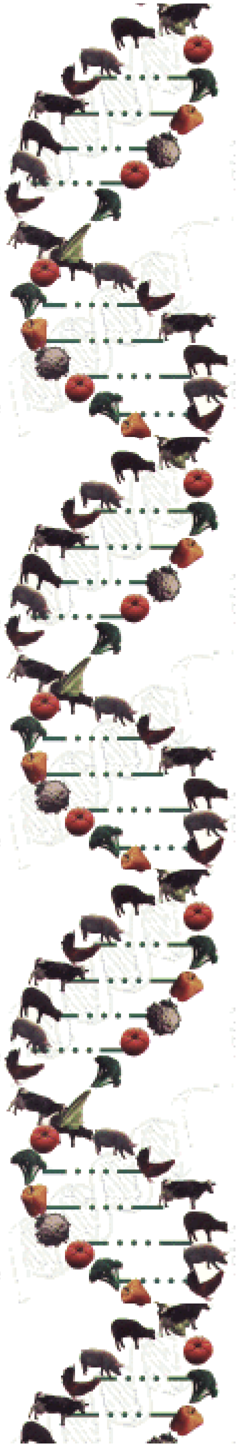


ГЕНОМИКА

30 марта 2020, Понедельник:

1) Эпигеномика (Epigenomic mechanisms of gene regulation and adaptation)

2) Приложения в геномике

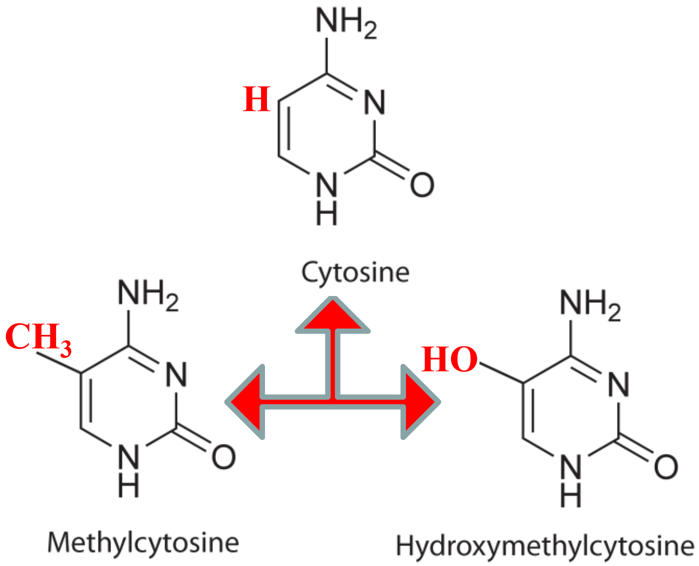
Outlines

- What is epigenetics
- Molecular basis of epigenetics
- Epigenetic marks and their maintenance; writers, readers and erasers of epigenetic marks
- Epigenetic regulations of stress response in plants
- Epigenetic memory (Norway spruce case)
- Epigenetic regulations and adaptation

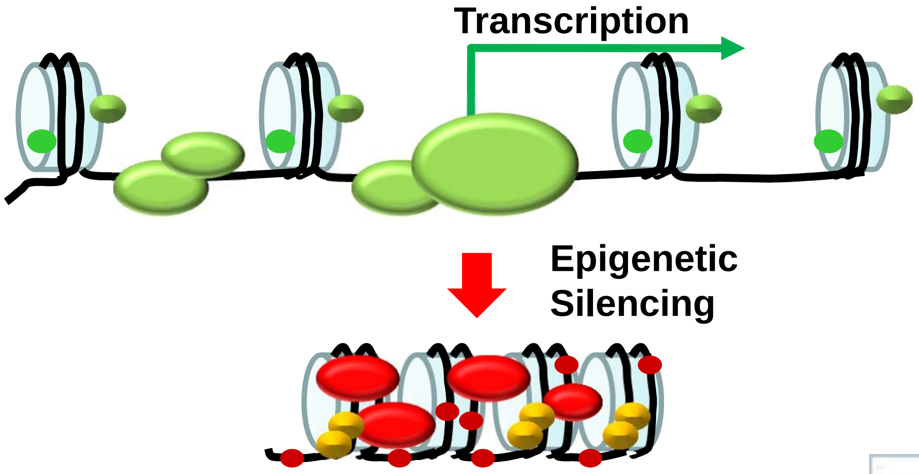
What is epigenetics

- studies heritable changes in phenotype and/or gene expression that occur without changes in the primary underlying DNA sequence (*Epi* (Greek) – in addition to, on)
- based on reversible modifications in the **DNA** or **chromatin** structure that do not involve nucleotide replacements, substitutions or indels in the DNA sequence

DNA



Chromatin



What is epigenetics

describes phenomena, in which genetically identical cells or organisms express their genomes differently, causing phenotypic differences

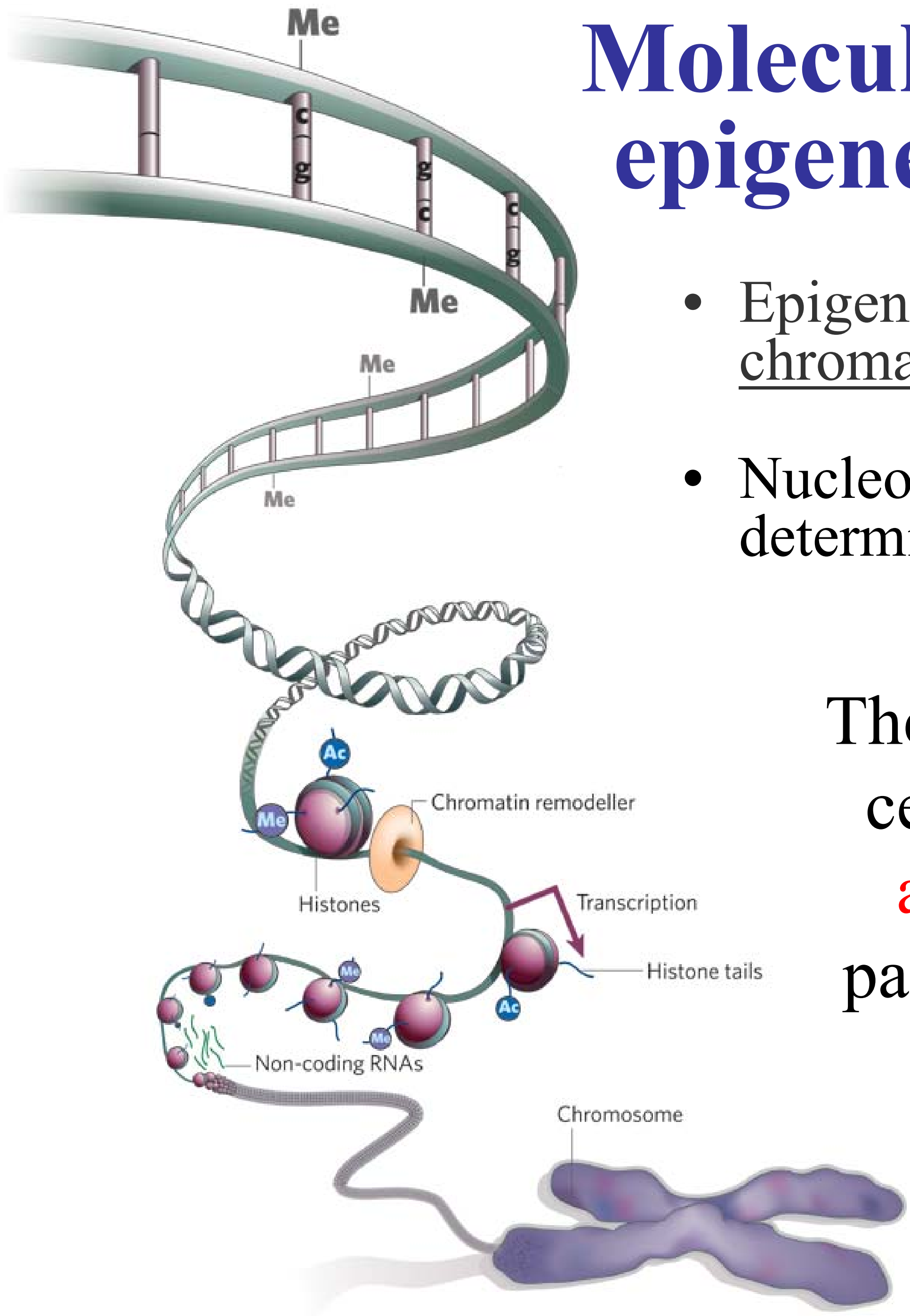
different epigenetic modifications leading to different expression patterns

genetically identical cells or individuals

different tissues or phenotypes

- **reversible changes in DNA and chromatin**
- **associated with phenotypic plasticity and norm reaction**
- **involved in tissue differentiation & developmental regulation**
- **affected by environmental factors**
- **affect adaptation and decease resistance**
- **can be very stable, transmitted and inherited!**

Molecular mechanisms of epigenetic modifications

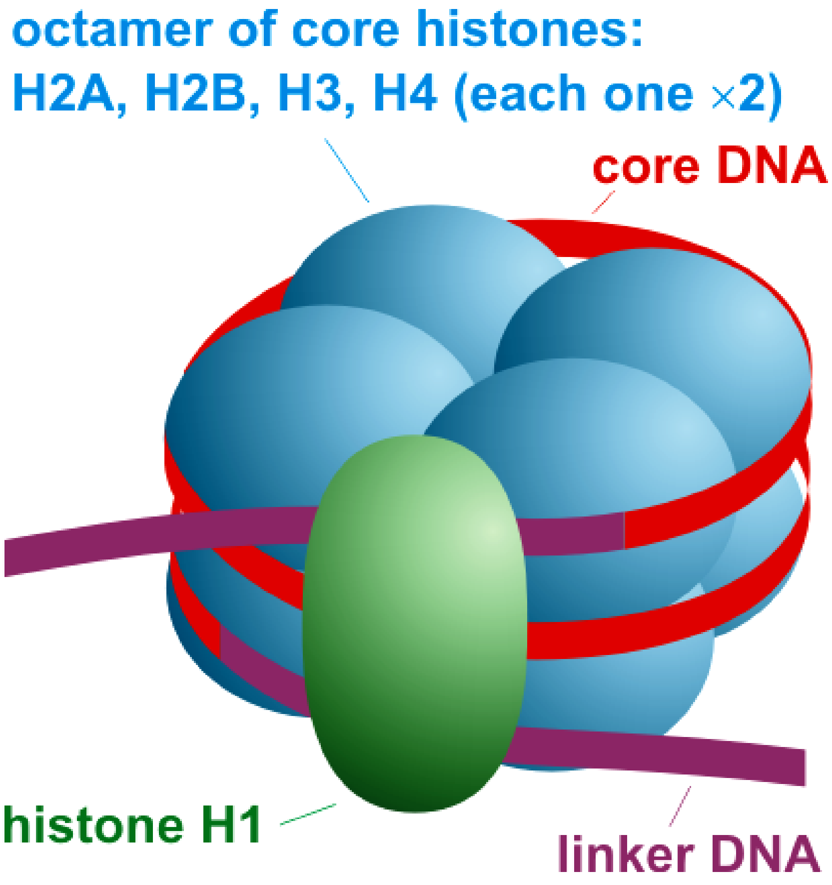


- Epigenetic regulations are mediated by <u>chromatin and DNA modifications</u>.
- Nucleosome structure considerably determines existence of epigenetics.

The DNA double helix in the cell nucleus does not exist alone and loosely and is packaged into chromatin by special proteins termed histones.

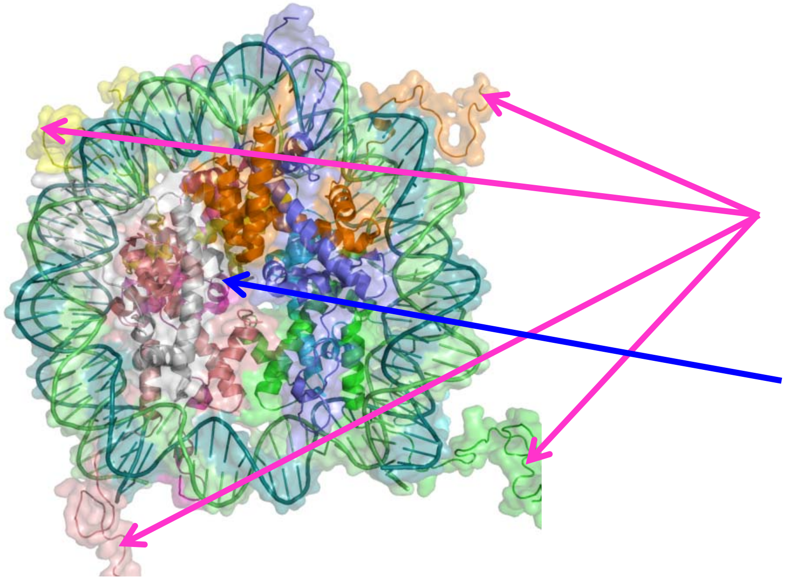
Feinberg, R (2008) Nature 454: 711-715

Molecular Components of Chromatin in Plants



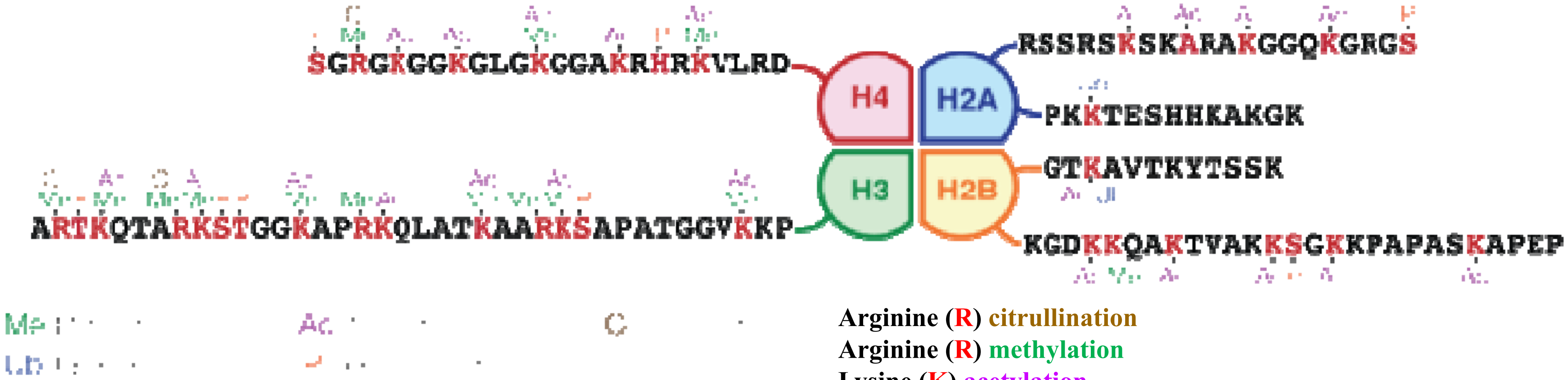
- Each nucleosome consist of 2 copies (dimers) each of the core histones **H2A**, **H2B**, **H3** and **H4**.
- Nucleosomes are linked with linker histone **H1/H5** and linker DNA.
- The DNA is wrapped around nucleosome (~147 bp) + linker – total coil ≈180 bp

Molecular Components of Chromatin in Plants



Histone tails could be modified

Core histones could be substituted, e.g. H2A ↔ H2A.Z

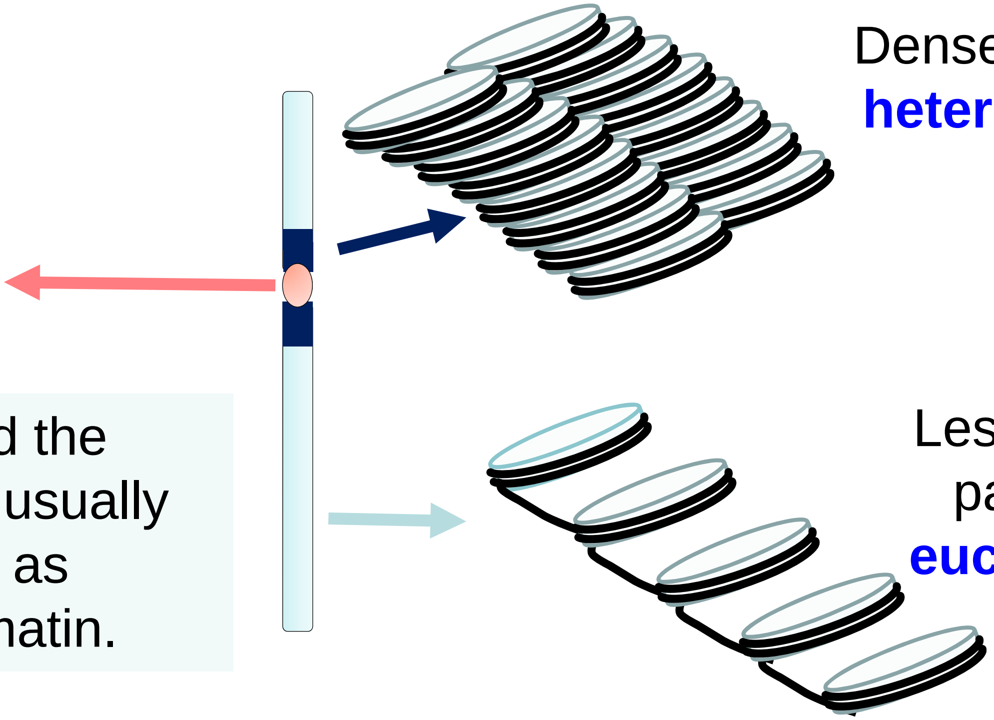


http://www.actrec.gov.in/histome/ptm_main.php

Arginine (R) citrullination
Arginine (R) methylation
Lysine (K) acetylation
Lysine (K) biotinylation
Lysine (K) methylation
Lysine (K) ribosylation
Lysine (K) ubiquitination
Serine (S) / Threonine (T) / Tyrosine (Y) phosphorylation

Molecular Components of Chromatin in Plants

- Chromatin can be generally classified as condensed, transcriptionally silent heterochromatin or less-condensed, transcriptionally active euchromatin.



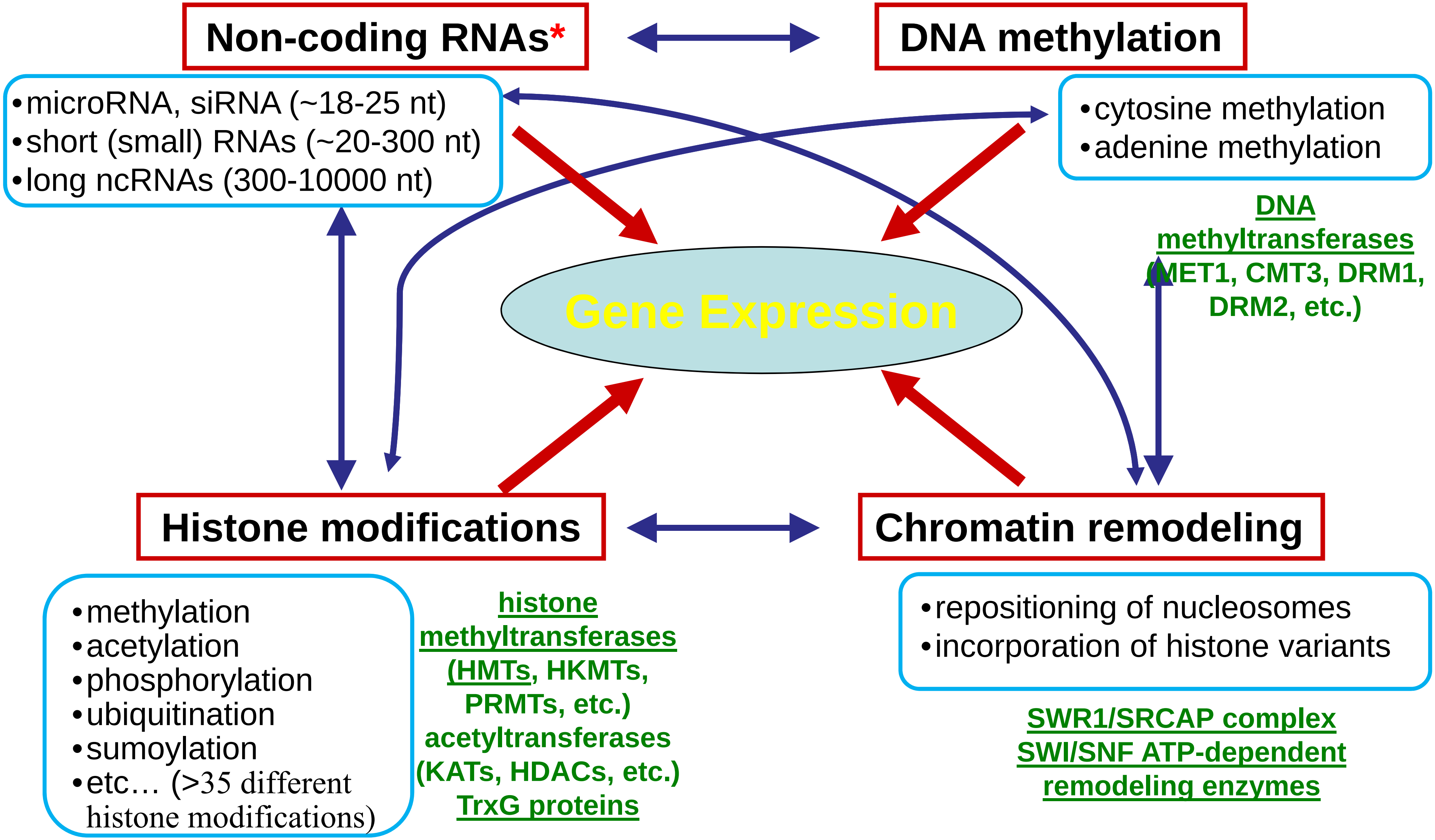
Densely packaged **heterochromatin**

CENTROMERE

DNA around the centromere is usually packaged as heterochromatin.

Less densely packaged **euchromatin**

Epigenetic modifications and regulation mechanisms



Non-coding RNAs*

- microRNA, siRNA (~18-25 nt)
- short (small) RNAs (~20-300 nt)
- long ncRNAs (300-10000 nt)

DNA methylation

- cytosine methylation
- adenine methylation

DNA methyltransferases (MET1, CMT3, DRM1, DRM2, etc.)

Gene Expression

Histone modifications

- methylation
- acetylation
- phosphorylation
- ubiquitination
- sumoylation
- etc… (>35 different histone modifications)

histone methyltransferases (HMTs, HKMTs, PRMTs, etc.) acetyltransferases (KATs, HDACs, etc.) TrxG proteins

Chromatin remodeling

- repositioning of nucleosomes
- incorporation of histone variants

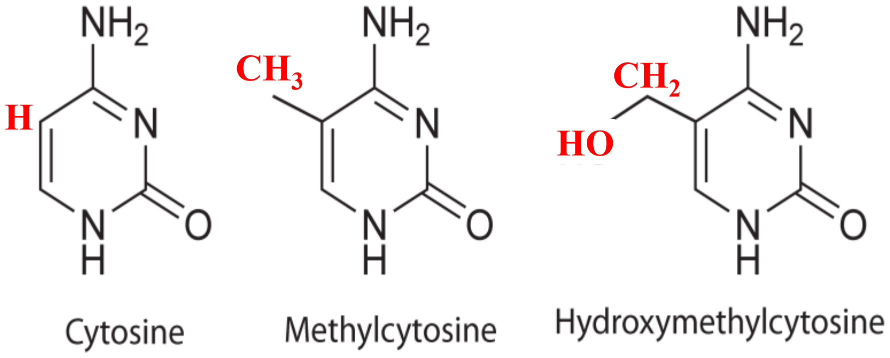
SWR1/SRCAP complex SWI/SNF ATP-dependent remodeling enzymes

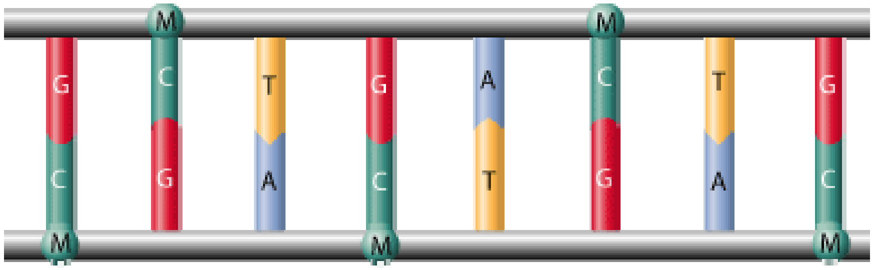
Epigenetic modifications need specific metabolic pathways and enzymes

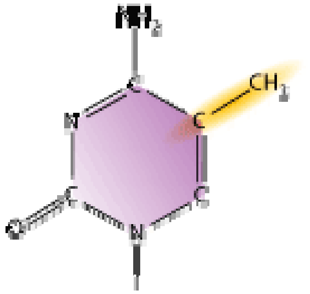
***98% of the total RNA transcribed in human cells**

DNA methylation and hydroxymethylation

- DNA methyltransferase transfers a **methyl** (**CH_3-**) or **hydroxymethyl** (**HO-**) group to **cytosine** (**C**)
- substitutes **H** at 5-carbon of the **cytosine** pyrimidine ring
- **cytosine** is *methylated* mostly in three sequence cites: **CG**, **C*H*G** and **C*HH*** (where ***H*** = **A**, **T** or **C**)
- **heritable markers !**







DNA methylation is the addition of a methyl group (M) to the DNA base cytosine (C).

- **hydroxymethylation** was recently discovered as another important epigenetic modification on DNA

Epigenetic modifications: DNA Methylation

DNA methyltransferases in Arabidopsis

MET1 (Methyltransferase 1)

- **5'-CG-3'** sites
- silencing of transposons, repetitive elements, some imprinted genes

CMT3 (Chromomethylase 3)

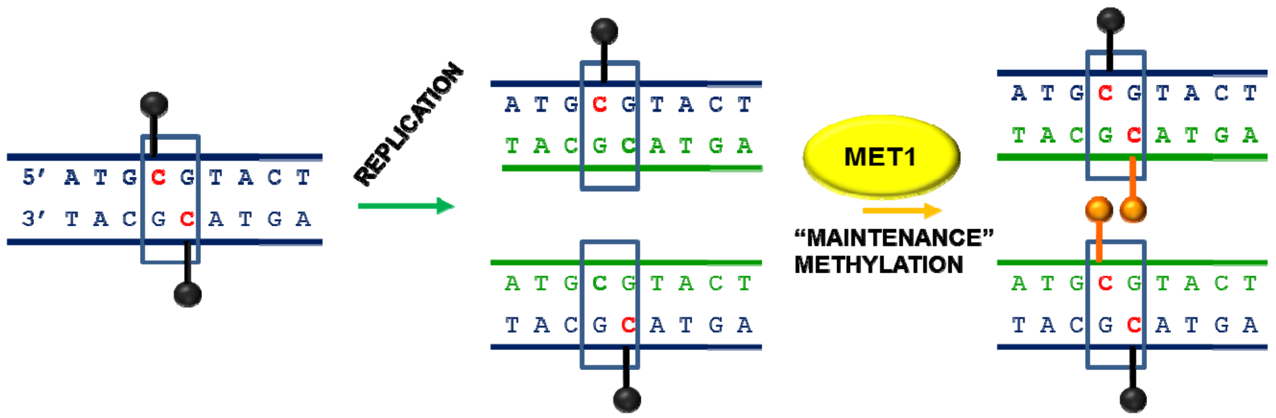
- **5'-CHG-3'** sites
- (H= A, C or T)
- interacts with histone mark

DRM1, DRM2 (Domains rearranged 1 and 2)

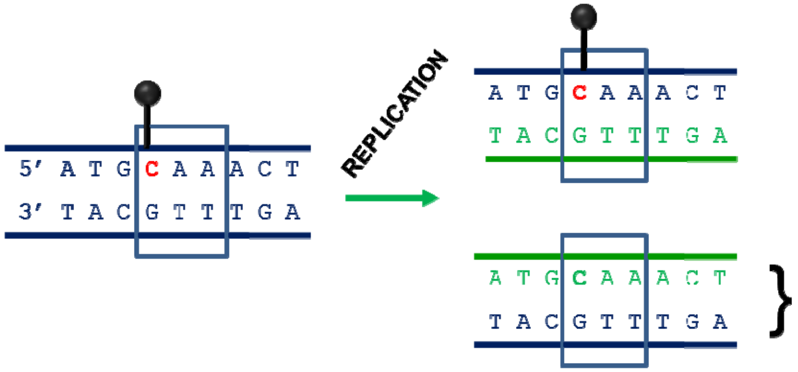
- **5'-CHH-3'** sites
- primarily targets repetitive elements
- requires the active targeting of siRNAs

Epigenetic modifications: DNA Methylation

CG methylation can be propagated during DNA replication



Asymmetric methylation sites require additional information

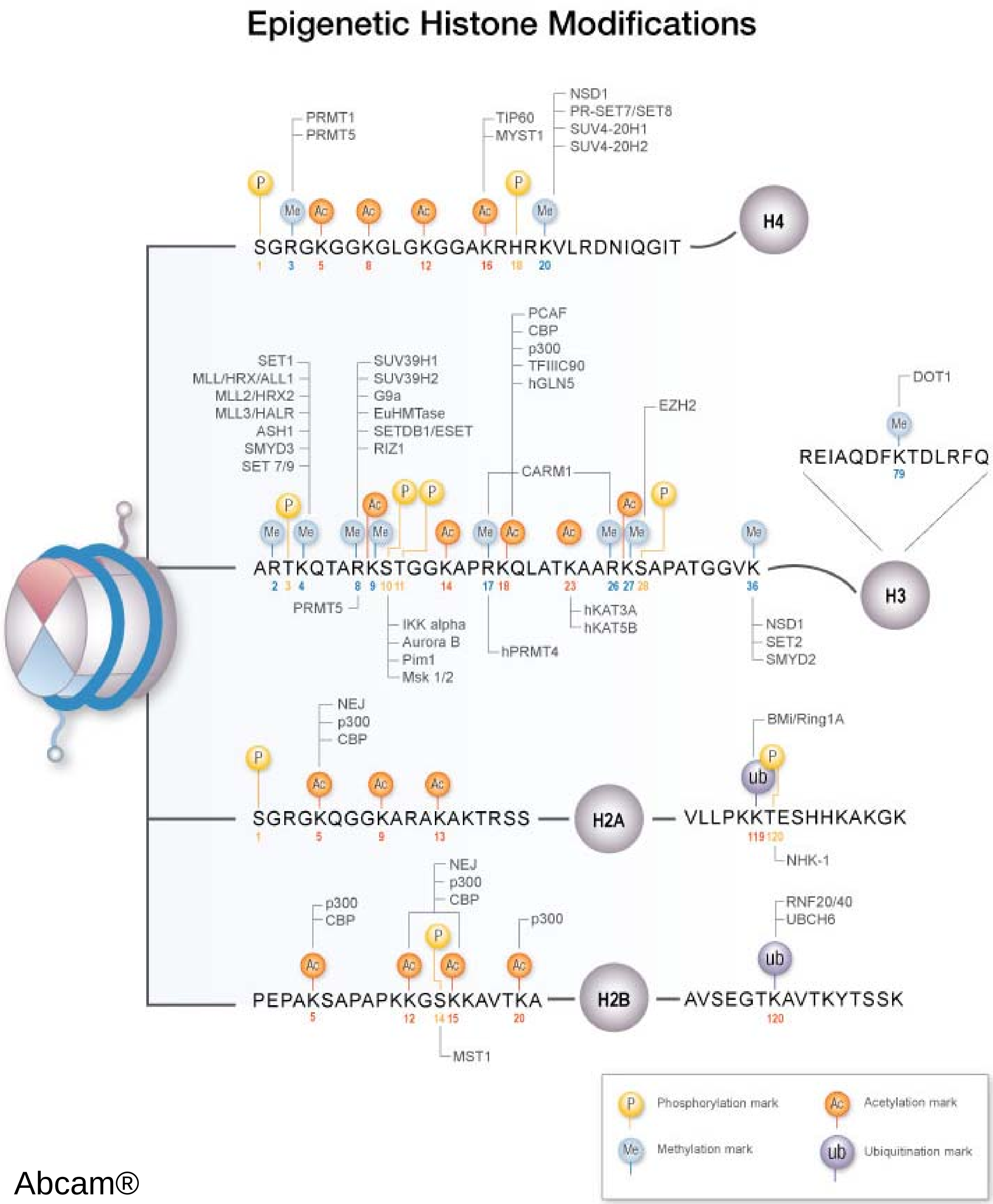


Requires
additional
information to
remethylate

Asymmetric methylation sites are maintained (and initiated) by RNA-directed DNA Methylation (RdDM), that directs DNA methylases to these sites

Epigenetic modifications: Histone modifications

- the amino terminal regions of the histone monomers that extend beyond the nucleosome are accessible for modification
- affects chromatin structure
- depending on their position lead to transcriptional activation or inactivation
- reversible
- heritable (both mitotically and meiotically)



Abcam®

There are more than 35 different histone modifications in all 4 core histones: including but not limited to

- lysine acetylation (Ac);
- lysine and arginine methylation (Me);
- serine and threonine phosphorylation (P);
- lysine ubiquitination (Ub) and sumoylation (Su);
- etc.

Epigenetic modifications: Histone modifications

Histone methylation & demethylation

Histone methylation

- Histone methyl transferases (HMTs)
  - – histone lysine methyl transferases (HKMTs) - methylate lysine (K) residues
  - – histone arginine methyl transferase (PRMTs) - methylate arginine (R) residues

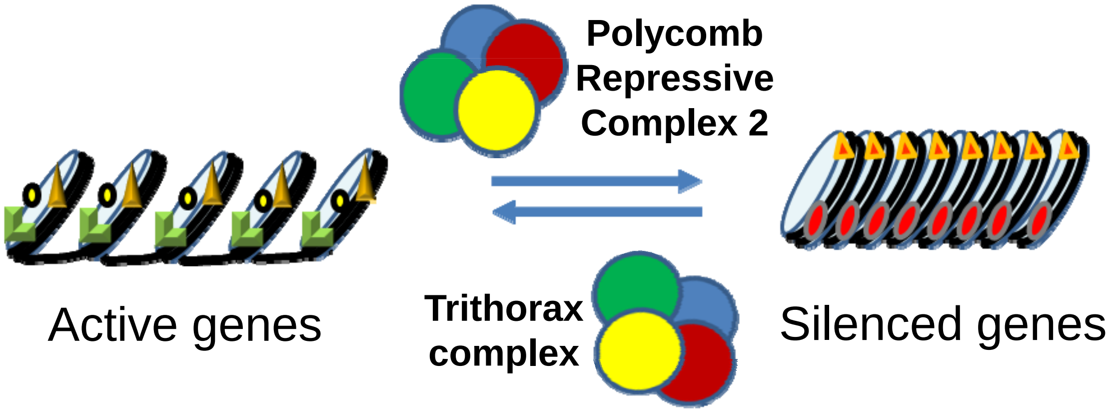
Methylation can result in activation or repression of expression

- all methylation of histone H3 at lysine 4 (H3K4) is an active mark for transcription
- monomethylation of of histone H3 at lysine 9 (H3K9) - a signal for transcriptional activation, but di- and trimethylation of histone H3 at lysine 9 (H3K9) - a signal for transcriptional silencing

Epigenetic modifications: Histone modifications

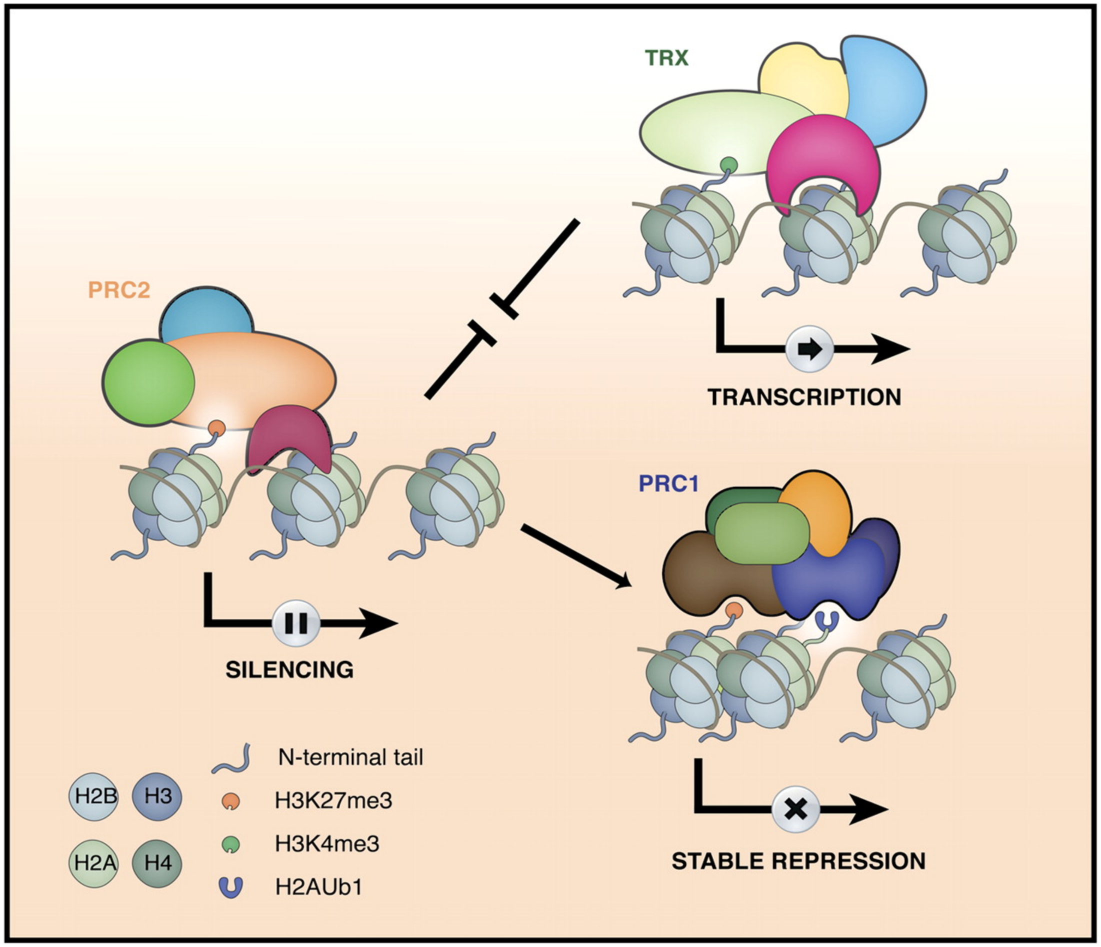
Epigenetic modifications affect the state of chromatin and gene expression

- Genome regulation by polycomb (PcG) and trithorax (TrxG) proteins
- PcGs forming the Polycomb Repressive Complex 2 (PRC2) cause gene silencing by trimethylation of lysine 27 of histone H3 (H3K27me3)



- The Trithorax complex activates gene transcription by inducing trimethylation of H3K4me3 at specific sites in chromatin
- This gene activation is reinforced by acetylation of histone H4.

The activity of flowering locus C (*FLC*) is also regulated by trithorax group (*trxG*) proteins



In the regulation of *FLC* and other genes, **trithorax group proteins** are generally antagonistic to **polycomb group proteins** including the *PRC2* complex

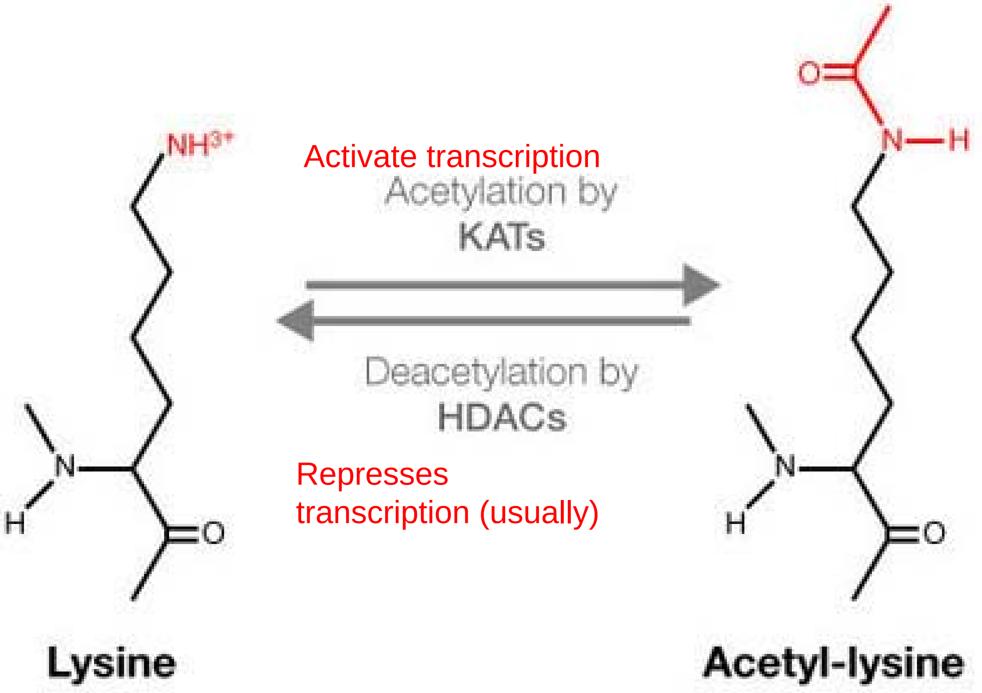
Pien, S., Fleury, D., Mylne, J.S., Crevillen, P., Inzé, D., Avramova, Z., Dean, C. and Grossniklaus, U. (2008). ARABIDOPSIS TRITHORAX1 dynamically regulates FLOWERING LOCUS C activation via histone 3 lysine 4 trimethylation. Plant Cell. 20: 580-588.

Holec, S. and Berger, F. (2012). Polycomb group complexes mediate developmental transitions in plants. Plant Physiol. 158: 35-43.

Epigenetic modifications: Histone modifications

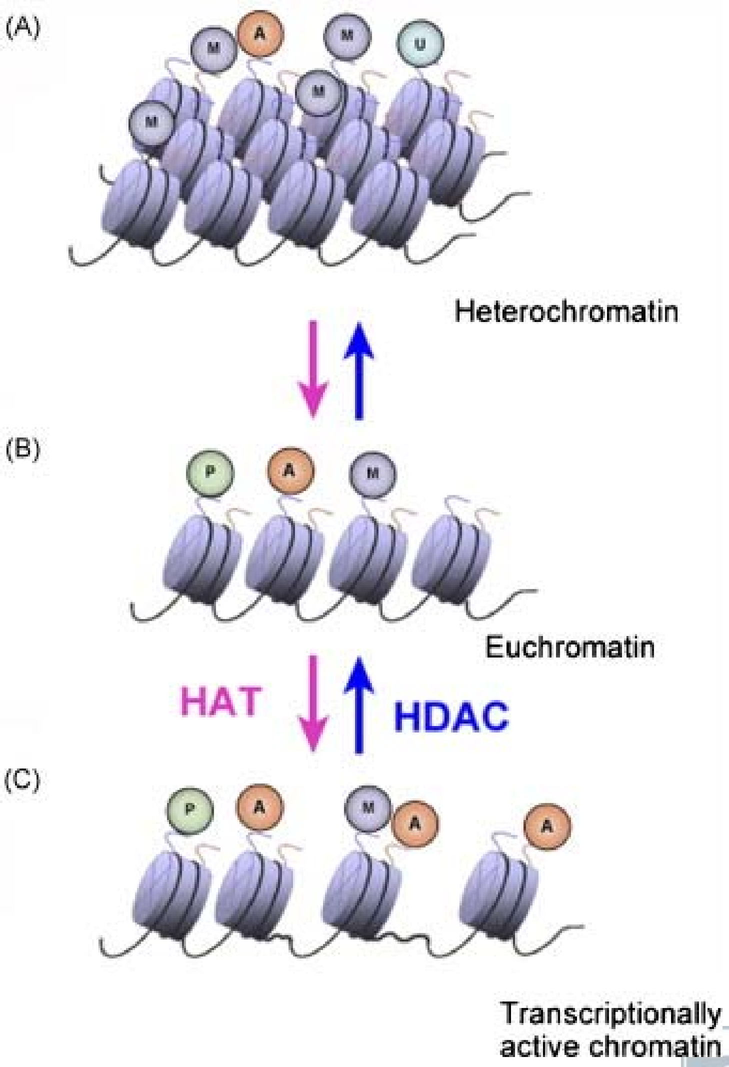
Histone Acetylation & Deacetylation

- **Acetylation has two functions:**
  - ✓ reduce the positive charge on the lysine residues
  - ✓ destabilize interactions between histone tails and structural proteins



Activate transcription

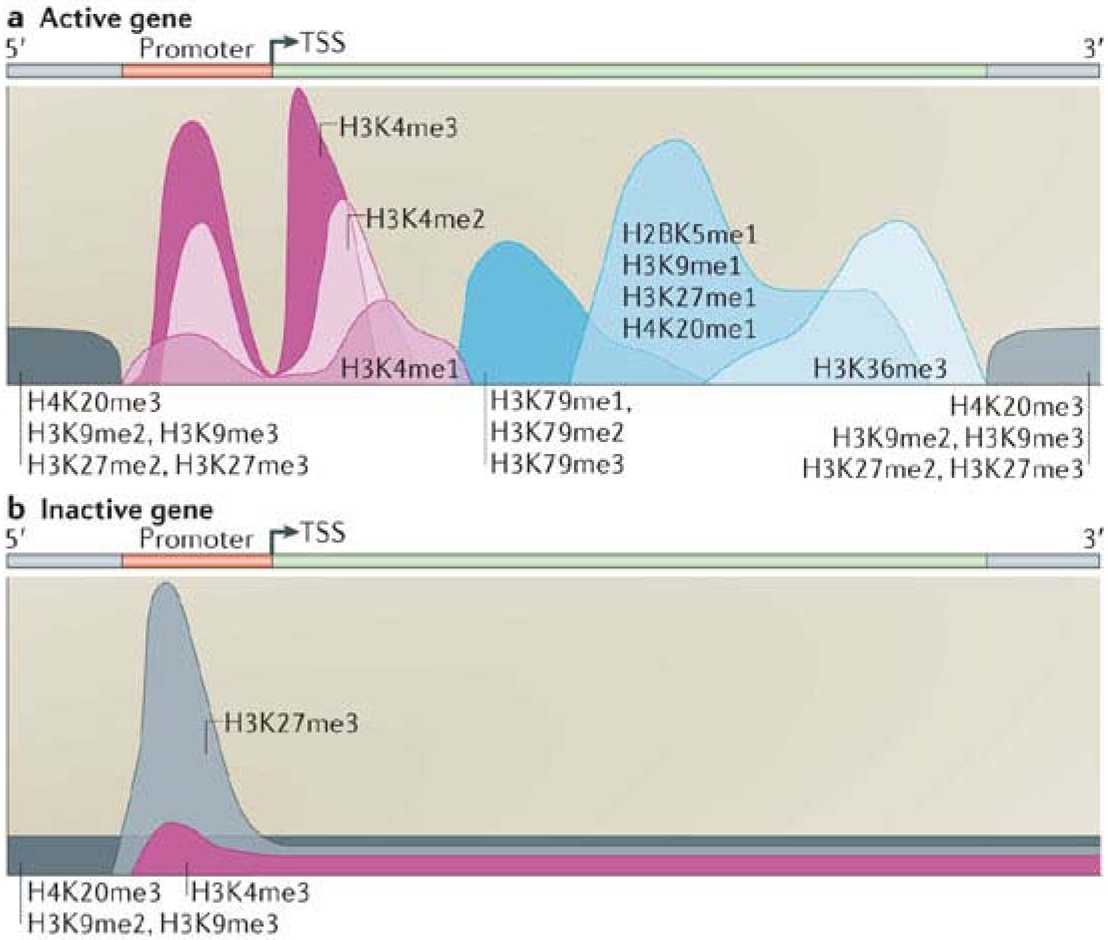
Represses transcription (usually)



Epigenetic modifications affect the state of chromatin and gene expression

Histone modifications are complex and redundant

Schematic representation of average patterns of histone methylation

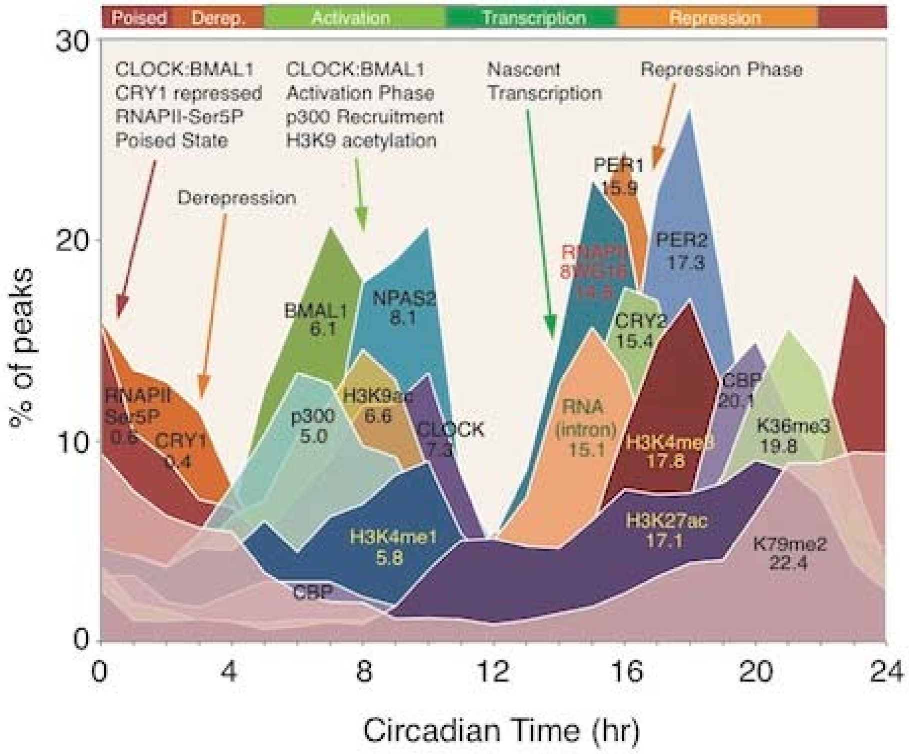


The exact location of the modifications has been implicated in their function, and therefore the enzymes that either deposit or remove methylation marks are thought to be involved in regulating distinct functions, including transcriptional initiation, elongation or gene repression.

Nature Reviews | Molecular Cell Biology

Epigenetic modifications affect the state of chromatin and gene expression

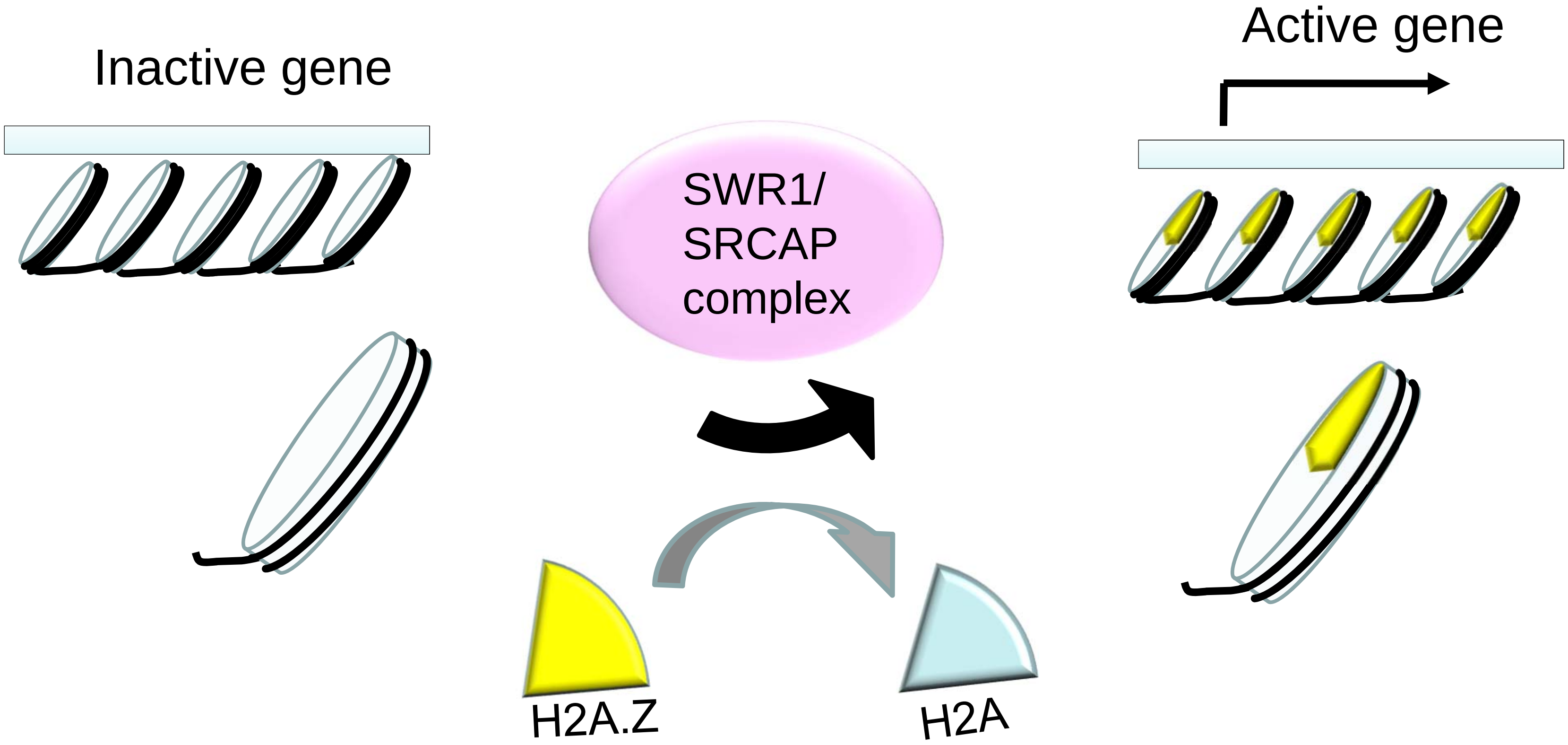
Histone modifications are dynamic and very different in permanence



- **Circadian transcriptional landscape**
- Phase distributions of circadian transcriptional regulators, nascent RNA transcripts, RNA polymerase II (RAPII) occupancy, and histone modification rhythms in mouse liver.

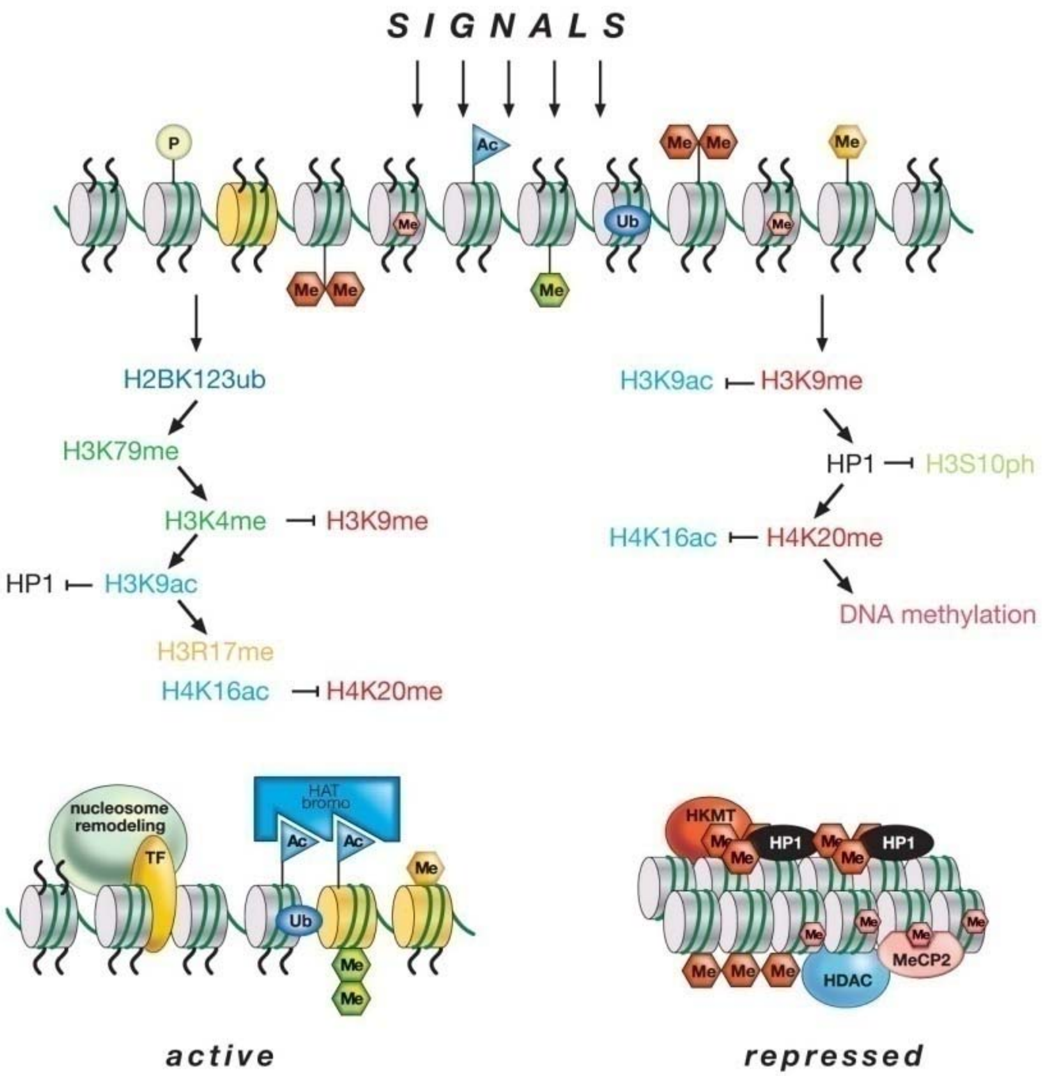
- Experiments on the dynamics of histone modifications reveal a striking kinetic difference between methylation, phosphorylation and acetylation, suggesting different roles of these modifications in epigenetically fixing specific gene expression patterns.

An H2 variant, H2A.Z is associated with some active genes



- The histone variant H2A.Z promotes transcription and is swapped into the nucleosome by the SWR1/SRCAP complex
- H2A.Z is temperature dependant and incorporated at elevated temperatures

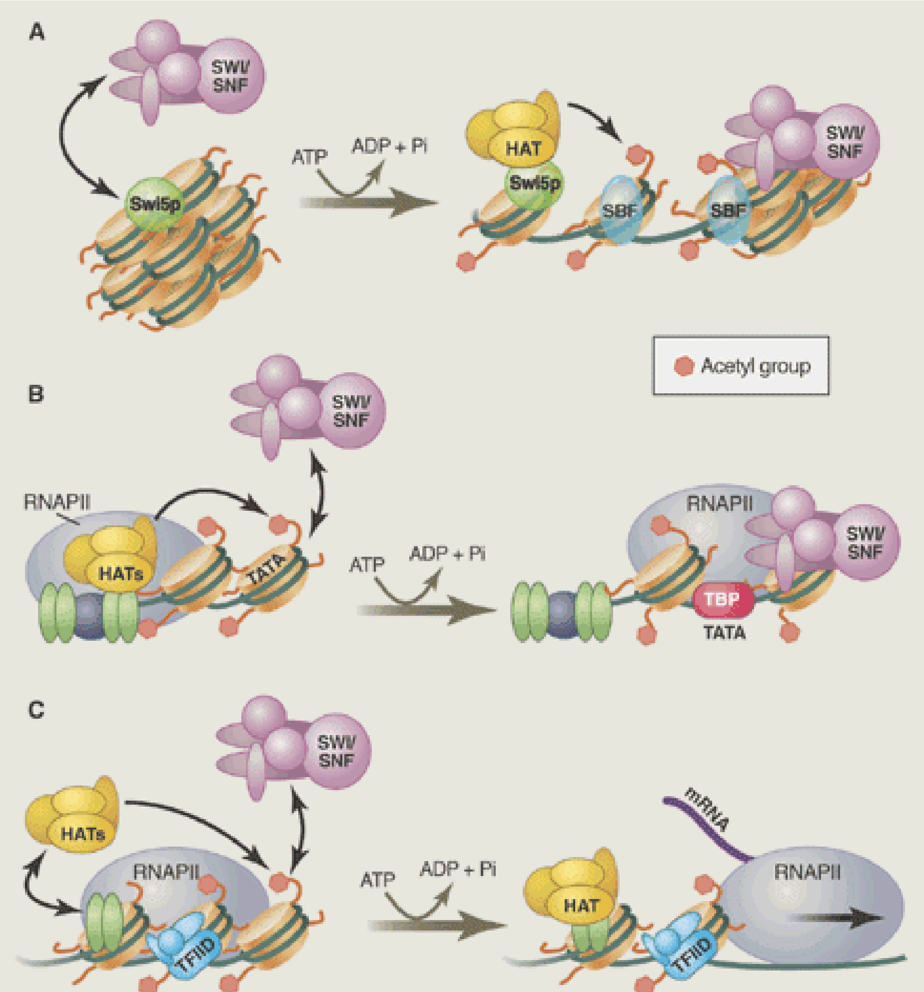
Coordinated modification of chromatin



The transition of a naïve chromatin template to active euchromatin (*left*) or the establishment of repressive heterochromatin (*right*), involving a series of coordinated chromatin modifications. In the case of transcriptional activation, this is accompanied by the action of nucleosome-remodeling complexes and the replacement of core histones with histone variants (*yellow*, namely H3.3).

Histone code???

Alternations in chromatin remodeling could lead to changes in gene expression



Science 295, pg 1848 (2002)

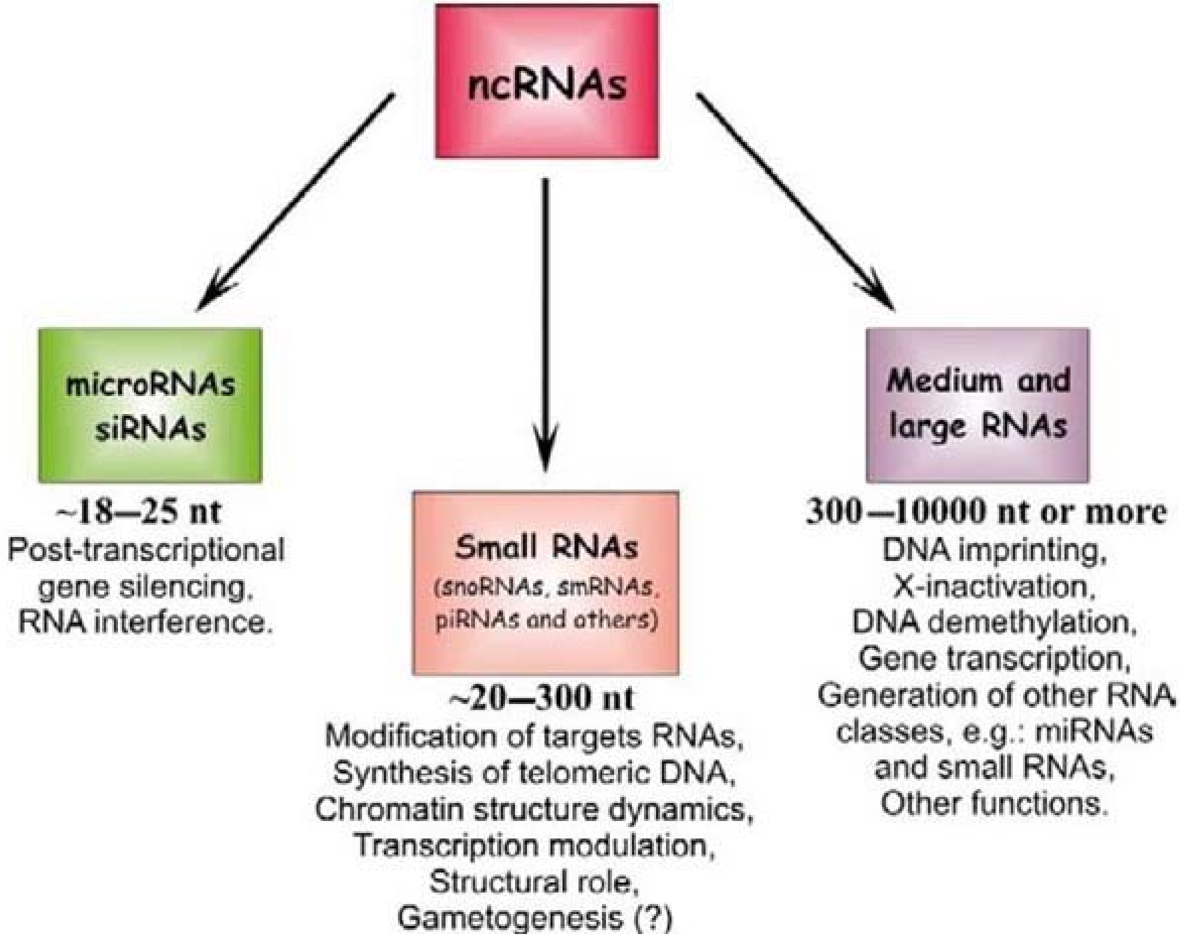
(Fry and Peterson)

Complex compacted state of DNA and its interaction with the histone proteins must be "remodeled" to allow interactions of the transcription factors and RNA polymerase

SWI/SNF ((SWItch/Sucrose Non-Fermentable)) ATP-dependent remodeling enzyme

Control of gene expression by RNA molecules

Largest part of transcriptome (up to 98 % of the RNA transcribed in human cells) does not code for protein and called non-coding RNAs (ncRNAs)



ncRNAs

microRNAs siRNAs

~18–25 nt

Post-transcriptional gene silencing, RNA interference.

Small RNAs

(snoRNAs, smRNAs, piRNAs and others)

~20–300 nt

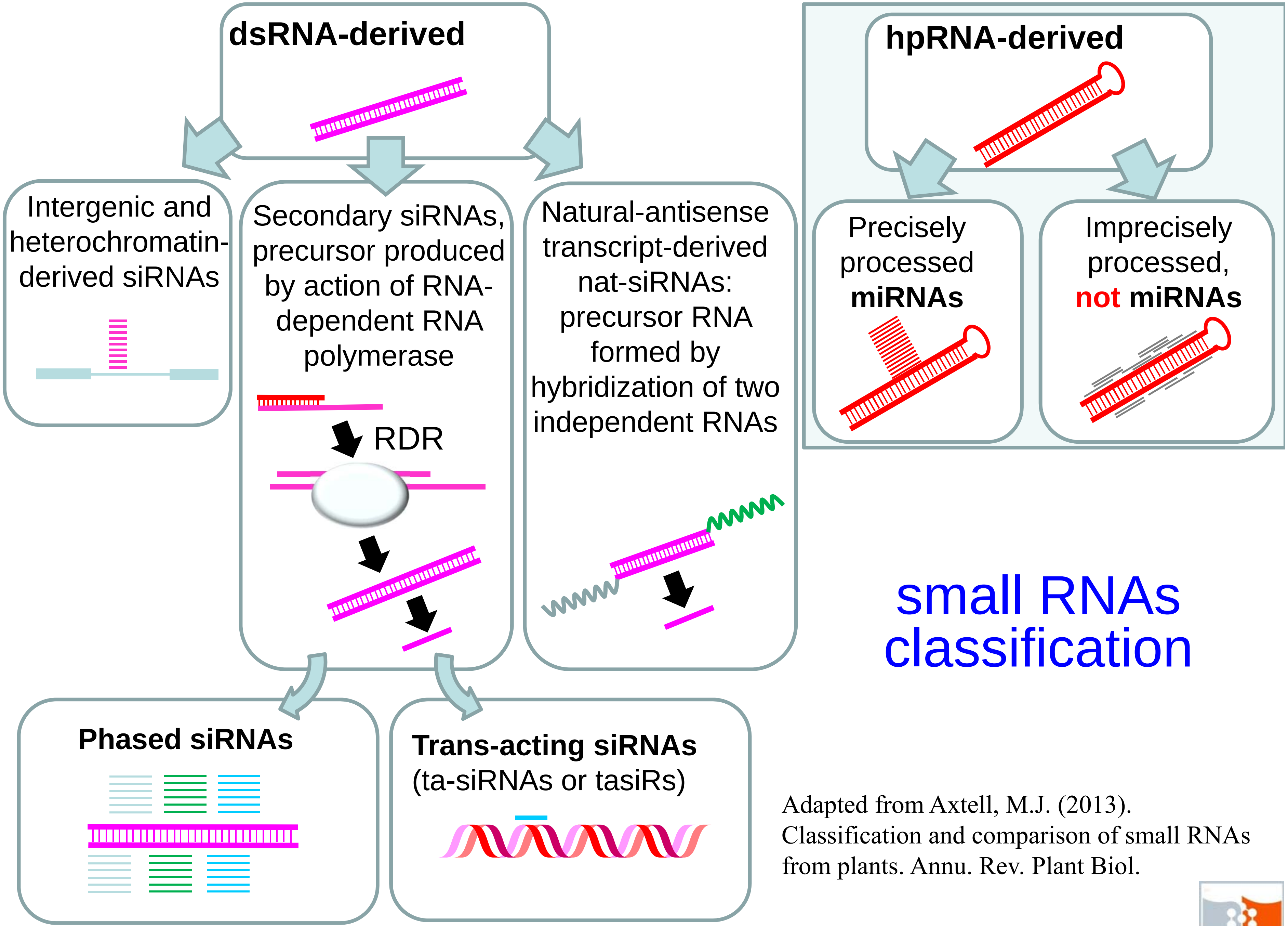
Modification of targets RNAs,
Synthesis of telomeric DNA,
Chromatin structure dynamics,
Transcription modulation,
Structural role,
Gametogenesis (?)

Medium and large RNAs

300–10000 nt or more

DNA imprinting,
X-inactivation,
DNA demethylation,
Gene transcription,
Generation of other RNA classes, e.g.: miRNAs and small RNAs,
Other functions.

small RNAs classification



dsRNA-derived

Intergenic and heterochromatin-derived siRNAs

Secondary siRNAs, precursor produced by action of RNA-dependent RNA polymerase

RDR

Natural-antisense transcript-derived nat-siRNAs: precursor RNA formed by hybridization of two independent RNAs

Phased siRNAs

Trans-acting siRNAs (ta-siRNAs or tasiRs)

hpRNA-derived

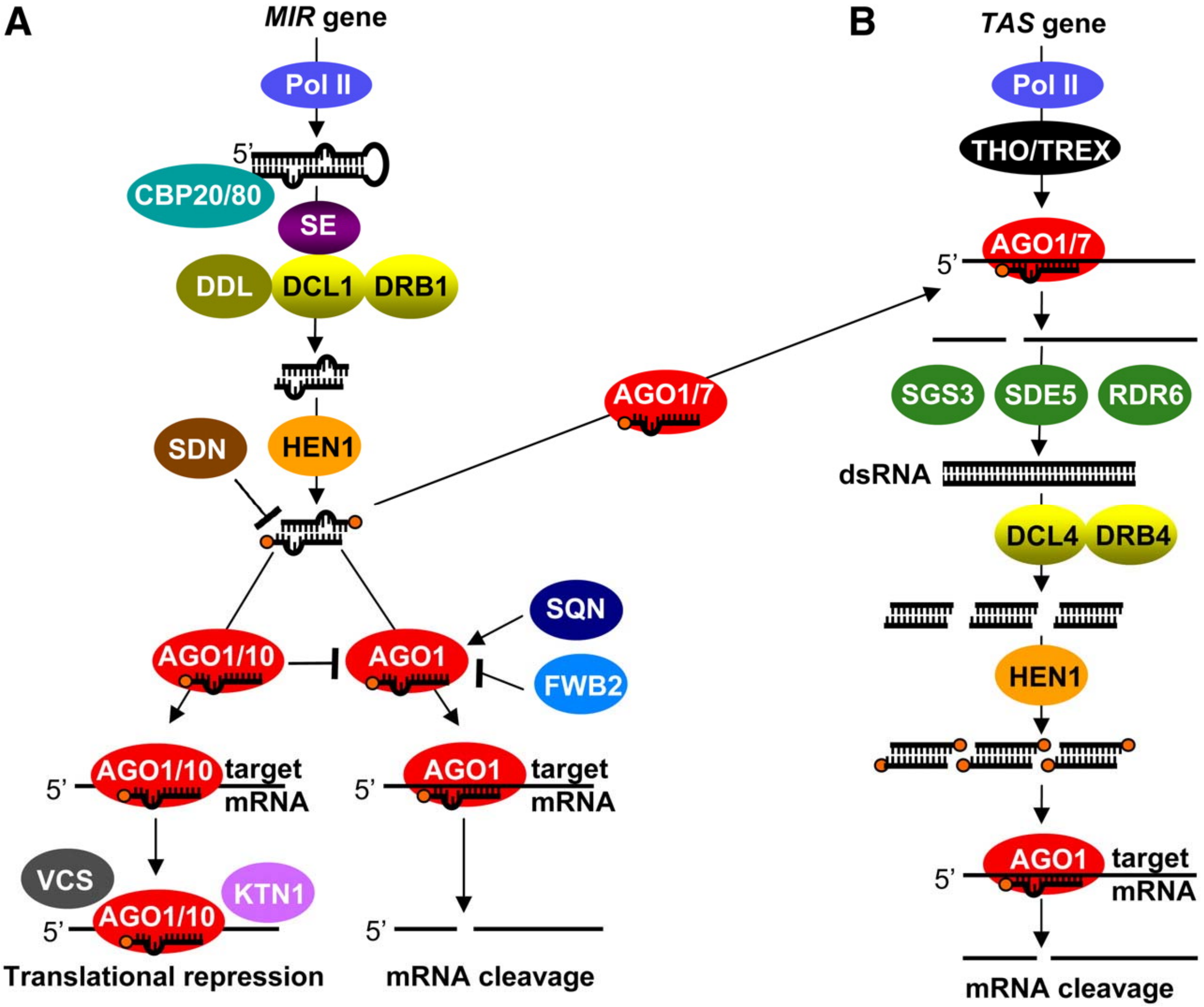
Precisely processed **miRNAs**

Imprecisely processed, **not miRNAs**

Adapted from Axtell, M.J. (2013). Classification and comparison of small RNAs from plants. Annu. Rev. Plant Biol.

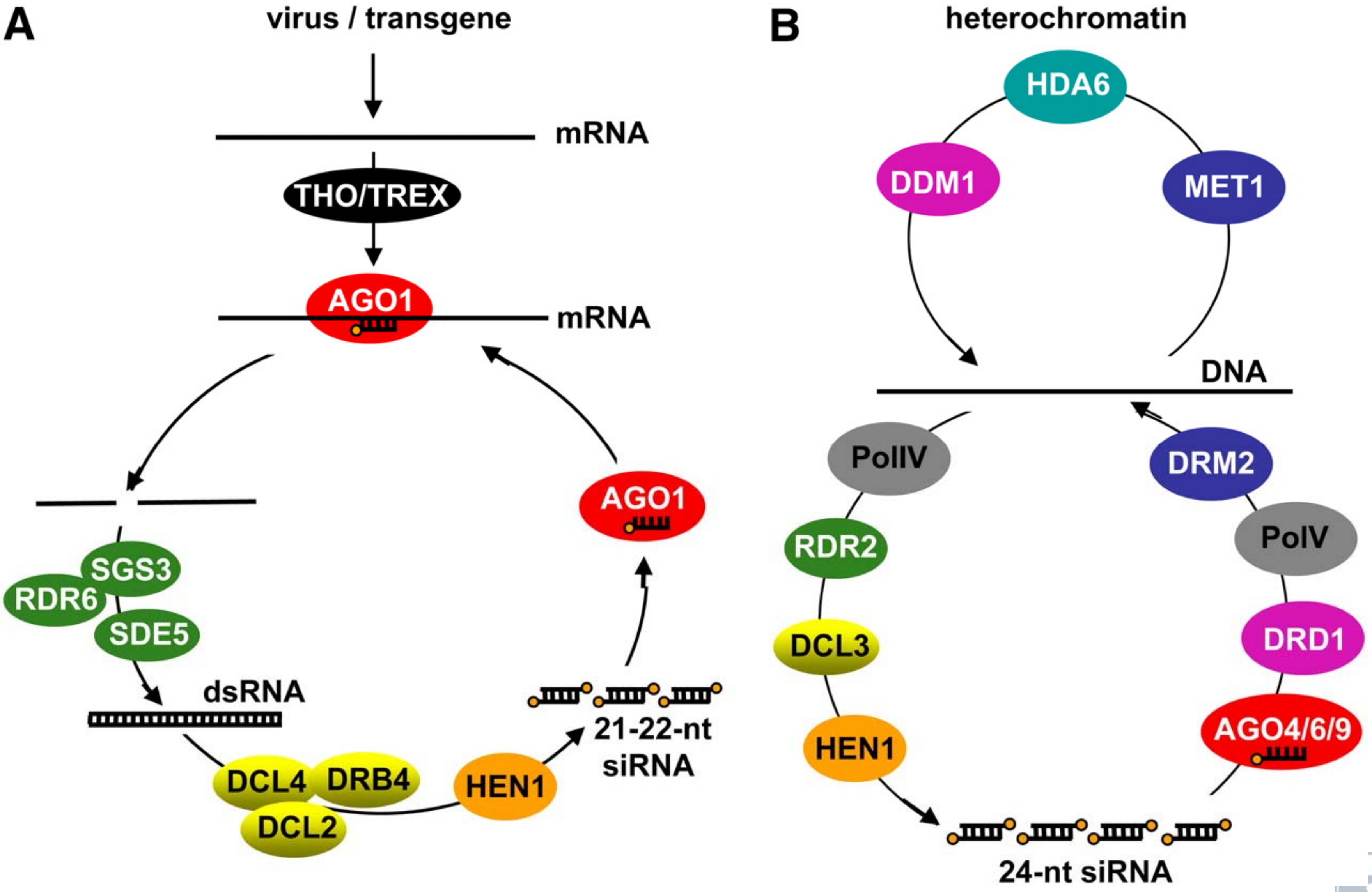
trans-silencing: miRNA and ta-siRNA Pathways

The miRNA pathway **ta-siRNA pathway**



Mallory A, Vaucheret H. Plant cell 2011;22:3879-3889

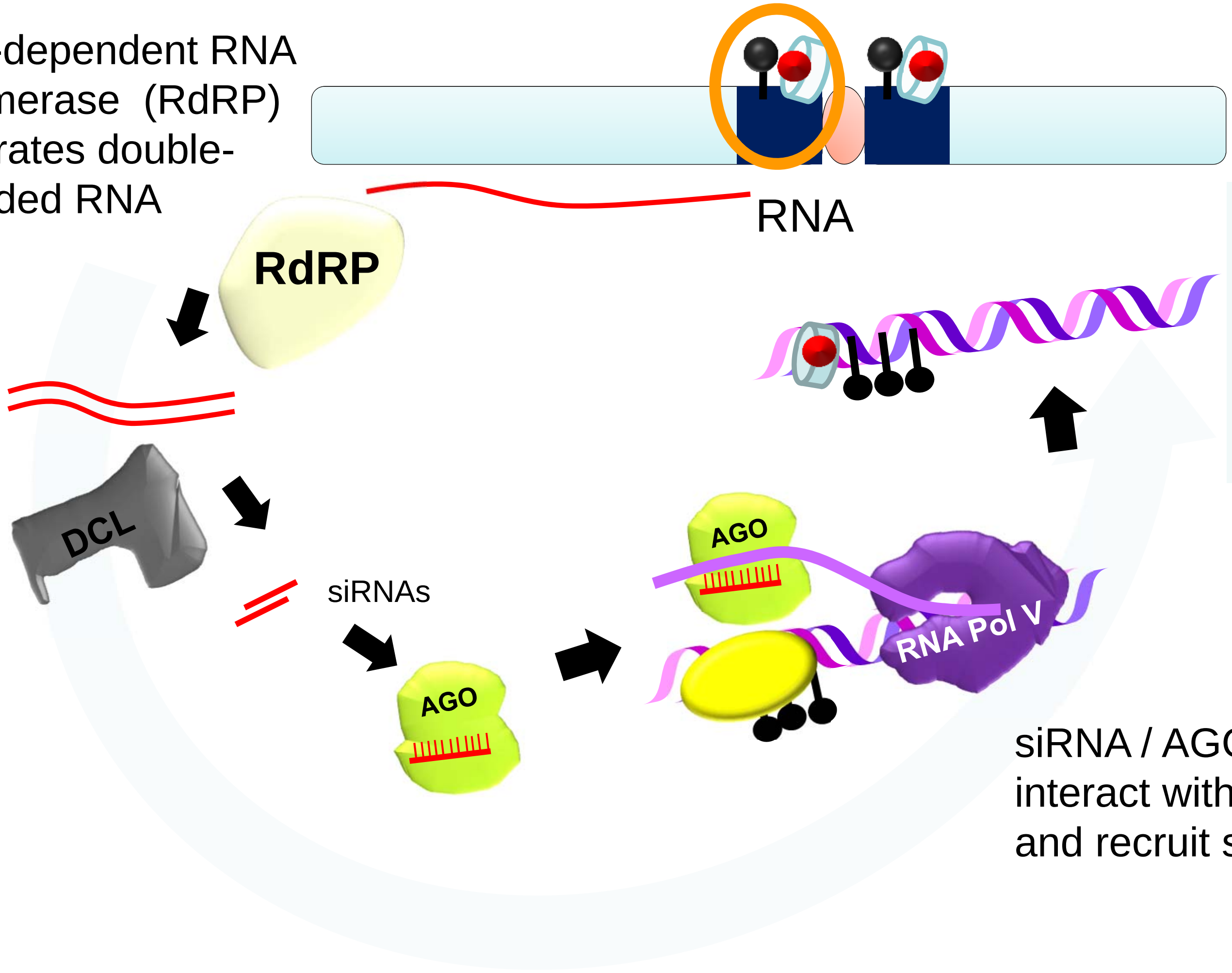
cis-Silencing: The Virus/Transgene (A) and Heterochromatin siRNA Pathways (B)



Mallory A, Vaucheret H. Plant cell 2011;22:3879-3889

Transposon and repetitive DNA silencing

siRNAs recruit DNA methylases and histone-modifying enzymes to targets

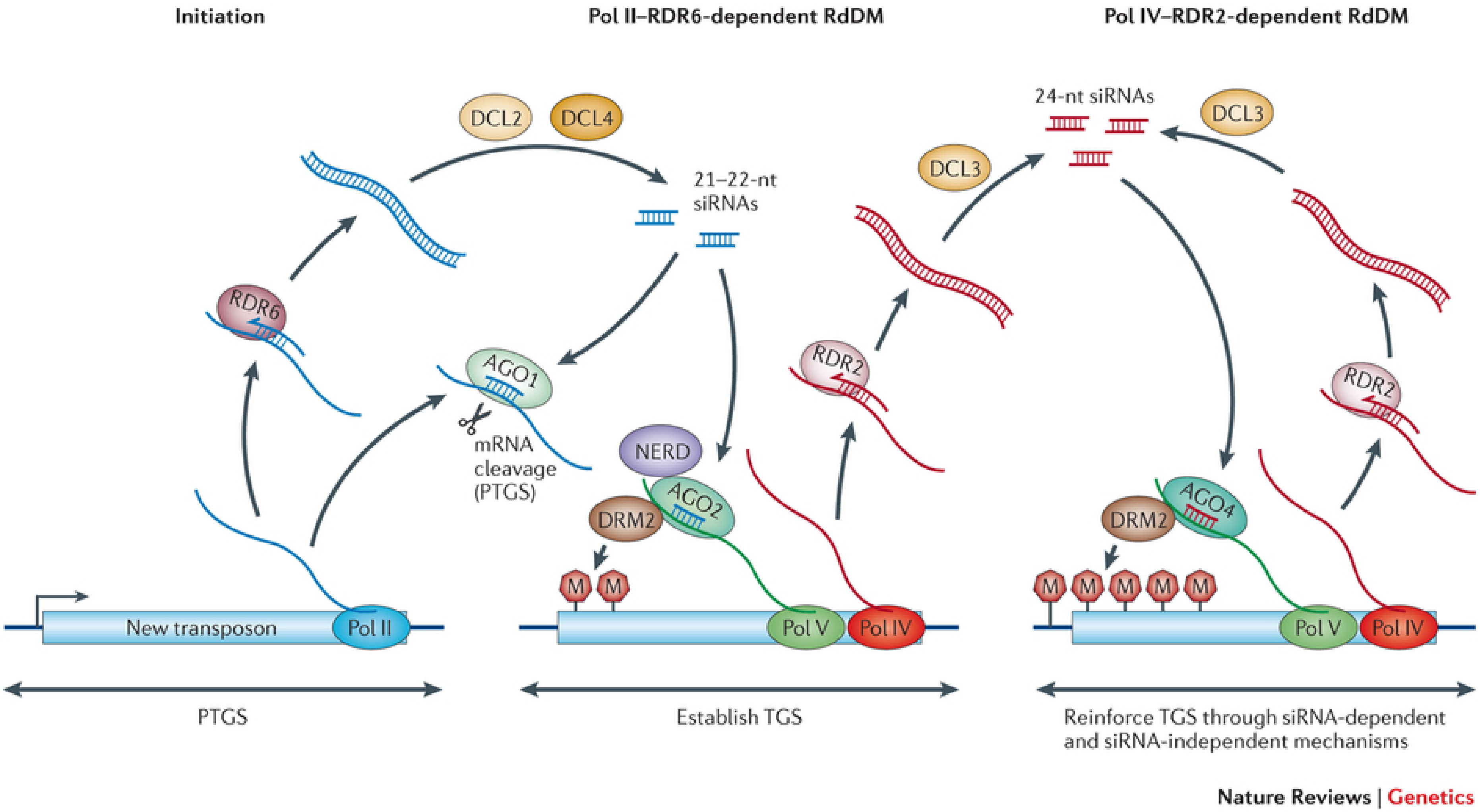


RNA-dependent RNA Polymerase (RdRP) generates double-stranded RNA

Plant-specific RNA Polymerases (IV and V) are involved in silencing

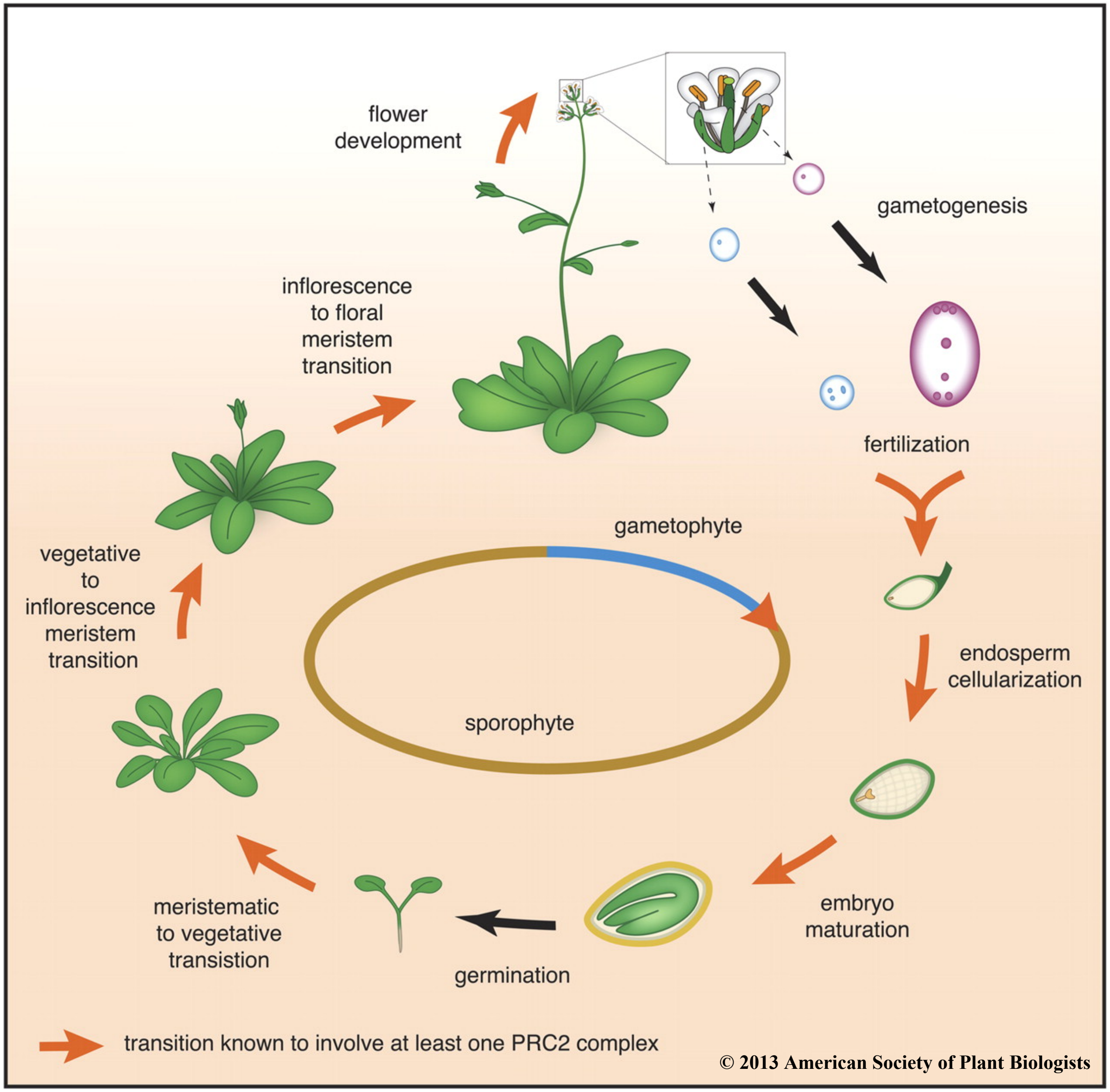
siRNA / AGO complexes interact with RNA transcripts and recruit silencing machinery

RNA-directed DNA methylation (RdDM)



Matzke & Mosher, 2014

Many developmental genes and switches are epigenetically regulated

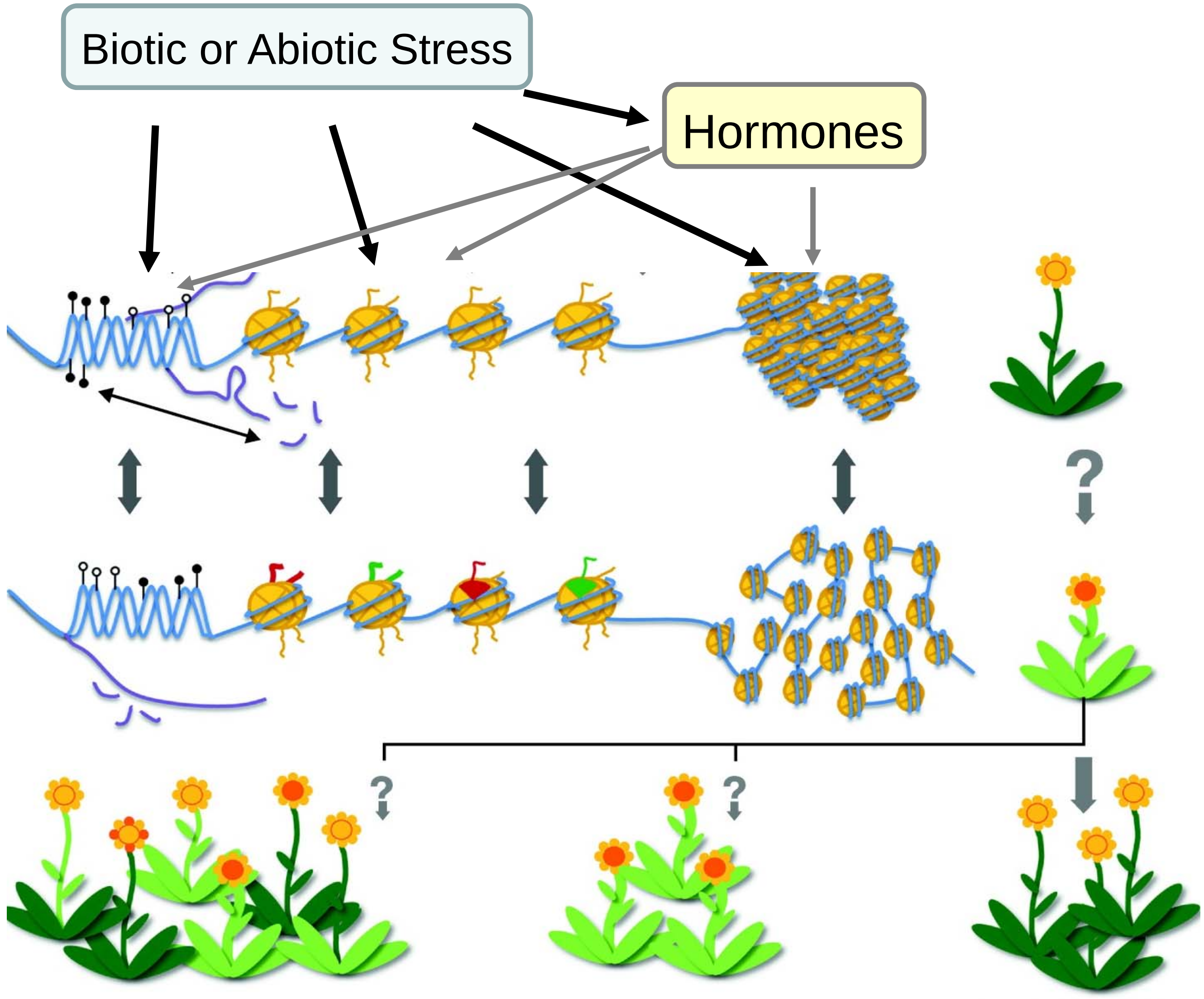


- **flowering and vernalization**
- **genomic imprinting (FWA, MEA)**
- **transposon and repetitive elements silencing and activation**

etc…

Holec, S. and Berger, F. (2012).
Plant Physiol. 158: 35-43.

Stress response, acclimation and adaptation are epigenetically regulated



Current Opinion in Plant Biology

Stress signalling may or may not involve hormones

1. Many stress-responsive genes are epigenetically regulated

2. Stress affects chromatin

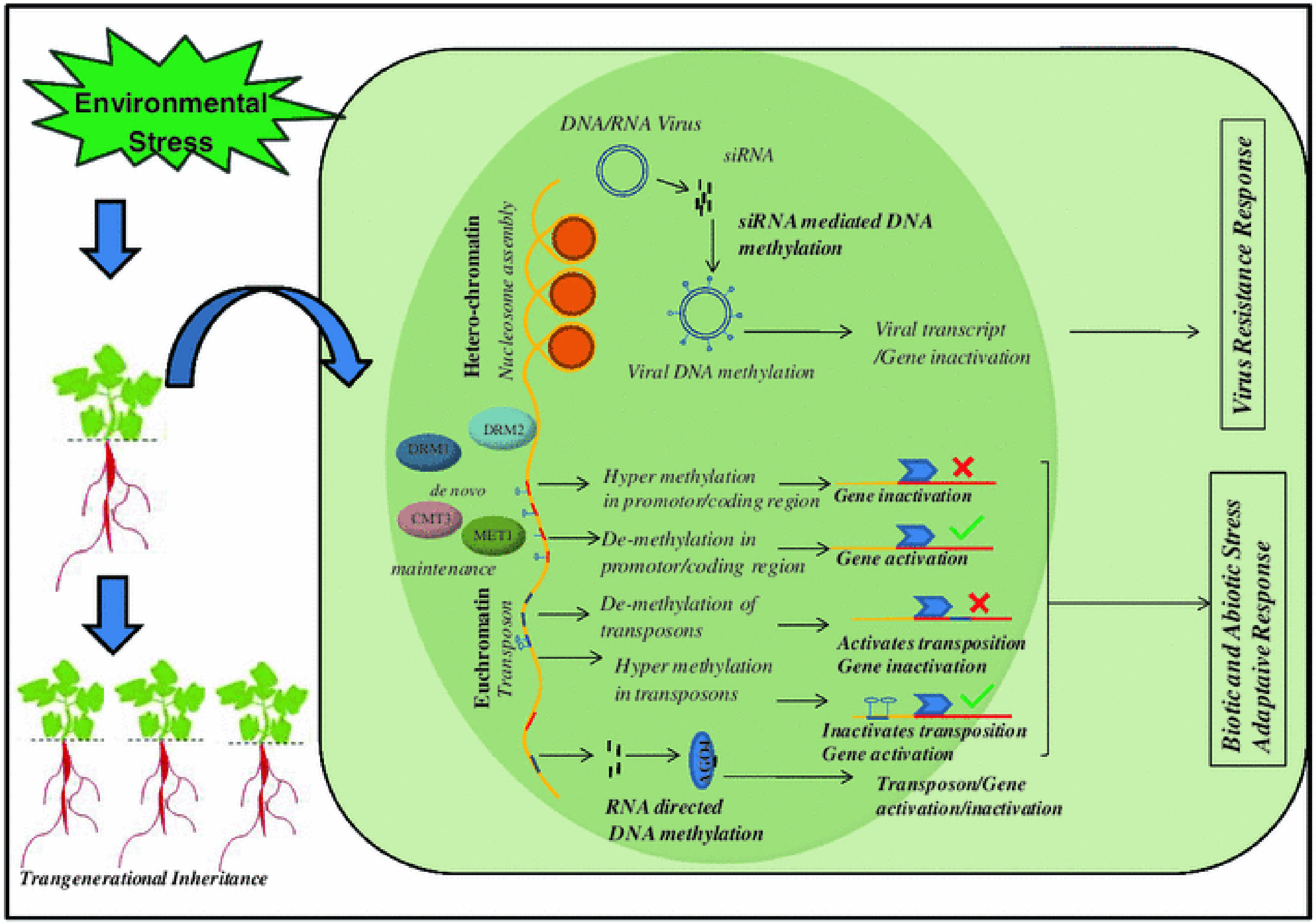
3. Heritable epigenetic changes, potential for lasting adaptation

Gutzat, R. and Mittelsten Scheid, O. (2012). Epigenetic responses to stress: triple defense? Curr. Opin. Plant Biol. 15: 568-573,

The stress-responsive phenotype is usually not transmitted to progeny, but sometimes it can be heritable, when chromatin and DNA modifications are transmissible

Stress response, acclimation and adaptation are epigenetically regulated

- Growing evidence suggest that methylation of DNA in response to stress leads to the variation in phenotype.
- Transposon mobility, siRNA-mediated methylation and host methyltransferase activation have been implicated in this process.

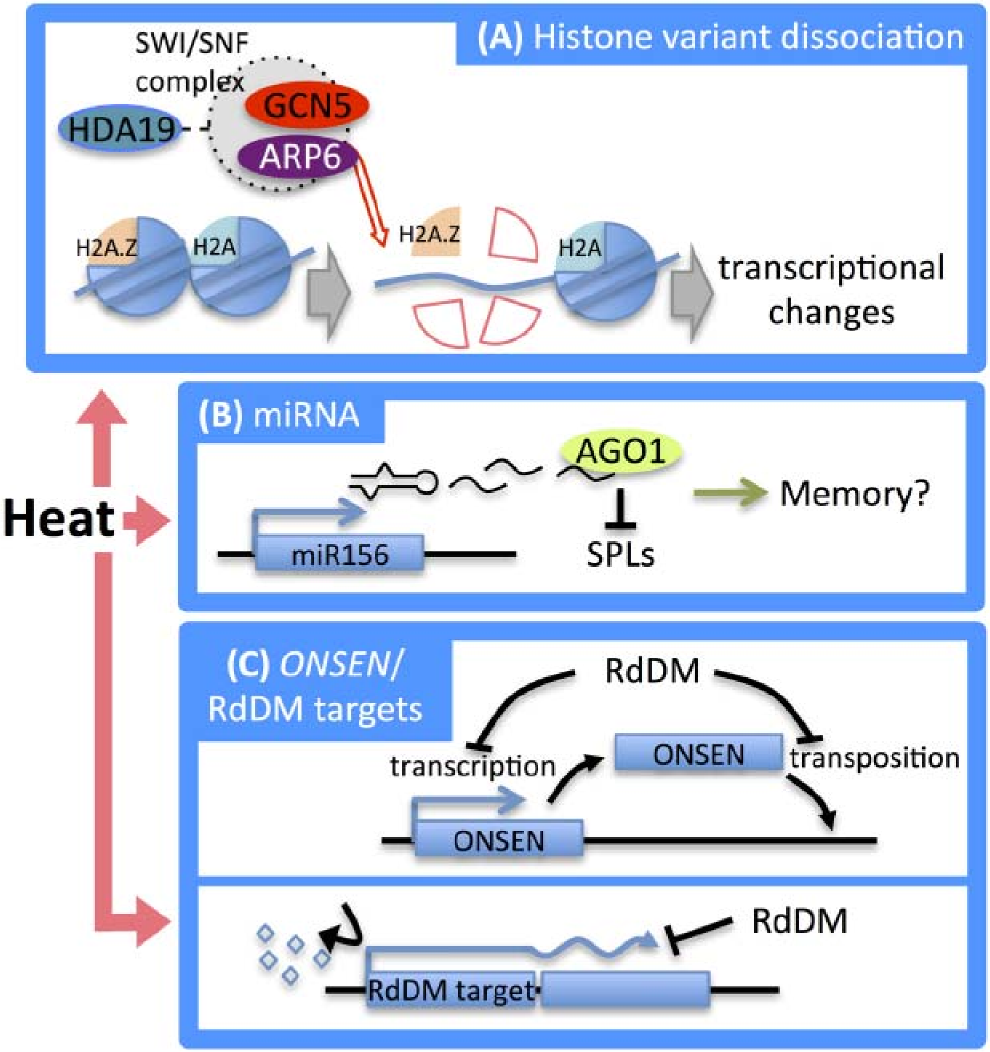


Sahu *et al.*, Plant Cell Rep, 2013

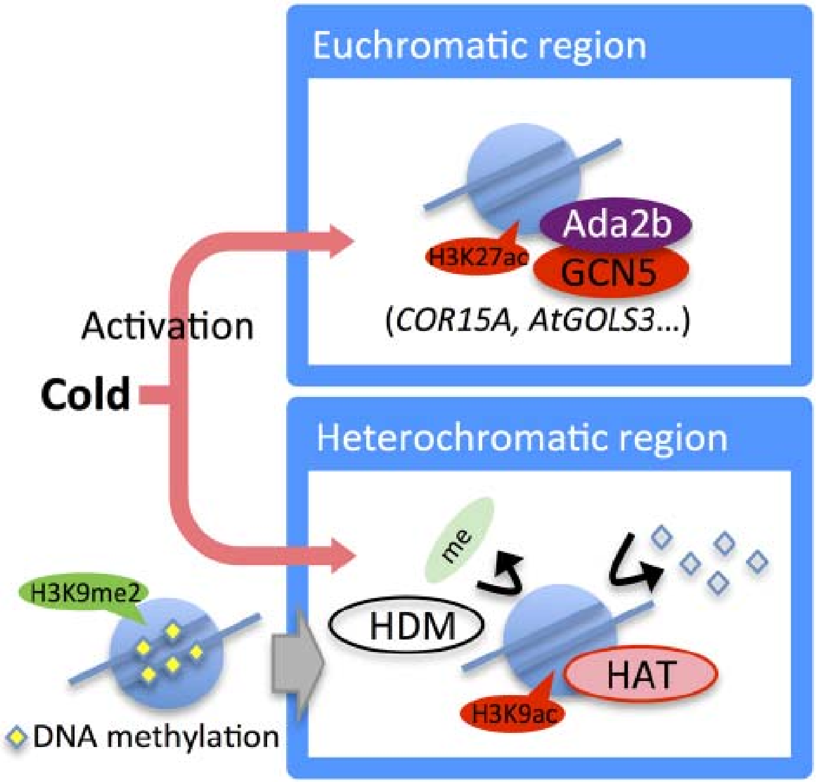
Stress response, acclimation and adaptation are epigenetically regulated

Epigenetic regulation in

the heat stress response



the cold stress response



Kim et al., Front. Plant Sci., 2015

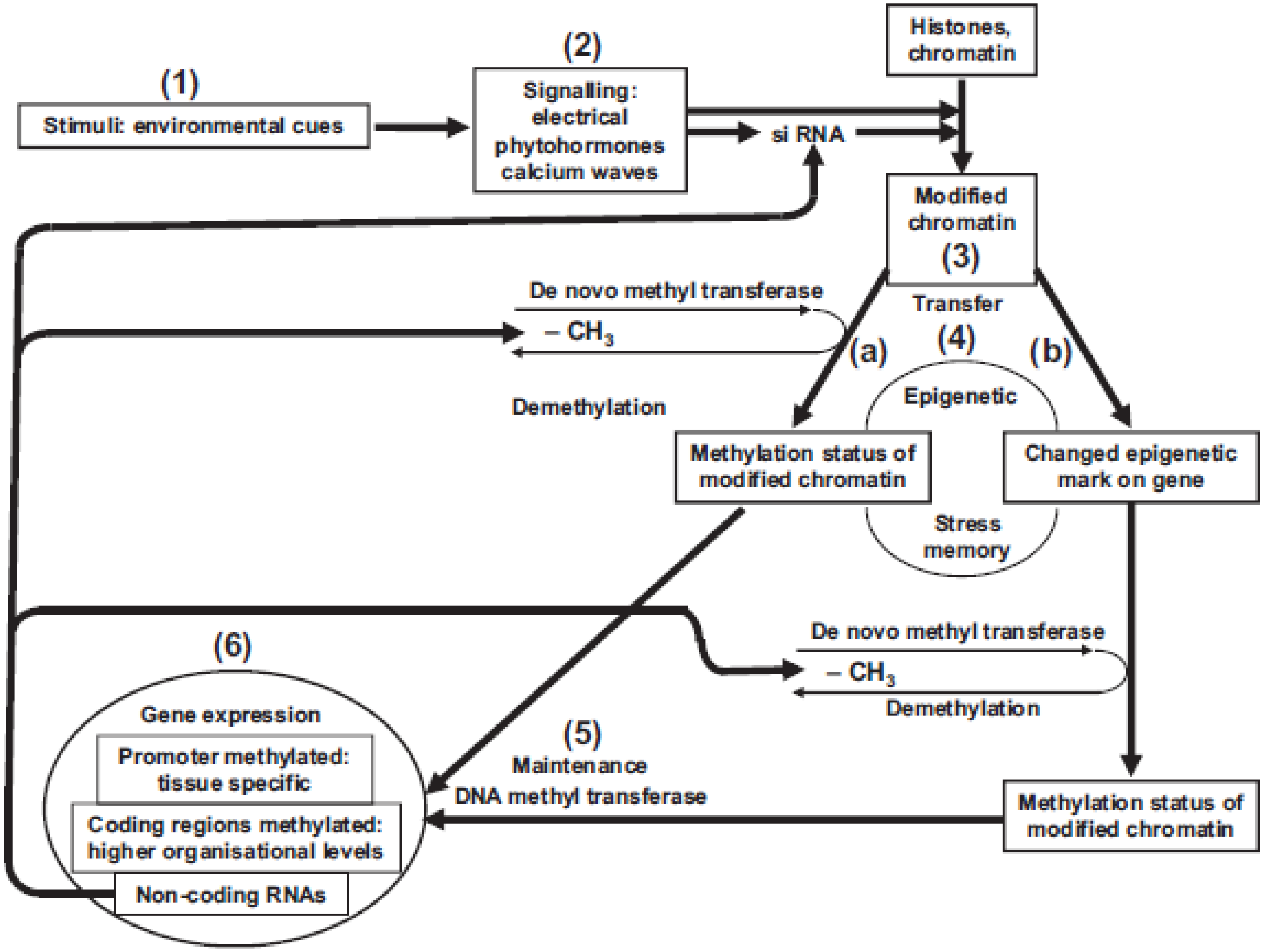
Epigenetic markers and epigenetic memory

- Chromatin and/or DNA modifications that are established or removed by a stimulus-activated gene network are defined as **epigenetic markers**, if they remain after the stimulus is removed and influence the future transcriptional behavior of associated genes
- **Stress memory** (priming) - a coordinated reaction at the organismal, cellular and gene/genome levels is thought to increase survival chances by improving the plant's tolerance/ avoidance abilities
- **Stress memory** may be a mechanism for acclimation and adaptation.
- Stable inheritable chromatin and DNA modifications can form **stress memory** that can be also called **epigenetic memory**

Epigenetic markers and epigenetic memory

Epigenetic memory defined as a **stable change in gene expression and phenotype** induced by developmental or environmental stimuli (D'Urso, Brickner, 2014)

Molecular model of epigenetic memory

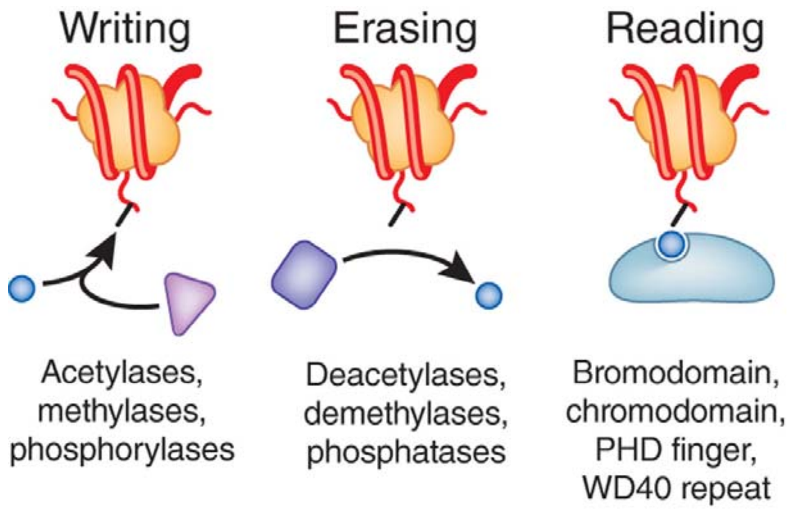


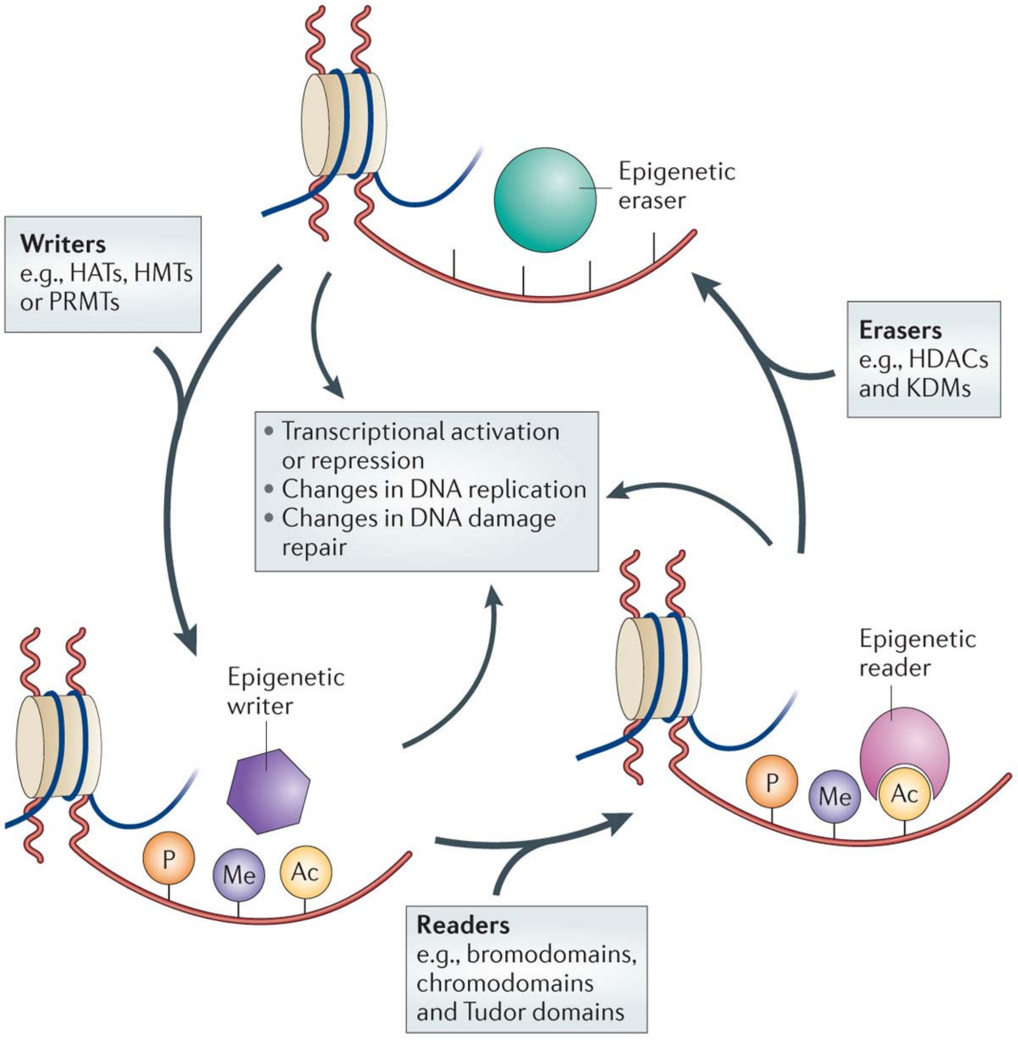
- **external and/or internal sequence specific signals**
- **“writers"**
- **“readers”**
- **“erasers"**
- **sRNA biogenesis**

Thellier & Luttge, 2012

Molecular basis of an epigenetic memory

All epigenetic-related genes can be divided into three main groups: “**writers**”, “**erasers**” and “**readers**” of epigenetic marks based on the type of epigenetic modification role





Falkenberg & Johnstone, 2014

Nature Reviews | Drug Discovery

Epigenetic memory in Norway spruce

- The temperature during zygotic embryogenesis and seed maturation shifted the growth cycle program of the embryos resulting in significant and long lasting phenotypic changes in the progeny (Johnsen et al., 2005; Skrøppa et al. 2007; Kvaalen & Johnsen, 2008; Yakovlev et al. 2012)
- The timing of the following phenologic traits was affected:
  - dehardening and bud burst in the spring
  - leader shoot growth cessation in the summer
  - bud set and cold acclimation in the autumn
- The significant global transcriptomic changes were found during development of somatic embryos of Norway spruce with the same genotype under different cultivation temperatures (Yakovlev et al. 2014):
  - clear trend of increasing of the number of upregulated genes with increasing of temperature
  - nearly half of the genes related to epigenetic regulation were differentially expressed at different growing temperatures (DNA methyltransferases, DNA demethylases, DCL1-like, Argonauts, etc.)

Epigenetic memory in Norway spruce: Conclusions

- formation of epigenetic memory during embryogenesis by different temperatures is associated with huge and characteristic transcriptional changes

- high amount of putative orthologs of epigenetic regulation-related genes involved in transcriptional changes

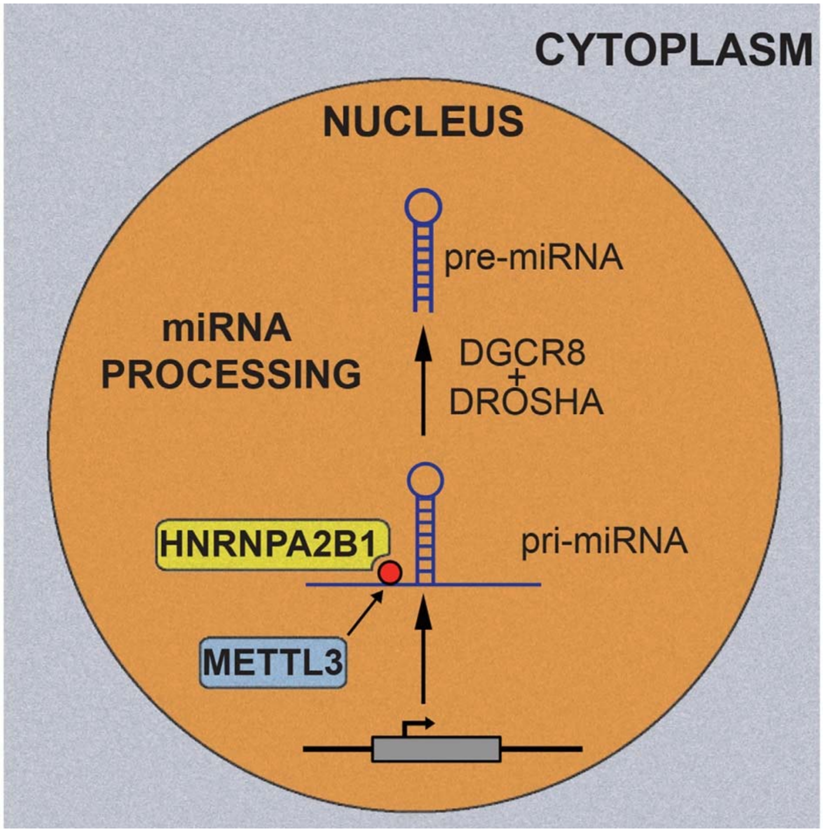
- many additional genes were found in the epigenetic regulator's gene families in spruce in comparison with orthologous gene families in *Poplar* and especially in *Arabidopsis*

- the highest amount of differentially expressed genes were epigenetic regulation genes connected with methylation markers of DNA and histones, sRNA pathways and thermosensing genes.

- thus, further work should focus on methylation dynamics of DNA and chromatin during embryogenesis

RNA methylation

- RNA also can be methylated on adenine residues in precursor microRNAs (pri-miRNAs) , a modification called N^6-methyladenosine (m^6A)
- a protein, HNRNPA2B1 binds m^6A and physically interacts with the Microprocessor protein DGCR8 in the nuclei of human cancer cell lines to mediate mRNA splicing and microRNA maturation
- mRNA splicing alterations in cells depleted of HNRNPA2B1 tightly matched the impact of METTL3 depletion, suggesting the two proteins function in a single pathway

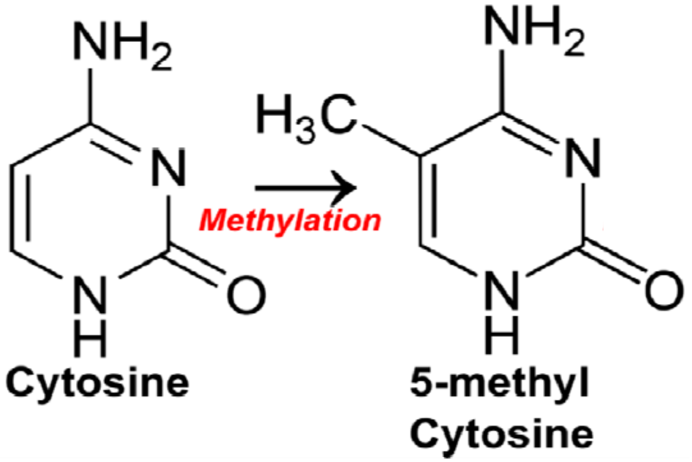


Summary

- Expression of DNA is controlled by epigenetic markers including DNA methylation, histone modifications and ncRNAs
- siRNAs contribute to epigenetic programming
- Epigenetic programming silences transposons and controls the timing of many genes that control plant development
- All epigenetic mechanisms shown to be involved in stress response and adaptation
- Epigenetic systems may act as the conduit for environmental cues initiating short- or long-term changes in gene expression in response to stress.
- It is very likely that epigenetic variation contributes to the adaptation potential of plants and, like genetic diversity, is under selection by environmental conditions

Summary

- All epigenetic mechanisms are involved in stress response and adaptation.
- Epigenetic systems may act as the conduit for environmental cues initiating short- or long-term changes in gene expression in response to stress.
- It is very likely that epigenetic variation contributes to the adaptation potential of plants and, like genetic diversity, is under selection by environmental conditions.
- DNA methylation occurs when DNA methyltransferase transfers a methyl group from S-adenosyl-methionine to cytosine in CpG dinucleotides.
- The methylation of 5' methyl cytosine (5mC) nucleotides is an important epigenetic change that regulates gene activity and impacts several cellular processes including differentiation, transcriptional control and chromatin remodeling.



There are more than 10 methods to study DNA methylation

2 main methods to study DNA methylation using sequencing:

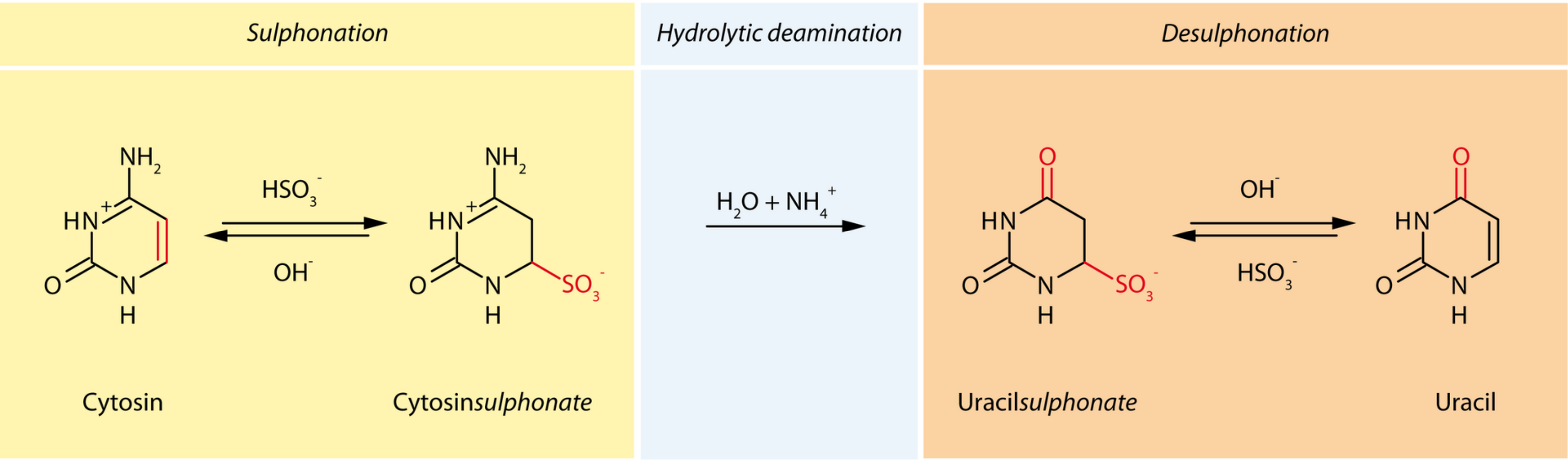
1) Bisulfite Sequencing (BS-Seq)

2) Methylation Sensitive Restriction Enzyme based Sequencing (MRE-Seq).

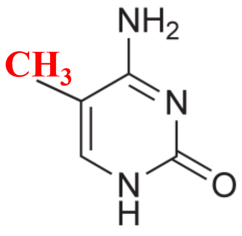
Bisulfite Sequencing (BS-Seq)

The bisulfite-mediated conversion of cytosine to uracil

Bisulfite-mediated conversion of cytosine to uracil



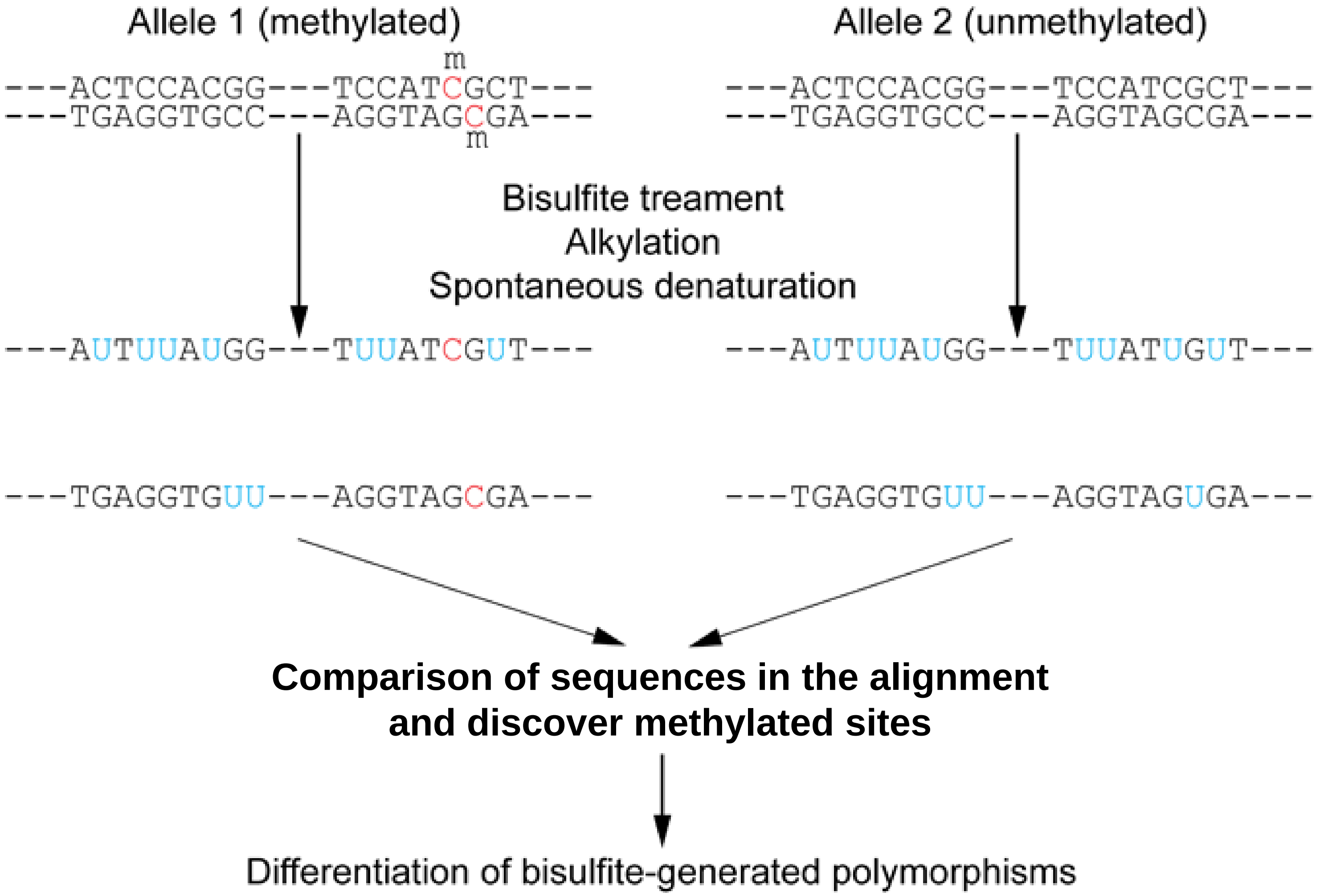
Tollefsbol T (ed.): Handbook of Epigenetics: The New Molecular and Medical Genetics. 1st edition. London, San Diego: Academic Press, 2011.



Methylcytosine

is resistant to the bisulfite-mediated conversion of cytosine to uracil

Bisulfite Sequencing (BS-Seq)



Allele 1 (methylated)

Allele 2 (unmethylated)

```
               m
---ACTCCACGG---TCCATCGCT---     ---ACTCCACGG---TCCATCGCT---
---TGAGGTGCC---AGGTAGCGA---     ---TGAGGTGCC---AGGTAGCGA---
                     m
```

Bisulfite treament
Alkylation
Spontaneous denaturation

```
---AUTUUAUGG---TUUATCGUT---     ---AUTUUAUGG---TUUATUGUT---

---TGAGGTGUU---AGGTAGCGA---     ---TGAGGTGUU---AGGTAGUGA---
```

Comparison of sequences in the alignment and discover methylated sites

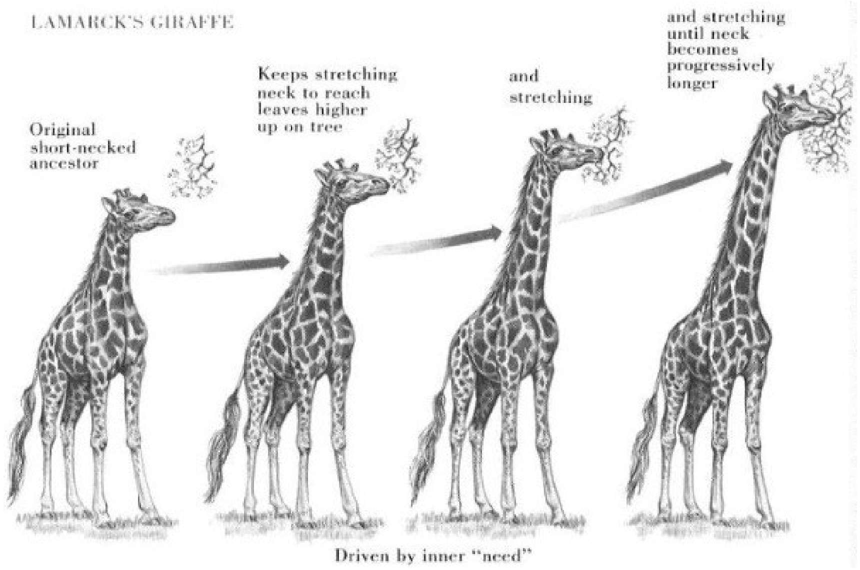
Differentiation of bisulfite-generated polymorphisms

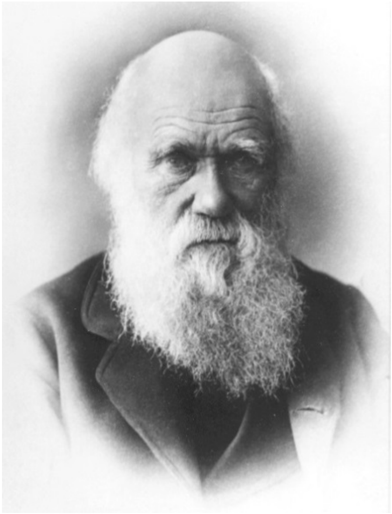
Nucleotides in **blue** are unmethylated cytosines converted to uracils by bisulfite, while **red** nucleotides are 5-methylcytosines resistant to conversion

Epigenetics, adaptation and evolution

Lamarckism vs. Darwinism

Jean-Baptiste Lamarck
(1744-1829)





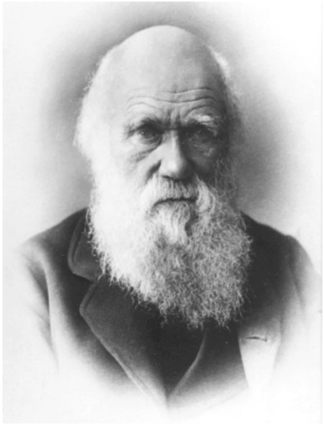
Charles Darwin
(1809-1882)

- The first evolutionary theory that internal vital force, appetency, organ practice, environmental and acquired traits explains the mechanism of evolution was proposed by Jean-Baptiste Lamarck and called „**Lamarckism**“.

- The evolutionary theory that natural selection explains the mechanism of evolution was later proposed by Charles Darwin and called „**Darwinism**“.

Epigenetics, adaptation and evolution

Lamarckism
vs.
Darwinism

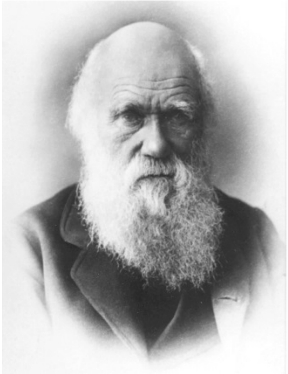


Jean-Baptiste Lamarck (1744-1829)	**Charles Darwin (1809-1882)**
1. There is an internal vital force in all organisms.	1. It does not believe in the internal vital force.
2. It considers new needs or desire produce new structures and change habits of the organism.	2. They do not form part of Darwin's natural selection theory.
3. If an organ is constantly used it would be better developed, whereas disuse of organ results in its degeneration.	3. An organ can develop further or degenerate only due to continuous variations.
4. Lamarckism does not consider struggle for existence.	4. Struggle for existence is very important in this theory.
5. All the acquired characters are inherited to the next generation.	5. Only useful variations are transferred to the next generations.
6. Lamarckism does not believe in survival of the fittest.	6. Darwin's natural selection theory is based on survival of the fittest.

Epigenetics, adaptation and evolution

**Jean-Baptiste Lamarck
(1744-1829)**

**Lamarckism
vs.
Darwinism**



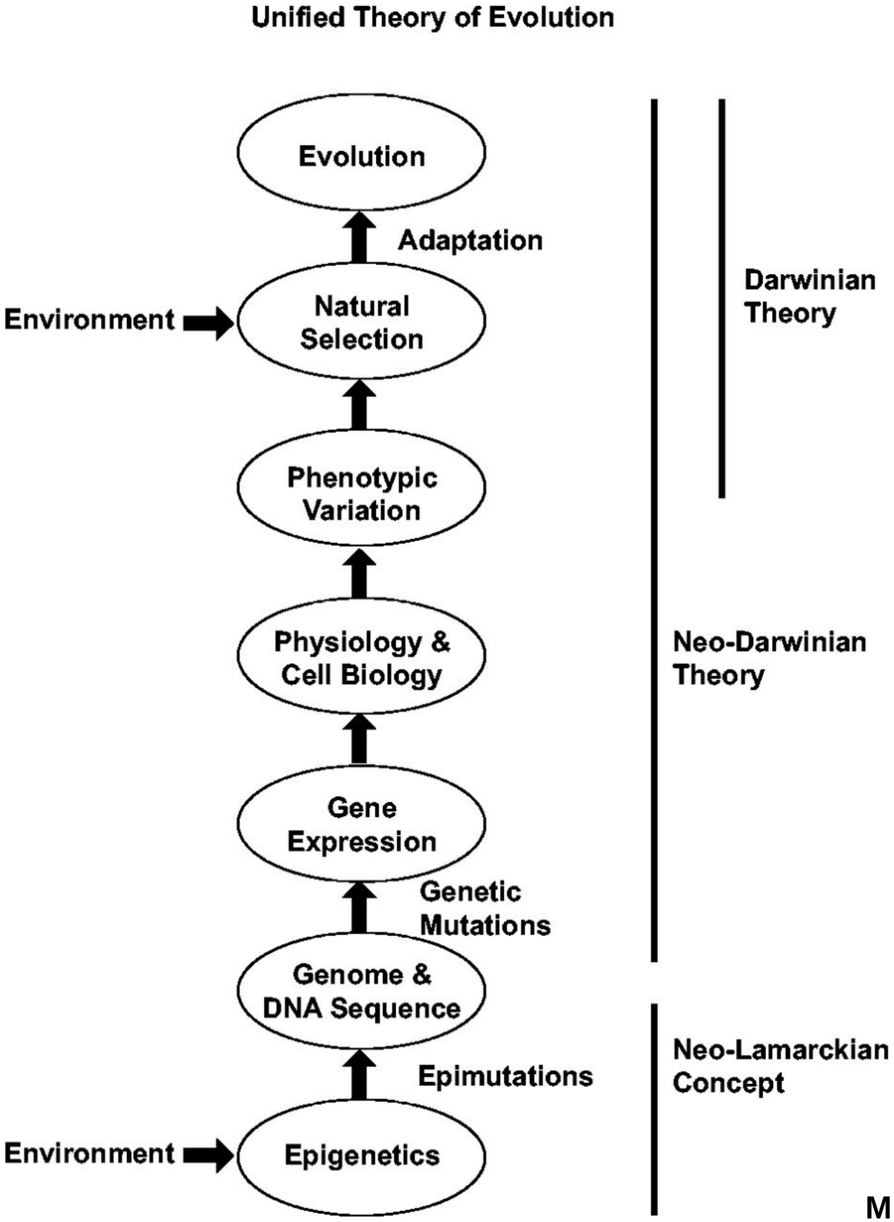
**Charles Darwin
(1809-1882)**

- Epigenetic regulation mediates adaptation to the environment by the genome lending plasticity that translates into the presenting phenotype, particularly under “mismatched” environmental conditions.

- In his book The Origin of Species Darwin wrote: “I have hitherto sometimes spoken as if the variations … were due to chance. This, of course, is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the cause of each particular variation. [The facts] lead to the conclusion **that variability is generally related to the conditions of life to which each species has been exposed during several successive generations**.”

- “Hence, both Darwin and Lamarck, two of the founders of evolutionary theory, predicted that evolution itself may favor the development of self-guiding mechanisms, maximizing variability where and when it is most likely to yield positive changes while minimizing phenotypic variability when and where it is not needed”, supporting the general idea of nonrandom evolution (Rando O. J., Verstrepen K. J. 2007. Timescales of genetic and epigenetic inheritance. Cell 128(4): 655–668.)

Epigenetics, adaptation and evolution



Unified Theory of Evolution

Evolution

Adaptation

Environment → Natural Selection

Phenotypic Variation

Physiology & Cell Biology

Gene Expression

Genetic Mutations

Genome & DNA Sequence

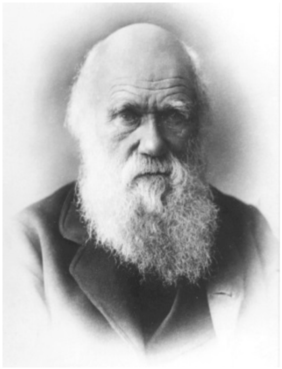
Epimutations

Environment → Epigenetics

Darwinian Theory

Neo-Darwinian Theory

Neo-Lamarckian Concept

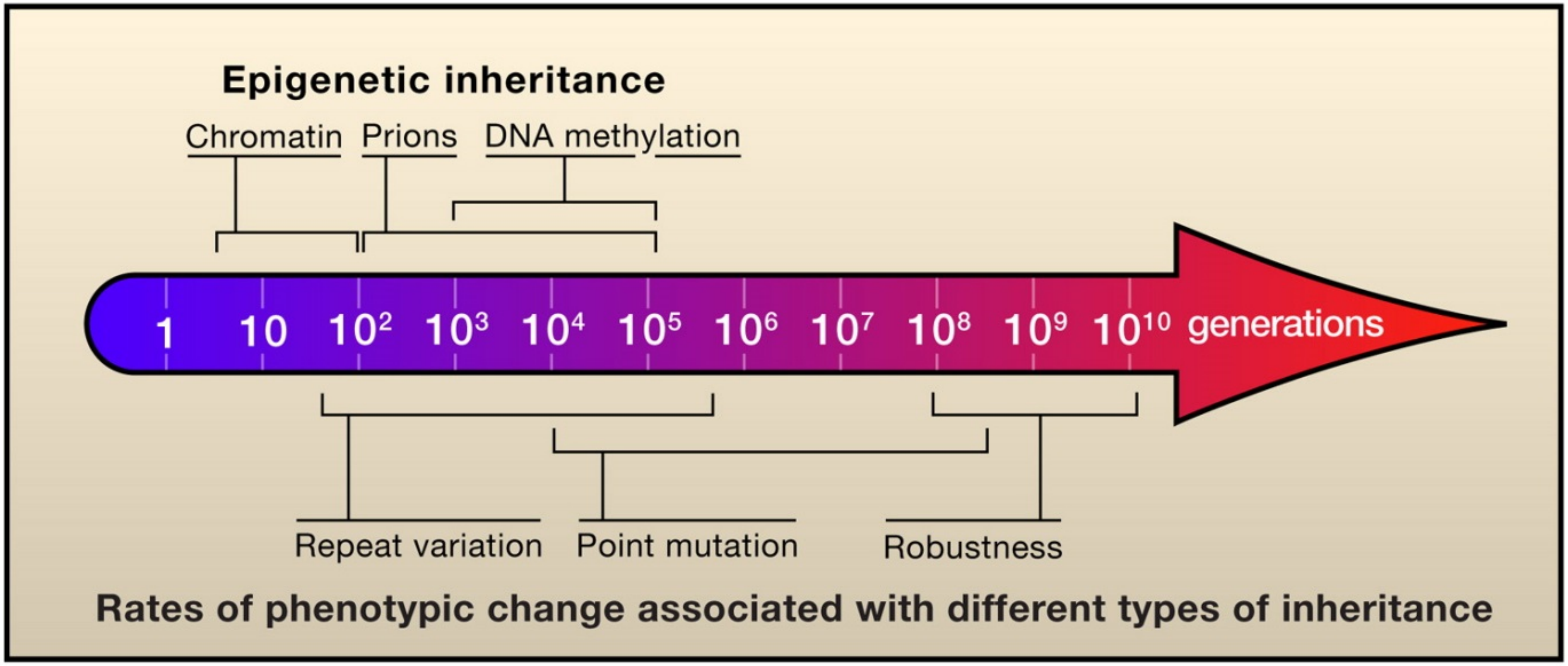


- no controversy between:
  - Lamarkism & Darwinism
  - epigenetics & genetics
  - epimutations & genetic alleles
- they both are equally important components of evolutionary theory

Michael K. Skinner Genome Biol Evol 2015;7:1296-1302

Epigenetics, adaptation and evolution

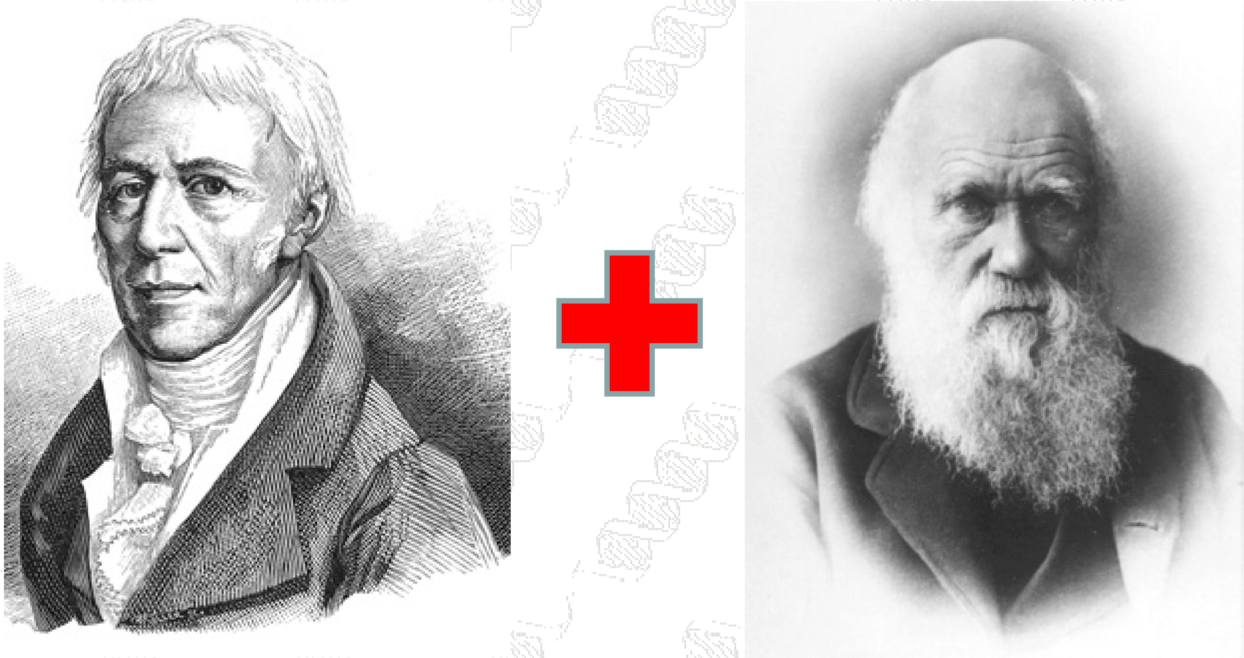
The timescales of inheritance



Rates of phenotypic change associated with different types of inheritance

- Epigenetic modifications are more fast and flexible.
- Phenotypes inherited epigenetically often exhibit rapid variation and stabilization, whereas genetically robust phenotypes are stabilized against random mutation

(Rando & Verstrepen, Cell, 2007)

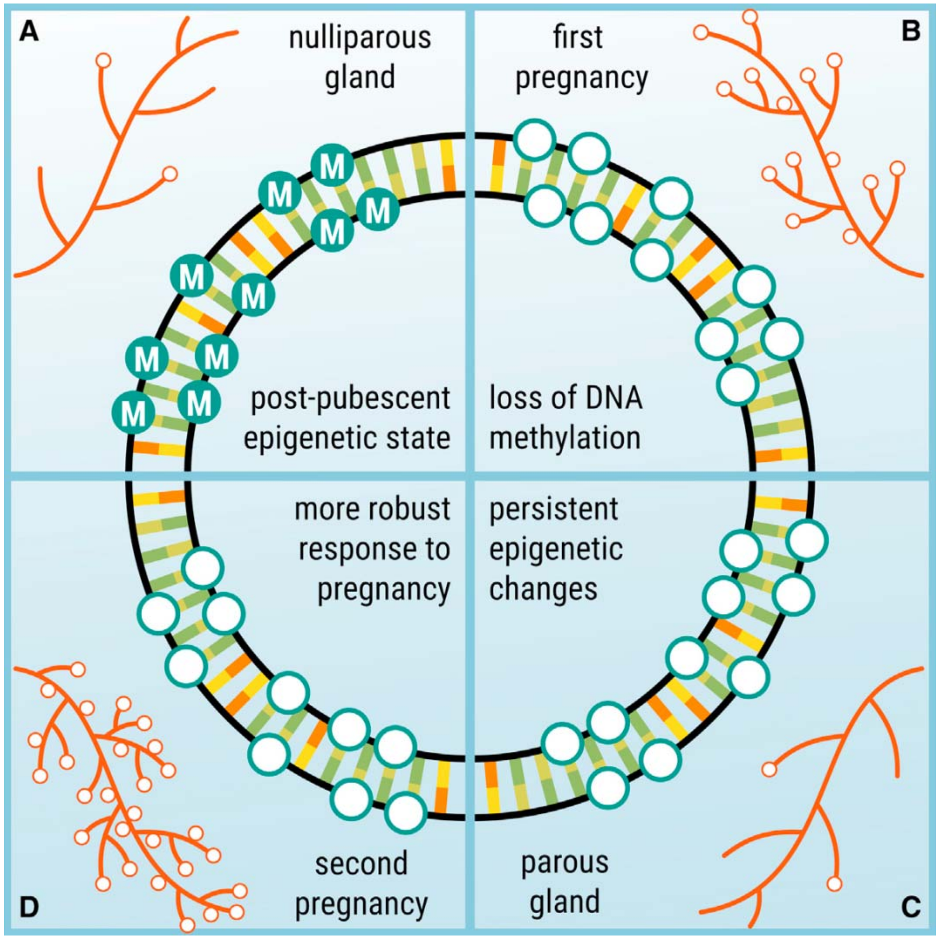


XXI century revolution in Biology:

Genomics + Epigenomics =

Grand Unified Theory of Evolution

Case study: An Epigenetic Memory of Pregnancy in the Mouse Mammary Gland



- Mammary glands from parous animals react more robustly to a subsequent pregnancy.
- This phenotype correlates with DNA methylation established during the first pregnancy cycle, the presence of which is associated with a rapid increase in gene expression of specific genes.
- Globally, these changes represent a memory of past pregnancies.

(dos Santos et al., 2015, Cell Reports 11, 1–8)

Case study: Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort

- 193 differentially methylated regions (DMRs) were identified in paternal sperm in families with autistic infants (12 months of age in offspring).
- The DMRs clustered near genes involved in developmental processes, including many genes in the SNORD family, within the Prader-Willi syndrome gene cluster.
- Epigenetic differences in paternal sperm may contribute to autism risk in offspring.
- Directionally consistent, potentially related epigenetic mechanisms may be operating in the cerebellum of individuals with autism.

(Feinberget al., 2015, Int. J. Epidemiol. Advance Access published April 14, 2015)

Case study: DNA Methylation Signatures Triggered by Prenatal Maternal Stress Exposure to a Natural Disaster: Project Ice Storm

- Five months after the 1998 Quebec ice storm women who had been pregnant during the disaster were assessed for their degrees of objective hardship and subjective distress.

- Thirteen years later, their DNA methylation profiling was investigated in T cells obtained from 36 children and compared with results obtained from the same children at age 8.

- Prenatal maternal objective hardship was correlated with DNA methylation levels in 1675 CGs affiliated with 957 genes predominantly related to immune function.

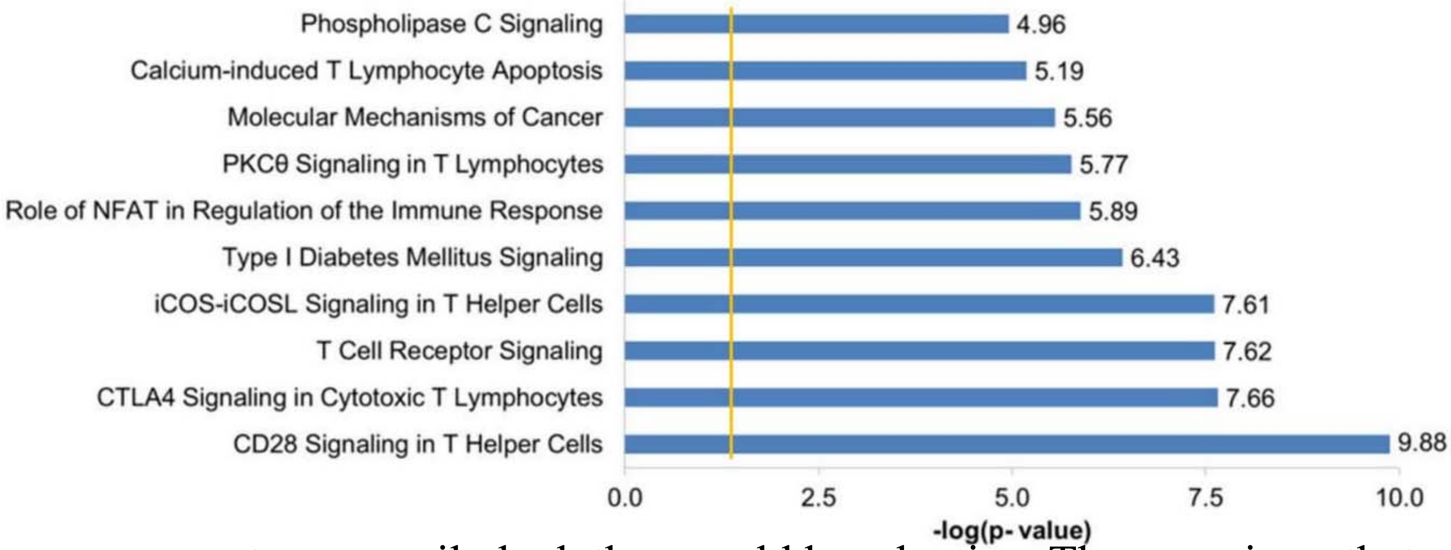
- **Prenatal maternal stress (PNMS)** results in a lasting, broad, and functionally organized DNA methylation signature in several tissues in offspring.

- Epigenetic processes may be responsible for the **PNMS** effects that predicts a wide variety of behavioral and physical outcomes in the offspring.

Cao-Lei, L., Massart, R., Suderman, M.J., Machnes, Z., et al (2014). DNA Methylation Signature Triggered by Prenatal Stress Exposure to a Natural Disaster: Project Ice Storm. PLoS One 9:9(e107653).

Case study: DNA Methylation Signatures Triggered by Prenatal Maternal Stress Exposure to a Natural Disaster: Project Ice Storm

- Genes with altered methylation patterns were clustered in immune pathways.



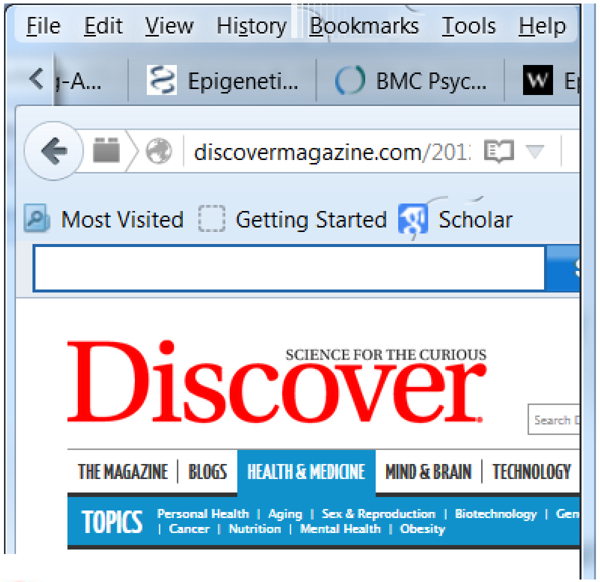
- The methylation changes are not necessarily bad, they could be adaptive. The organisms that were exposed to stress in utero could be getting ready to be exposed to stress during its life.

- It makes sense that these changes would impact the immune system, one of the body's front lines against stress.

- The researchers haven't yet looked at what these methylation changes mean for the children's immune systems, but this study provides a proof that there is some sort of causal relationship between experience and methylation years later.

- More work will be needed to determine exactly how stress hormones that cross the placenta into an embryo's bloodstream interact with pathways altering methylation.

Cao-Lei, L., Massart, R., Suderman, M.J., Machnes, Z., et al (2014). DNA Methylation Signature Triggered by Prenatal Stress Exposure to a Natural Disaster: Project Ice Storm. PLoS One 9:9(e107653).



Good Mothering

A good rat mother licks and grooms her pups. She gives them extra space to suckle against her underside.

Bad Mothering

A bad rat mother barely licks her pups and provides almost no tactile stimulation.

Grandma's Experiences Leave a Mark on Your Genes

Your ancestors' lousy childhoods or excellent adventures might change your personality, bequeathing anxiety or resilience by altering the epigenetic expressions of genes in the brain.

By Dan Hurley | Thursday, June 25, 2015

RELATED TAGS: GENES & HEALTH

Allison Mackey/DISCOVER

[This article originally appeared in print as "Trait vs. Fate"]

Darwin and Freud walk into a bar. Two alcoholic mice — a mother and her son — sit on two bar stools, lapping gin from two thimbles.

The mother mouse looks up and says, "Hey, geniuses, tell me how my son got into this sorry state."

"Bad inheritance," says Darwin.

"Bad mothering," says Freud.

http://discovermagazine.com/2013/may/13-grandmas-experiences-leave-epigenetic-mark-on-your-genes