted. Modern studies were done with mice or plants. These data should be completed.

Conclusion

- The precise mechanisms underlying epigenetic gene control in the pathogenesis of several diseases remain unclear. But there are findings proving that the progression of such diseases can be eliminated or altered by modulating epigenetic programs.
- The data summarized to date show that GI cannot be explained only by DNA methylation/demethylation as the main factor of the imprinting for all genes. New models explaining GI regulation in plants, have been elaborated as functioning besides the parental DNA methylation asymmetries during the GI setting.

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