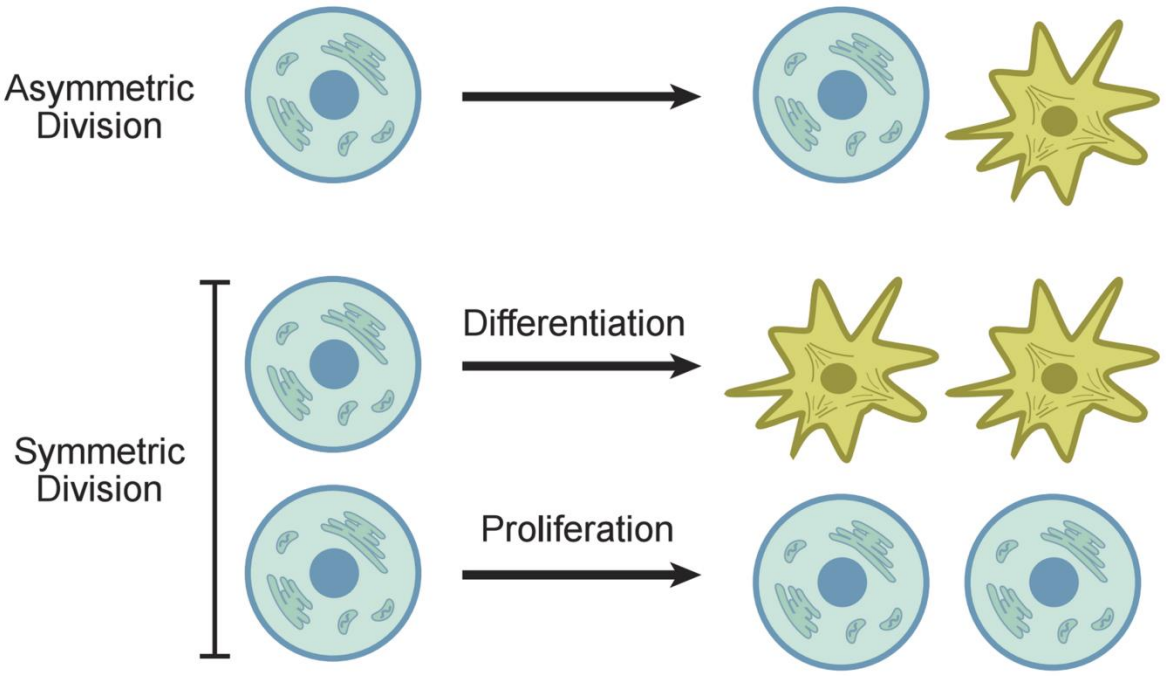
Ch 2 - L 1.2

- Mitotical inheritance of chromatin states

What happens to chromatin organization during cell division ?



establishment (programming)

maintenance

from Yang et al, 2015

Review

CellPress

Special Issue: Chromatin Dynamics

Epigenetic inheritance: histone bookmarks across generations

Textbook 2

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Multiple circuitries ensure that cells respond correctly to the environmental cues within defined cellular programs. There is increasing evidence suggesting that cellular memory for these adaptive processes can be passed on through cell divisions and generations. However, the mechanisms by which this epigenetic information is transferred remain elusive, largely because it requires that such memory survive through gross chromatin remodeling events during DNA replication, mitosis, meiosis, and developmental reprogramming. Elucidating the processes by which epigenetic information survives and is transmitted is a central challenge in biology. In this review, we consider recent advances in understanding mechanisms of epigenetic inheritance with a focus on histone segregation at the replication fork, and how an epigenetic memory may get passed through the paternal lineage.

mechanisms guiding the transmission of an **epigenetic memory** across multiple developmental stages

Mitotically inheritable
transmission of epigenetic memories by examining the most fundamental constituent of conveying information in a dividing cell, the nucleosome, with emphasis on the replication fork

Transgenerational
the complexities of inheritance across generations in multi-cellular organisms

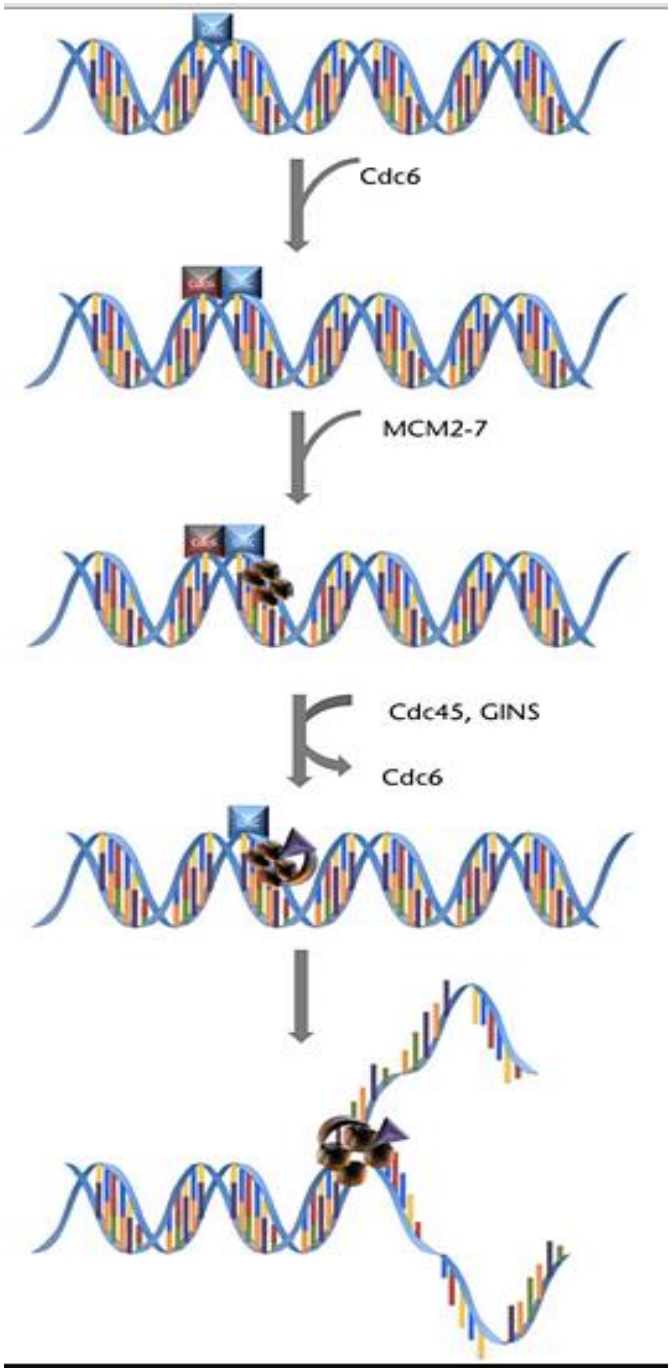
Glossary

Epigenetic inheritance: the inheritance of a phenotype in a manner that is independent of the DNA sequence and that remains self-perpetuating in the absence of the initial stimulus that caused the phenotype in the parental cell or organism.

Your textbook, 2nd paragraph

Dismantling and restoring chromatin throughout DNA replication

The post-replicative restoration of DNA methylation on the newly synthesized DNA via the maintenance DNA methyltransferase, DNMT1, is perhaps one of the better-understood examples of epigenetic inheritance (recently reviewed elsewhere [3]). By contrast, other epigenetic



DNA Replication

Mammalian origin recognition

From Smith et al., 2014

DNA Replication

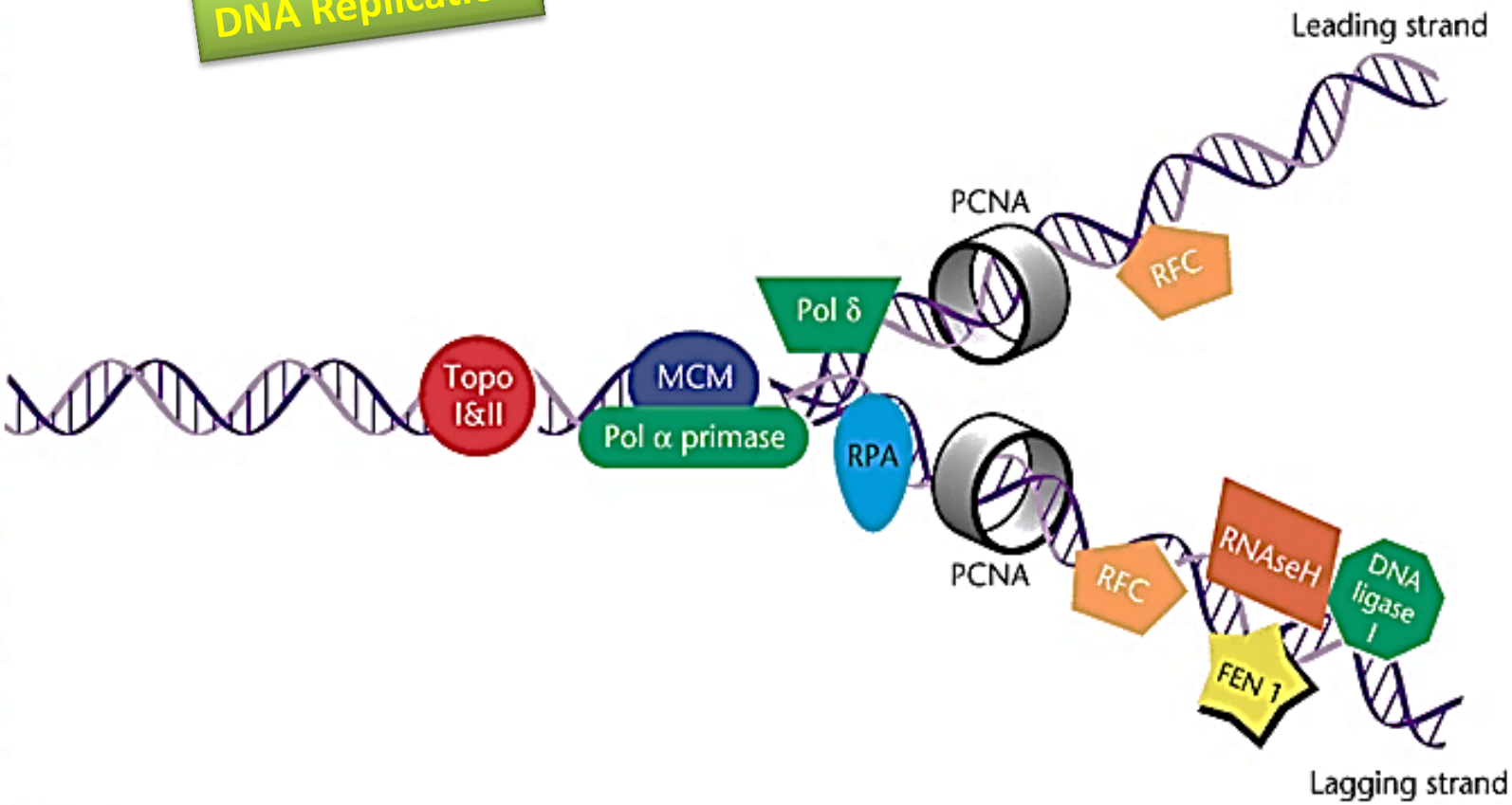
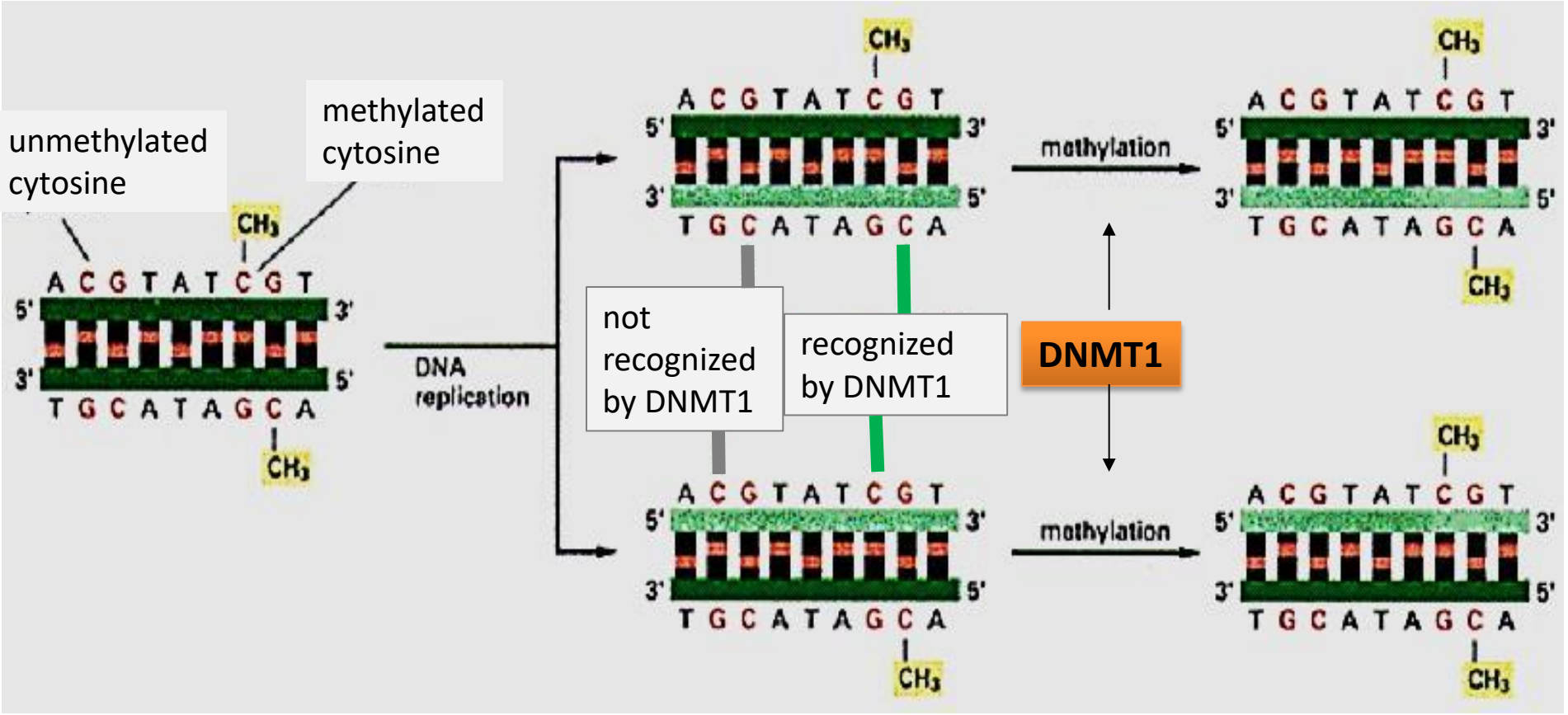


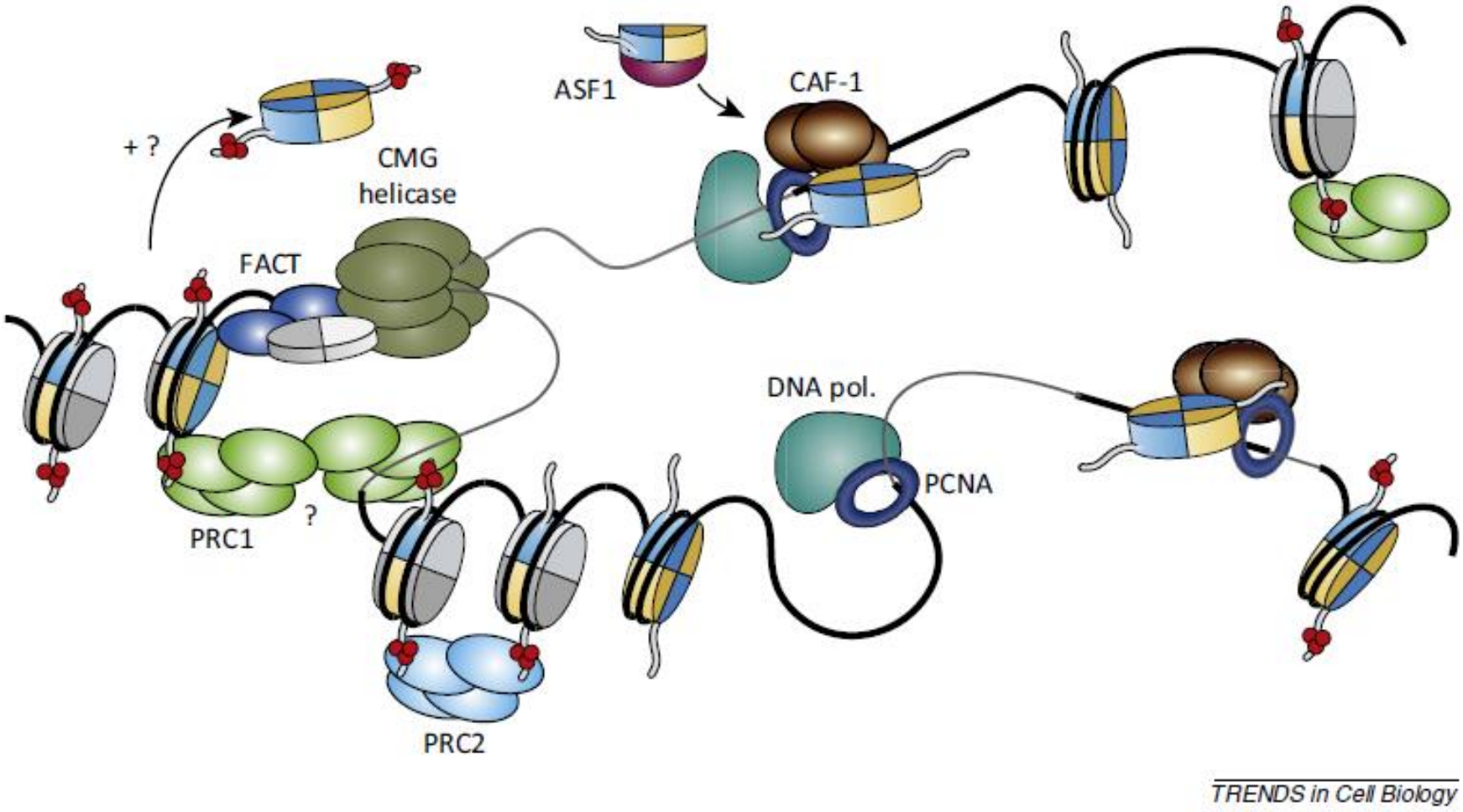
Figure 2.
Leading and lagging strand synthesis of mammalian DNA at the replication fork. After unwinding of the parental DNA, replication protein A (RPA) binds, stabilizing the DNA pol α-primase complex. Following primer synthesis, replicating factor C (RFC) loads proliferating cell nuclear antigen (PCNA) onto the leading strand. PCNA then acts as a scaffold to load polymerase δ (pol δ), continuing synthesis in the 5′→3′ direction. On the lagging strand, pol α-primase creates Okazaki fragments, which are extended by pol δ. When these fragments converge, a single-stranded flap is formed. This flap is then cleaved by flap endonuclease 1 (FEN1) and ribonucleic acidase (RNAse H). The resulting nick is sealed by DNA ligase 1.

Smith, SJ, Li, CM, Hickey, RJ, and Malkas, H(Nov 2014) DNA Replication: Mammalian.
In: eLS. John Wiley & Sons Ltd, Chichester. http://www.els.net [doi: 10.1002/9780470015902.a0001041.pub3]

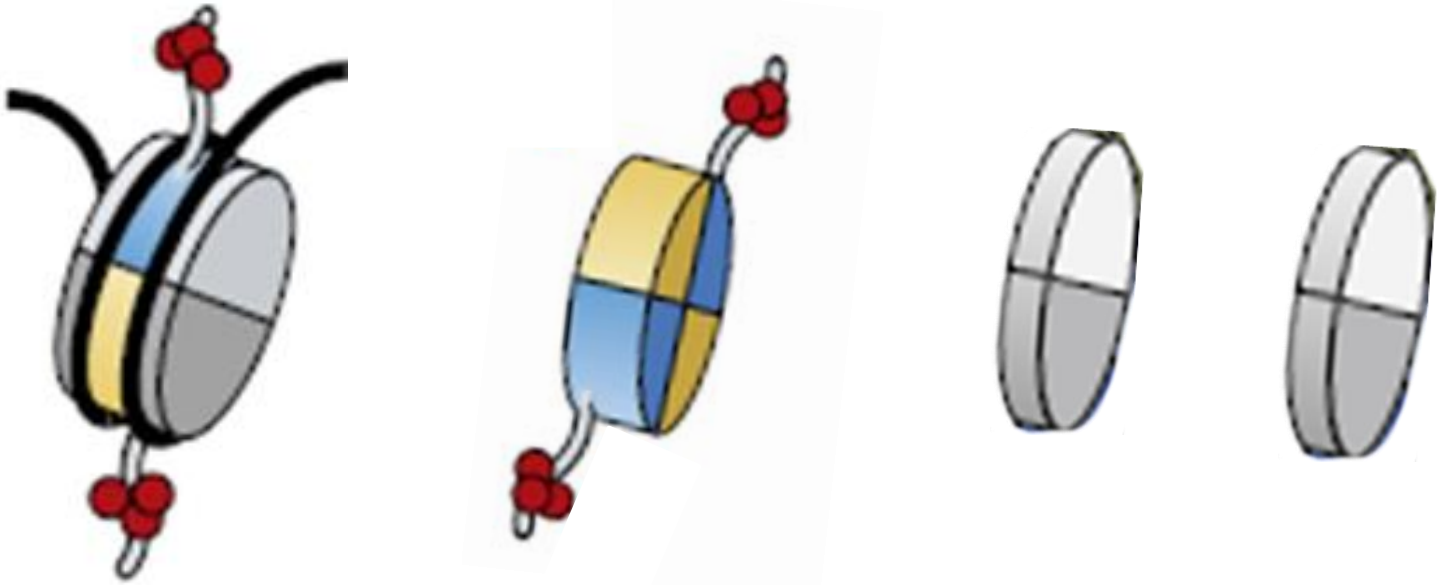
DNA CpG methylation is propagated at cell division using a very simple mechanism: DNMT1 is a methylation-dependent cytosine methyl transferase.



considering nucleosomes ….



Nucleosome octamer dissociation at the replication fork



Octamer

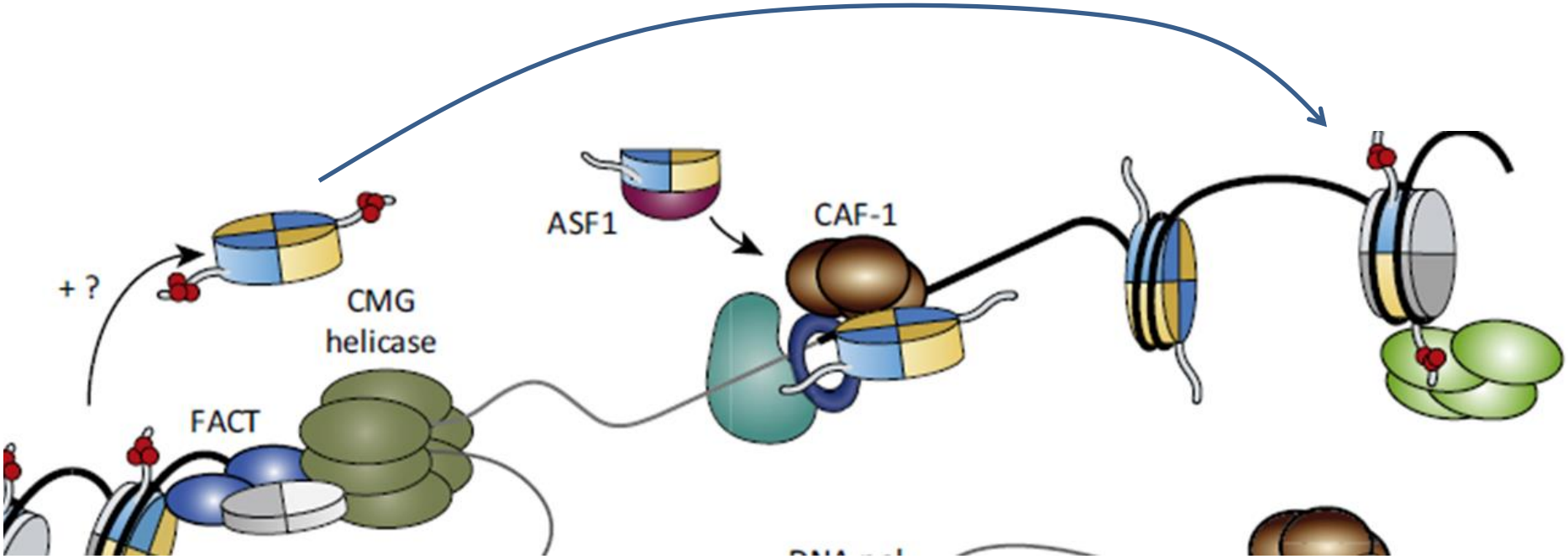
H3-H4 tetramer

H2A-H2B dimers

Histome PTNs are maintained in dissociated histones

H3-H4 tetramer immediately reassembles after the replication fork has passed, followed by 2x H2A-H2B dimers addition .

Histones **redistribute equally** to the daughter strands, so that new histones should be synthesized and incorporated. H3-H4 dimers arrive carried by ASF, then CAF-1 chaperones tetramer formation.



H3.1 and H3.2 are the replication-dependent H3 isoforms, whereas H3.3 is incorporated post-replicationally.

ASF1 (anti-silencing factor 1) is the carrier for all isoforms, but it binds primary to newly synthesized H3/H4 dimers, avoiding formation of H3/H4 tetramers.

ASF-1 interacts also with

- RFC replicative clamp loader (clamp is PCNA, the ring in figures)
- MCM subunits of replicative Helicase (CMG)

ASF/1 delivers H3/H4 to CAF/1 (Chromatin Assemly Factor chaperone), then tetramers are transferred to DNA.

Two competing models for H3-H4 redistribution:

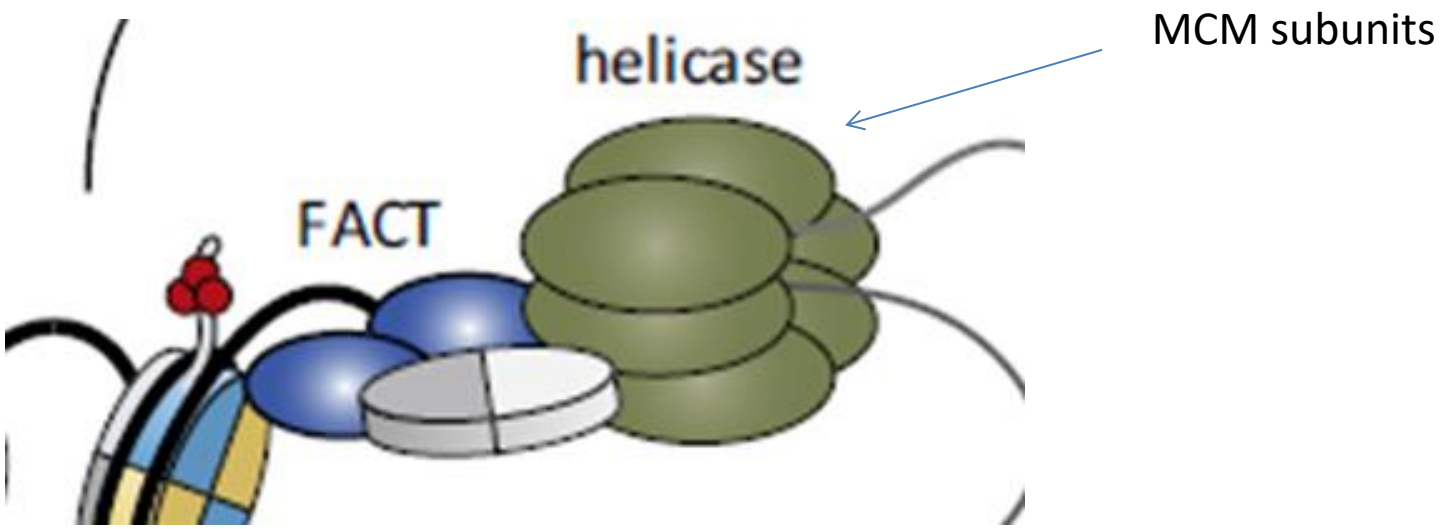
Splitting model:

ASF1 may split H3-H4 tetramer in two and distribute equally

Random tetramer model:

ASF1 distribute randomly tetramers

The **latter** is favoured today, since PTMs are non symmetrical in the two half-tetramers, whereas the PTMs are indeed conserved equally after replication in the two daughter chromatin molecules.



FACT is histone chaperone: it interacts mainly with H2A-H2B dimers and dissociates them from the core. MCM also interacts with H2A-H2B.

MCM mutants unable to interact with H2A-H2B show defects in telomeric heterochromatin.

Thus, this interaction possibly plays a role in correctly passing on PTMs-containing histones equally to daughter chromatin molecules.

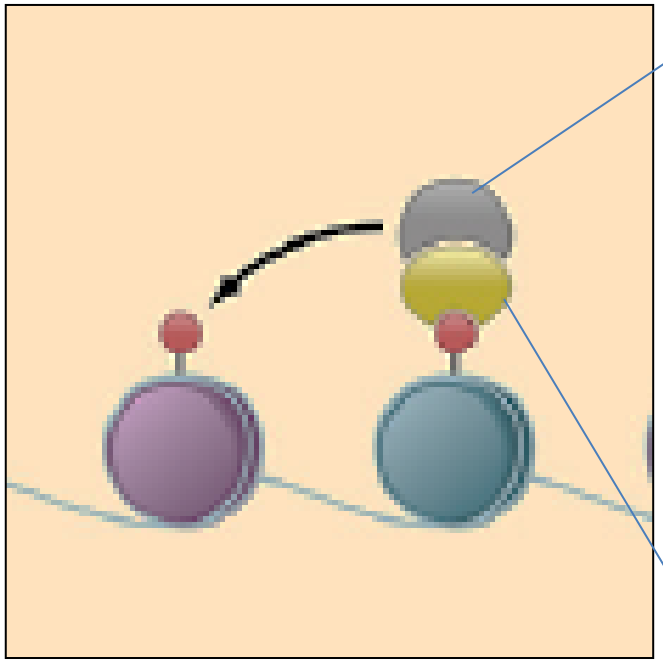
Of course, this kind of mechanism is fully compatible with the observation that chromatin domains are quite conservatively inherited by the two daughter cells after mitosis.

Copying mechanisms rely on protein complexes that contain Writers / Readers / Eraser systems

as examplified in the case of PCR2 and HP1-Suv39H1/2 complexes

maintenance

The R/W/E complex model



Moazed 2011, Cell, 146:510-8

first

The **HP1 – Suv39H1 – HDAC1** complex in **fission yeast**

Swi6 (HP1) possesses a chromodomain that is a «reader» of H3K9me2/3

Swi6 (HP1) interacts with Suv39H1

Suv39H1 and Suv39H2 are enzymes that methylate H3K9

Swi6 (HP1) also interacts with HDAC1 or SIRT1

The same in Mammals
with different names and components

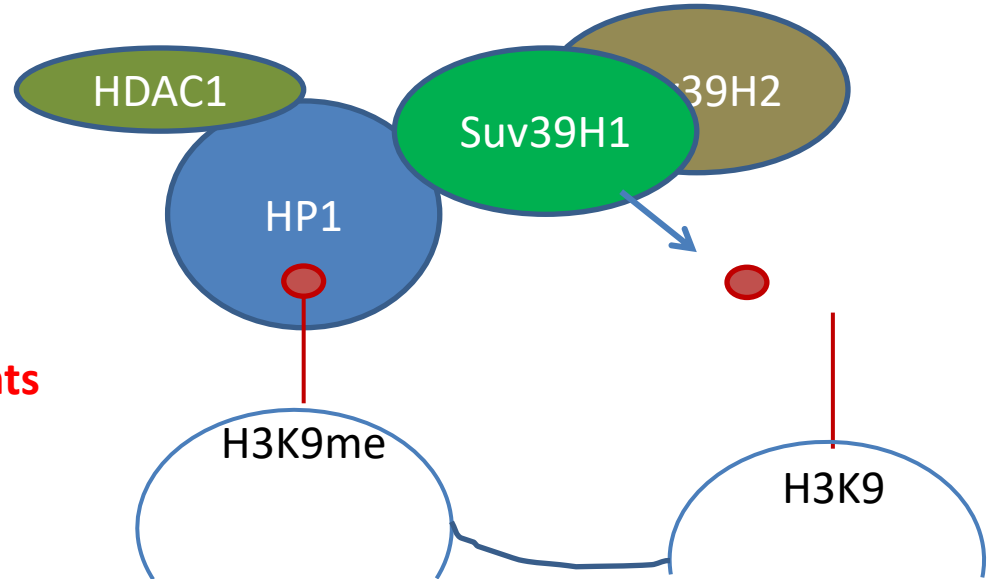
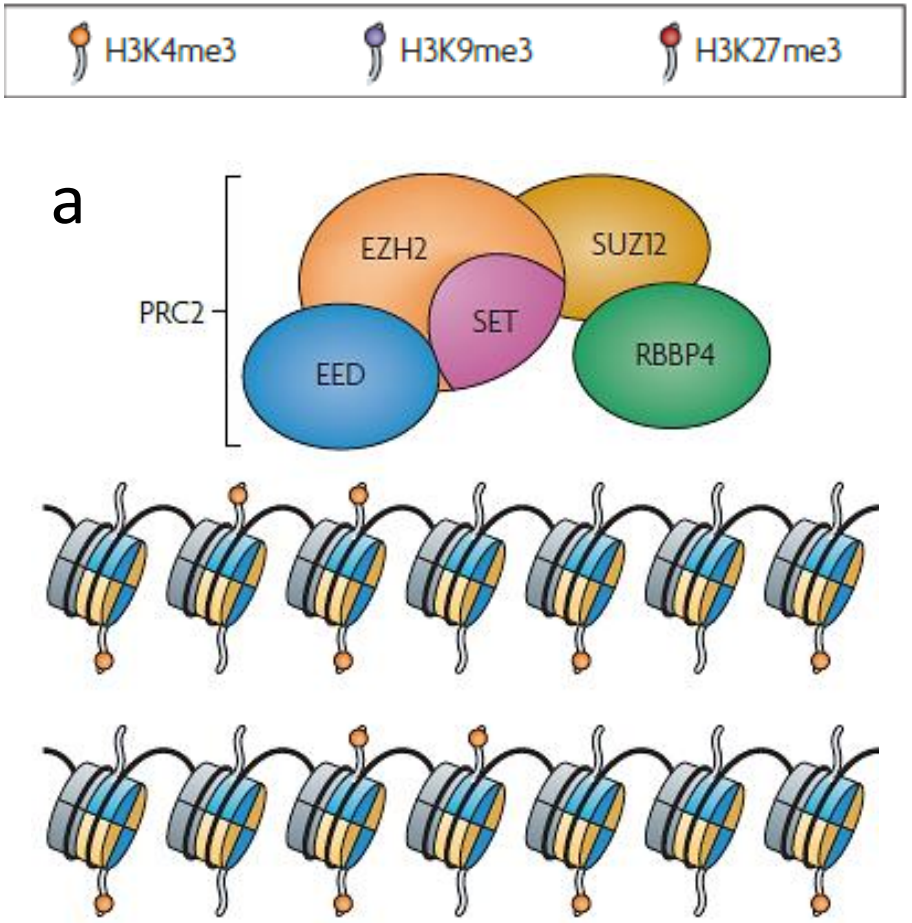


Figure 4 | **Propagation of histone 3 lysine 27 trimethylation by polycomb repressive complex 2.**
This scheme shows how pre-existing histone methylation marks regulate the polycomb repressive complex 2 (PRC2)-mediated spread of histone 3 lysine 27 methylation (H3K27me). For simplicity, only one type of histone methylation is presented for each domain, although *in vivo* there might be combination of these marks. Importantly, this scheme does not consider the recruitment of PRC2.
The components of PRC2 are indicated. Three examples are envisioned.

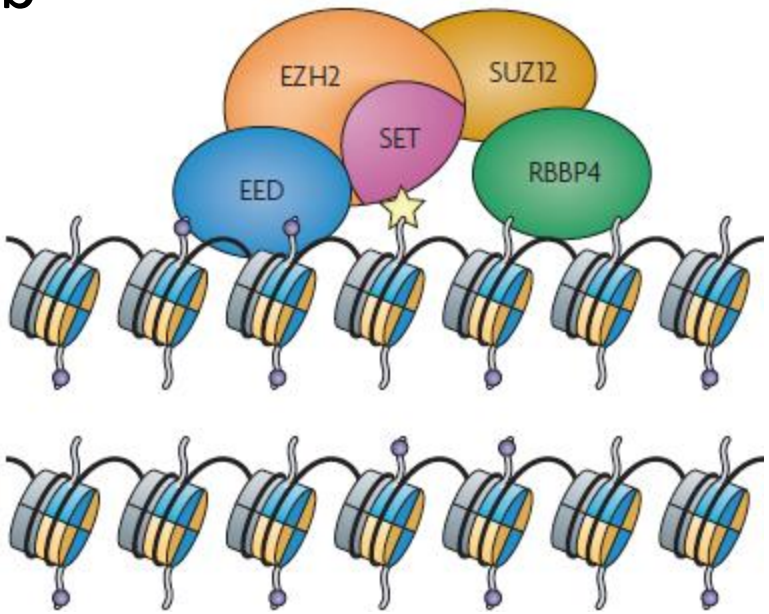
a A chromatin domain is enriched for an 'active mark' — such as H3K4 trimethylation (H3K4me3) — that is not recognized by PRC2 and therefore H3K27 is **not** methylated.



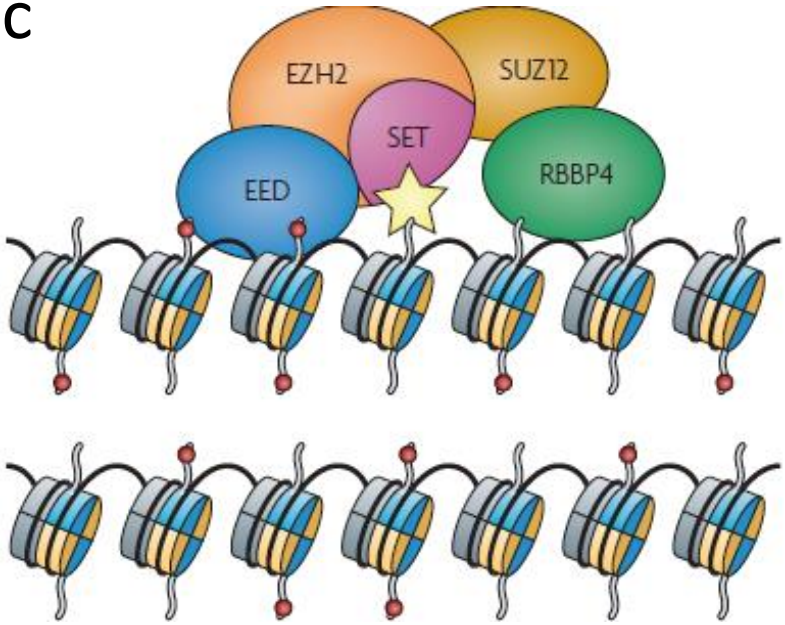
EED, embryonic ectoderm development;
EZH2, enhancer of zeste homologue 2;
RBBP4, retinoblastoma binding protein 4;
SUZ12, suppressor of zeste 12.

Margueron & Reinberg, Nature Rev Genet. 2010, 11:285-98

b



c



b | A chromatin domain is enriched for repressive marks — such as H3K9me3 (shown), H1K26me3 or H4K20me3 (not shown) — that are recognized by PRC2, but the enzymatic activity of PRC2 is only modestly increased (small yellow star).

c | A chromatin domain is enriched for **H3K27me3**, which is recognized by PRC2 and stimulates a robust increase in its enzymatic activity (large yellow star).

EED, embryonic ectoderm development; EZH2, enhancer of zeste homologue 2; RBBP4, retinoblastoma binding protein 4; SUZ12, suppressor of zeste 12.

Margueron & Reinberg, Nature Rev Genet. 2010, 11:285-98

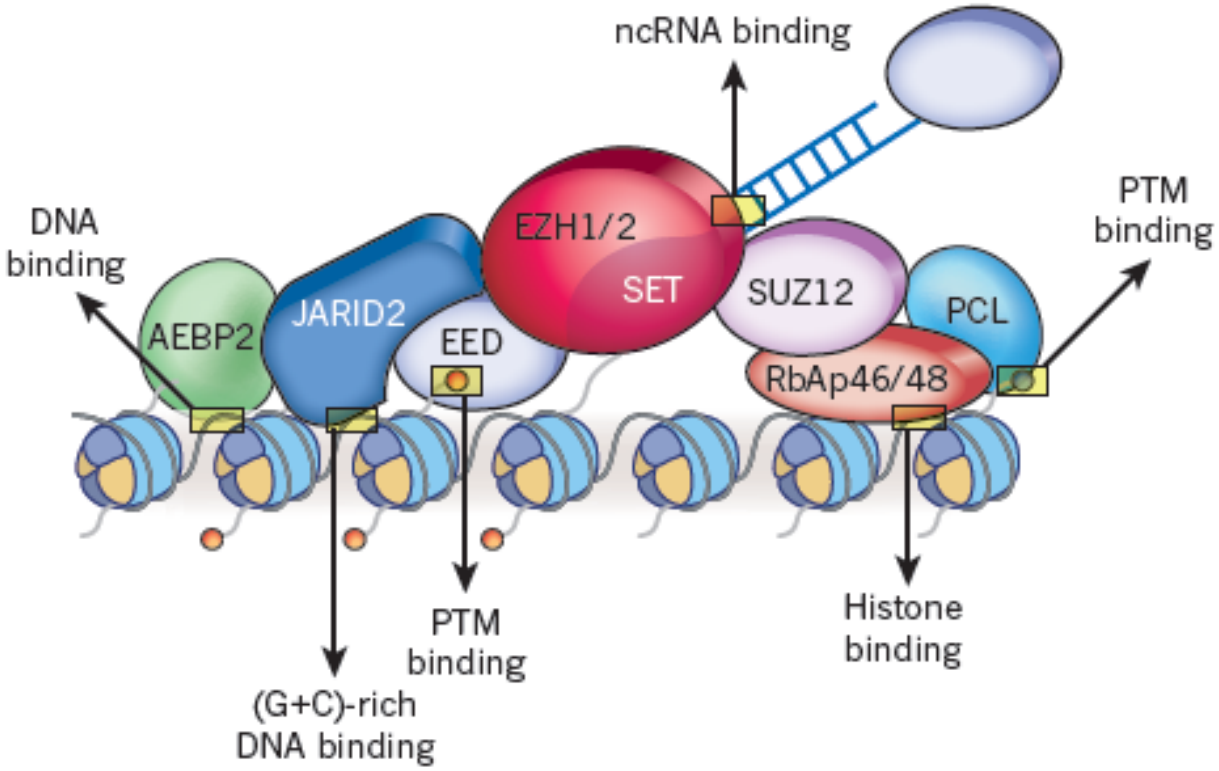
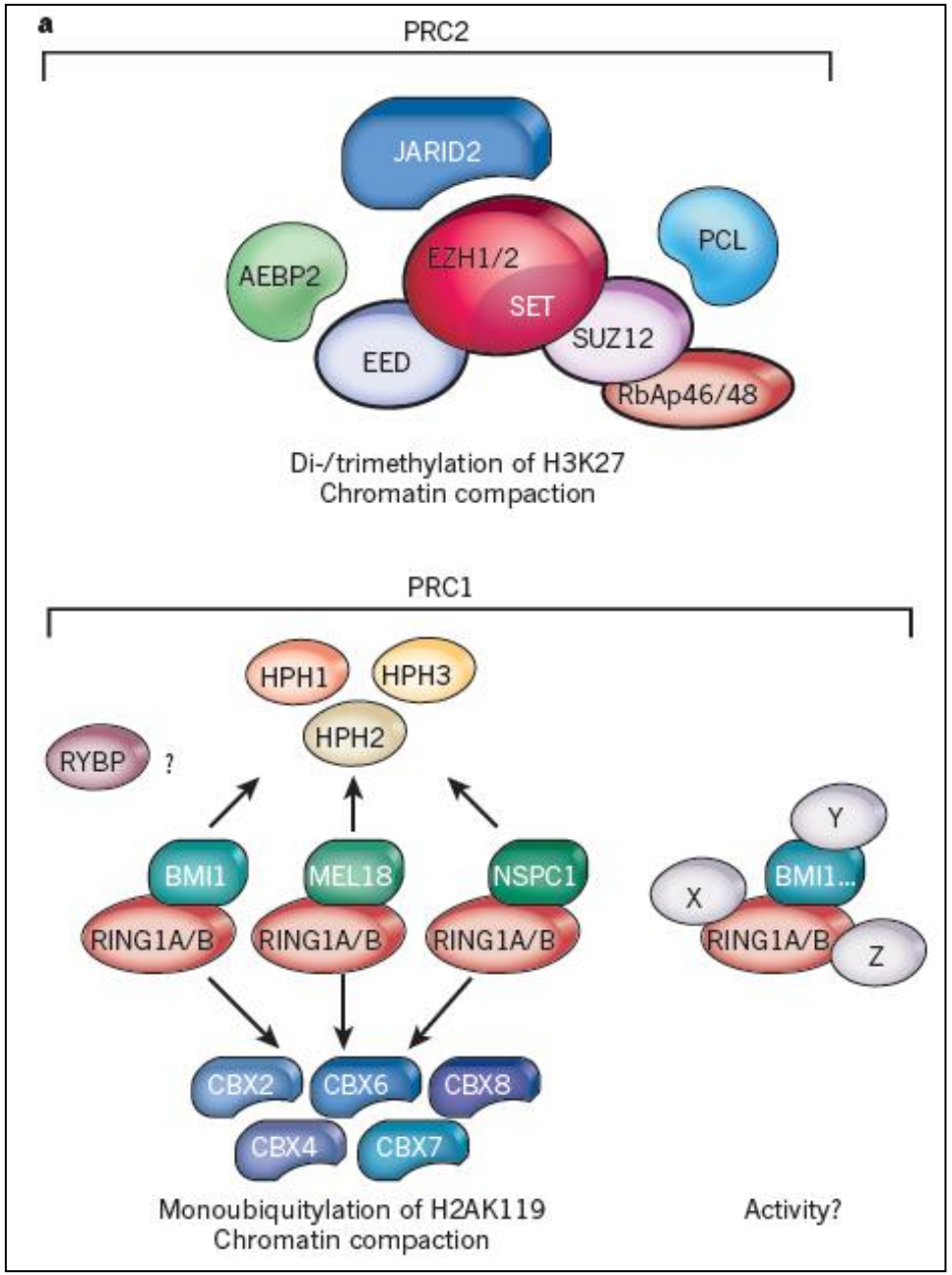


Figure 3 | The many interactions of PRC2 with chromatin. Schematic representation of the PRC2 holoenzyme at chromatin. Putative interactions with either DNA or histones that could explain PRC2 recruitment are highlighted.

From Margueron & Reinberg (2011) Nature 469: 343-49

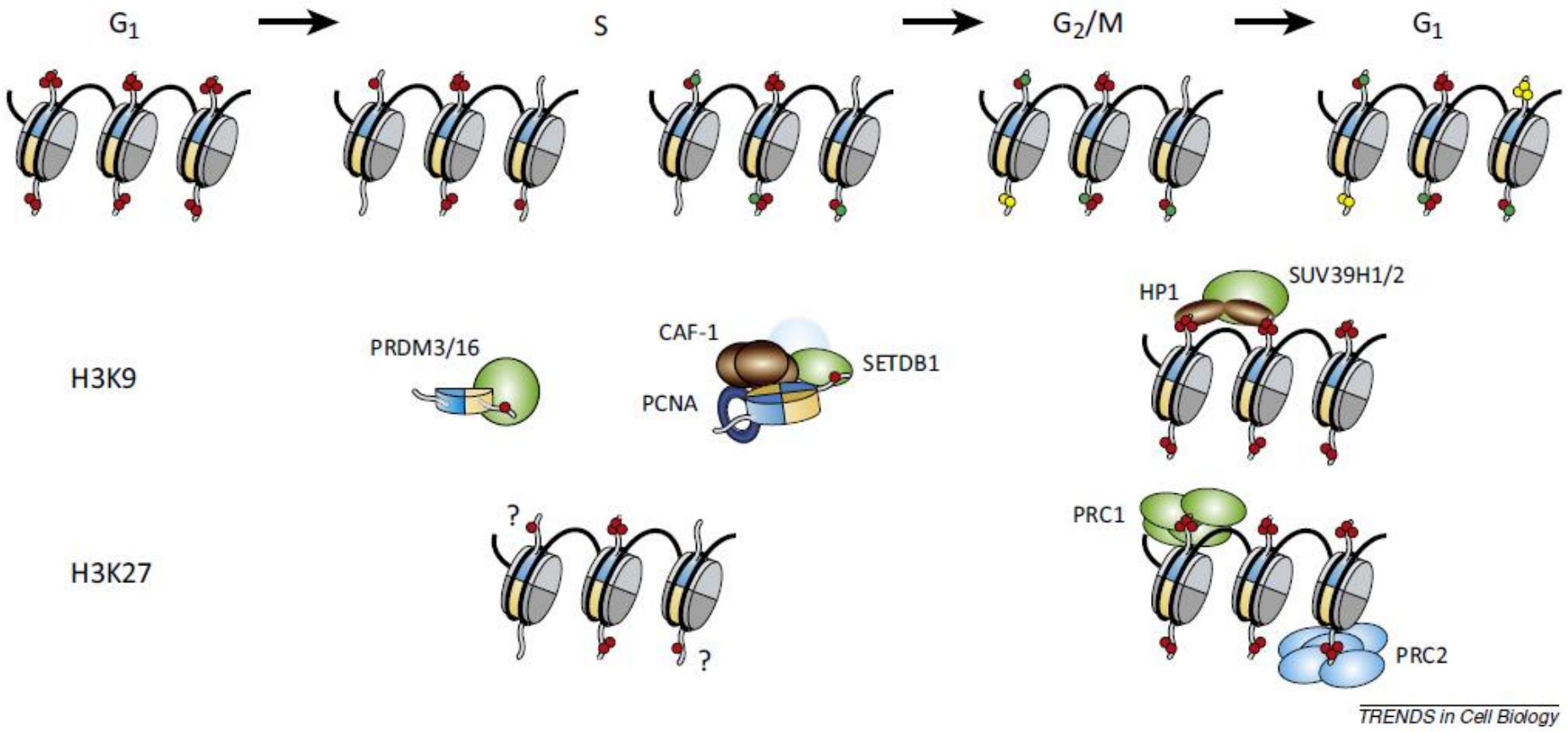
Figure 1 | The Polycomb complexes PRC1 and PRC2. a, Diagrams representing the composition of PRC2 and PRC1 are shown. In PRC1, the diagrams shown on the left correspond to the classical PRC1 complexes, whereas those on the right correspond to the so-called PRC1-like complexes.
Owing to their homology with the *Drosophila* PSC protein, we assumed that the BMI1-, MEL18- and NSPC1-containing PRC1 complexes could compact chromatin. The 'pocket' shape of the CBX proteins represents the chromodomain that specifically recognized H3K9/27me3. HPH1, 2 and 3 denote human polyhomeotic homologue 1, 2 and 3. X, Y and Z denote various proteins such as SCMH1/2, FBXL10, E2F6 and JARID1D that could contribute to the formation of PRC1-like complexes, whose exact composition is still enigmatic.



From Margueron & Reinberg (2011) Nature 469: 343-49

Histone marks: beyond S-phase

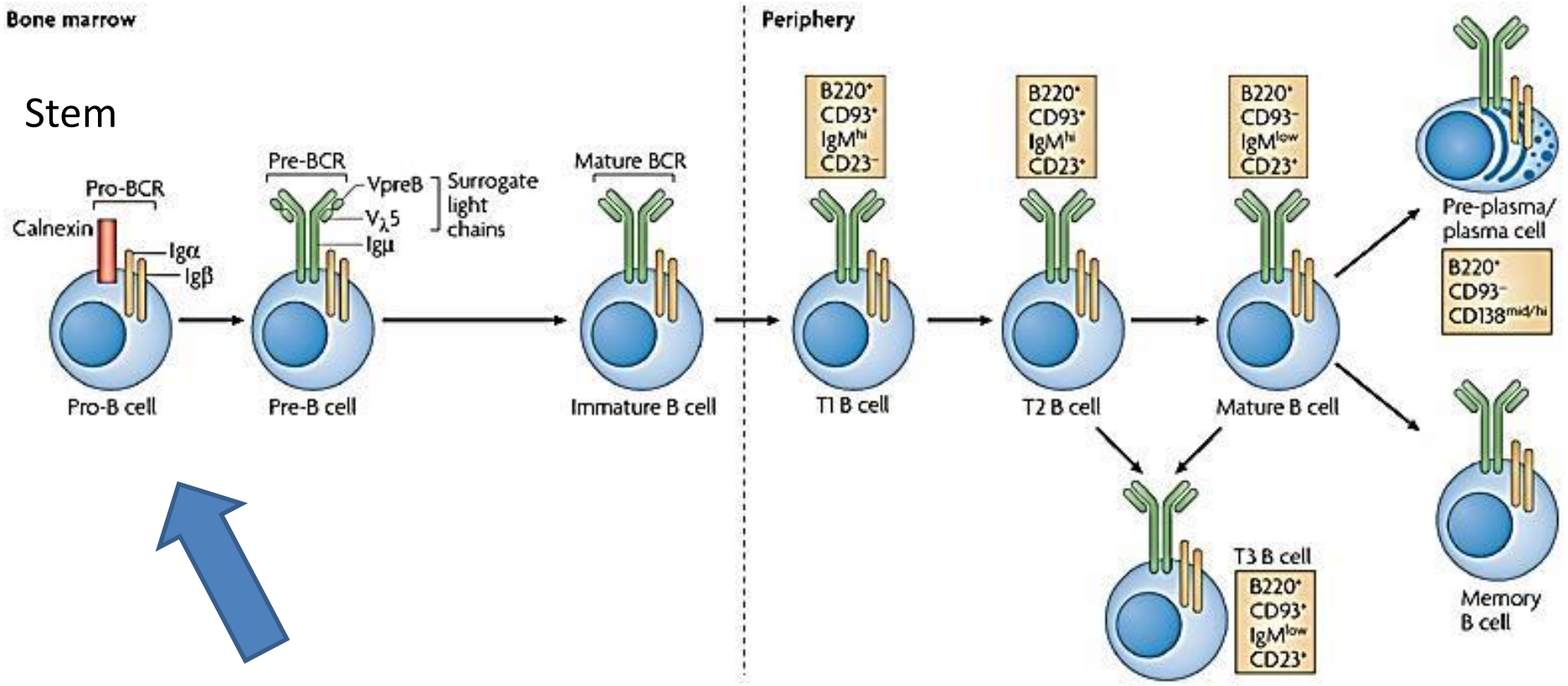
Interestingly enough, the restoration of parental histone PTMs is not restricted to S-phase (Figure 2). This is evident for both H3K27me2/3 and H3K9me2/3, two of the most commonly studied histone marks enforcing transcriptional silencing.



TRENDS in Cell Biology

Appendix

B cell development



Cambier et al., in [Nature reviews. Immunology](#) 7(8):633-43 (2007)