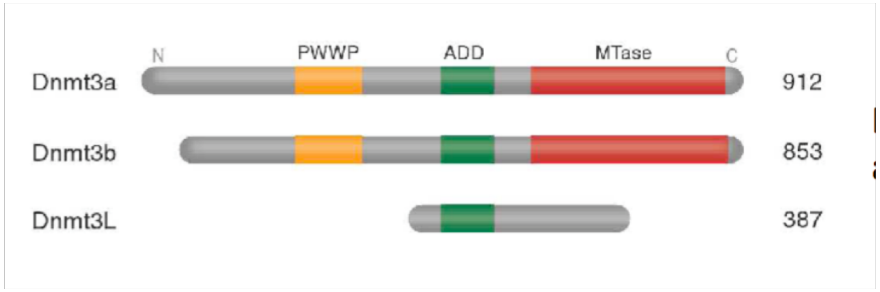
LECTURE 12

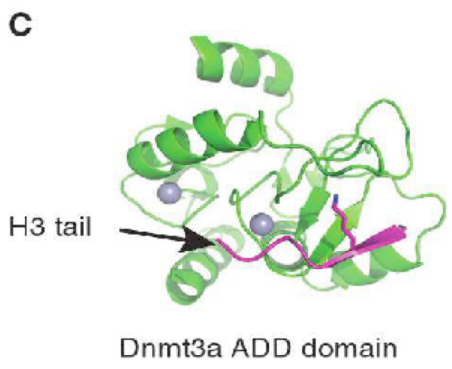
COORDINATION OF HISTONE AND DNA METHYLATION

Linking de-novo DNA methylation to histone methylation (DNMT3a, DNMT3b)



De-novo DNMT family has 2 enzymatic active members (DNMT3a, b) and one regulatory factor DNMT3L

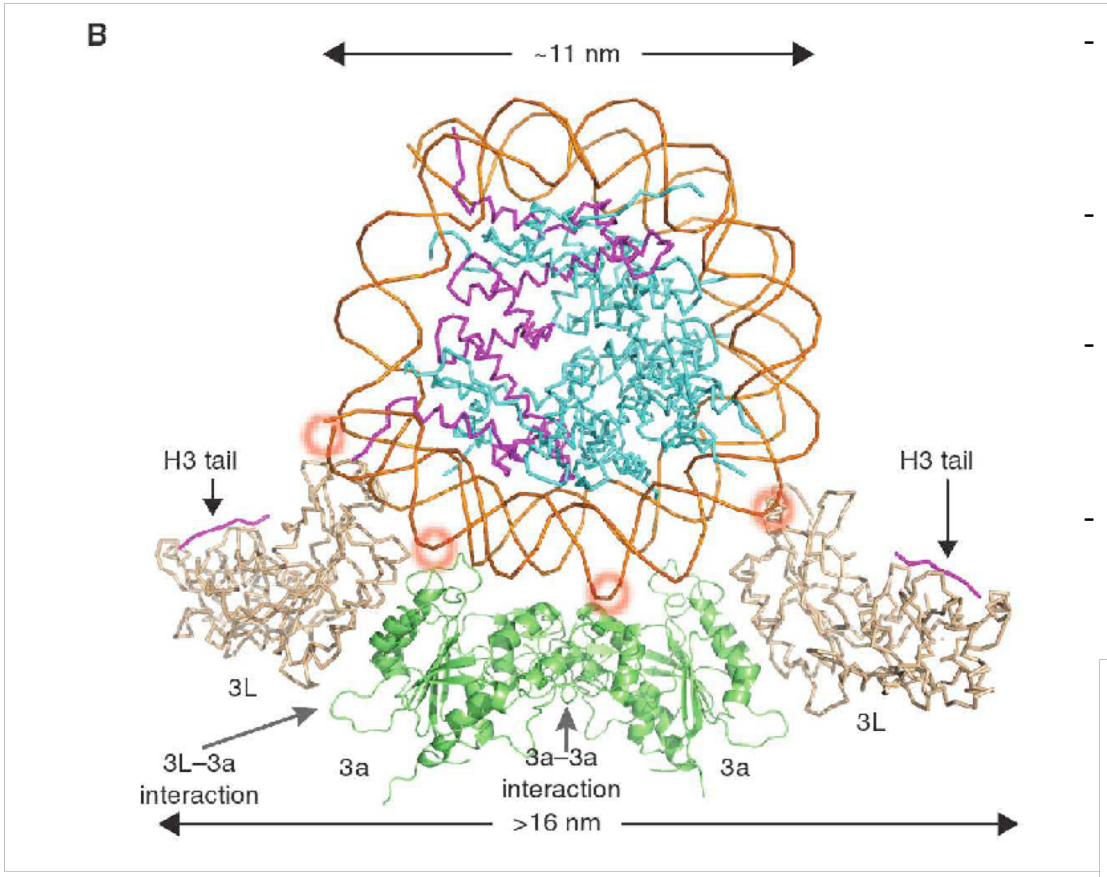
- PWWP (Proline-Tryptophane-Tryptophane-Proline) domain: protein or DNA interaction domain
- ADD (ATRX-DNMT3-DNMT3L) domain: highly similar between DNMT proteins: CAN INTERACT WITH HISTONE TAILS



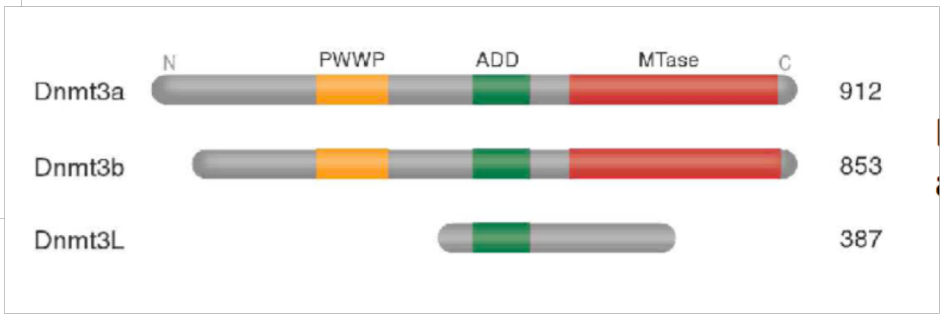
ADD domain of DNMT3a
*Interacts with the **unmethylated** Histone H3 tails*

→ *a link of de-novo DNMTs with histone methylation*

Linking de-novo DNA methylation to histone methylation



- DNMT3L forms a complex with DNMT3a → tetramer: 2x DNMT3L; 2x DNMT3a (best studied); DNMT3L also interacts with DNMT3b
- Phenotype of DNMT3L Knock-out = phenotype of DNMT3a =DNMT3a and DNMT3L are functionally linked
- Deletion of interaction domains that link DNMT3a to DNMT3L results in enzymatic inactivation = DNMT3a function depends on tetramer formation and DNMT3L!!
- Histone H3 tails interact with ADD domains of DNMT3a/b and DNMT3L (only DNMT3L shown); red circles: interaction with DNA



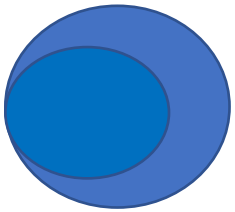
Linking de-novo DNA methylation to histone methylation

How can we find out whether there is a functional link between histone modifications and DNA methylation???

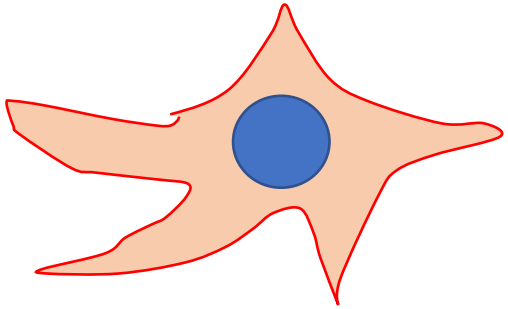
Linking de-novo DNA methylation to histone methylation

Embryonic stem cells

Olig1/2
Neuronal transcription factor: OFF



DIFFERENTIATION



Neuronal progenitor cells

Olig1/2
Neuronal transcription factor: ON

REDUCED REPRESENTATION BISULFITE SEQEUNCING (RRBS)

ChIP seq for active histone modification (H3K4me1,2,3)

ChIP seq for inactive histone modification (H3K27me3)

RNA-seq

Which genes are on/off?

Confront with bivalent/monovalent status (chromatin structure!!!)

Relate to DNA methylation at CpG islands ?

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DNMT3L links histone methylation to DNA methylation

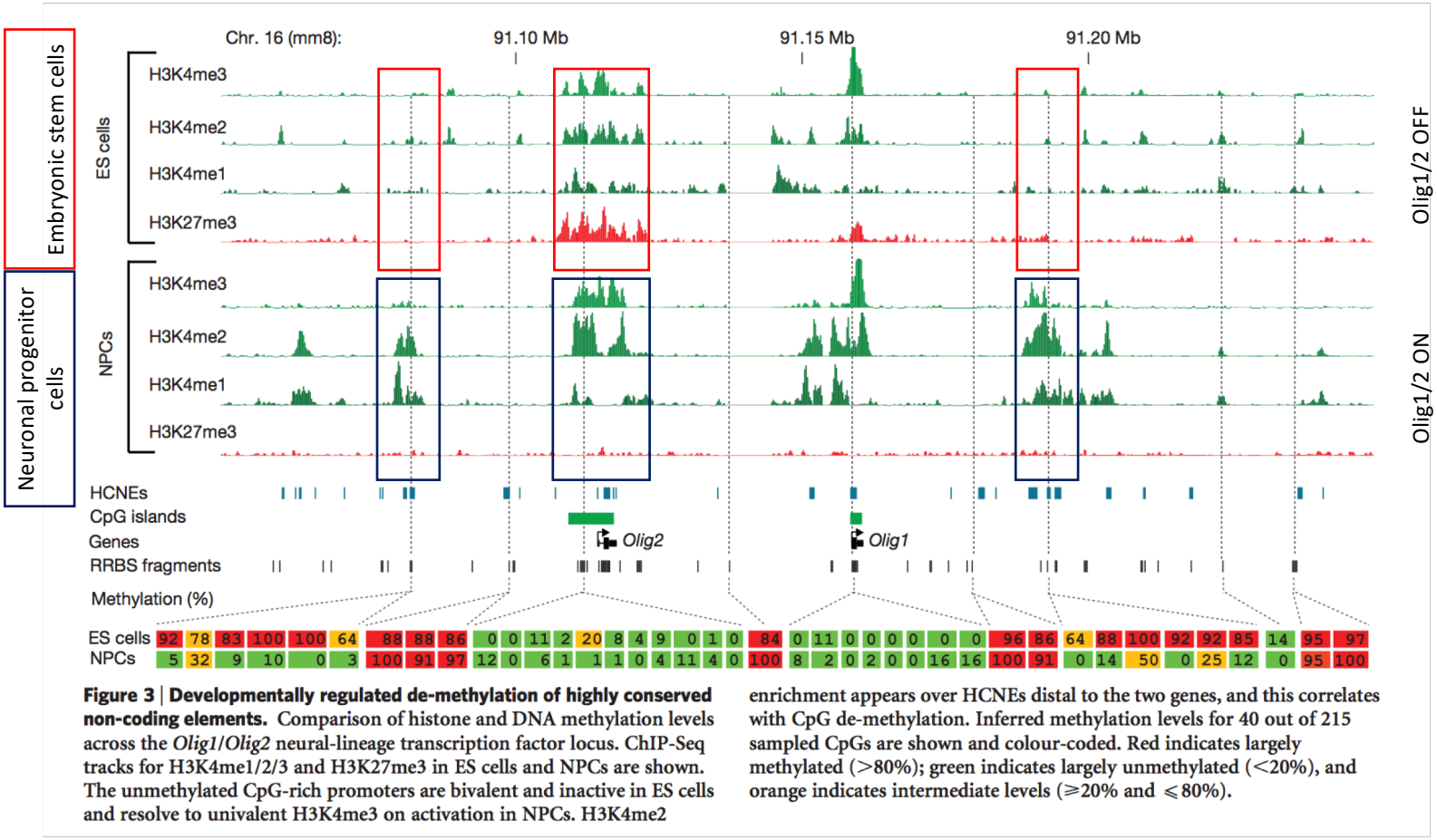


Figure 3 | Developmentally regulated de-methylation of highly conserved non-coding elements. Comparison of histone and DNA methylation levels across the *Olig1*/*Olig2* neural-lineage transcription factor locus. ChIP-Seq tracks for H3K4me1/2/3 and H3K27me3 in ES cells and NPCs are shown. The unmethylated CpG-rich promoters are bivalent and inactive in ES cells and resolve to univalent H3K4me3 on activation in NPCs. H3K4me2 enrichment appears over HCNEs distal to the two genes, and this correlates with CpG de-methylation. Inferred methylation levels for 40 out of 215 sampled CpGs are shown and colour-coded. Red indicates largely methylated (>80%); green indicates largely unmethylated (<20%), and orange indicates intermediate levels (≥20% and ≤80%).

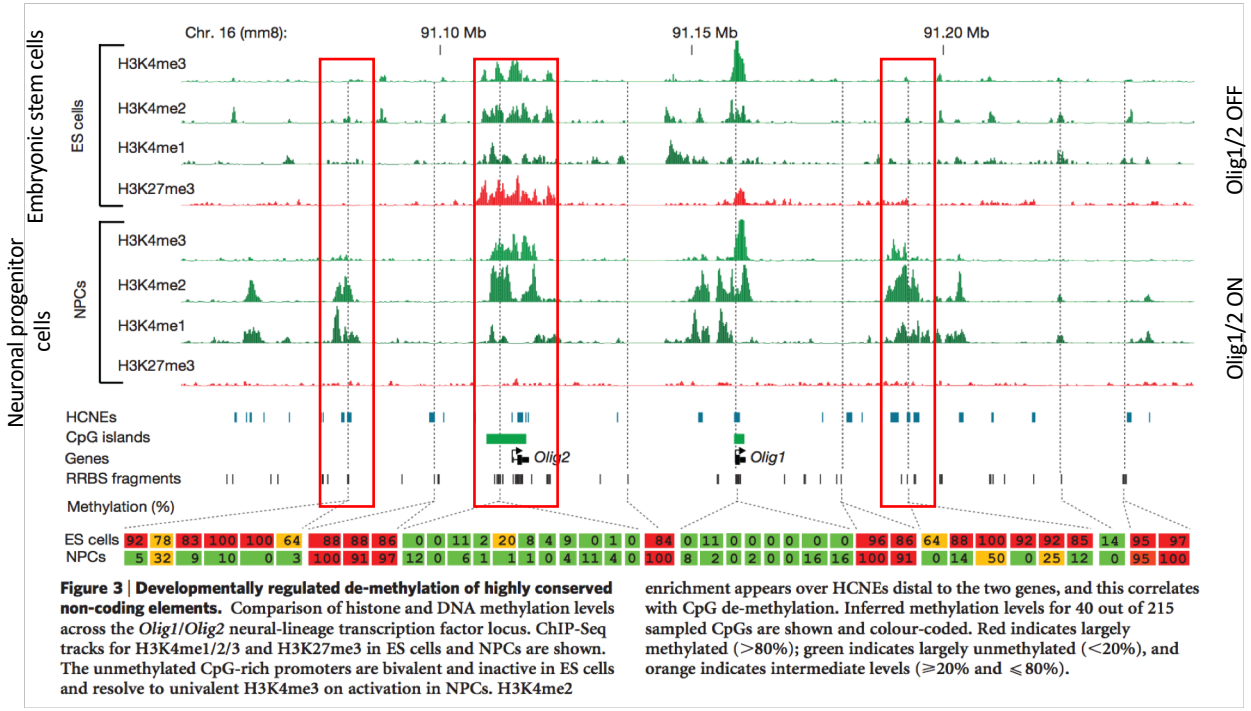
HCNE: A conserved non-coding sequence (CNS) is a DNA sequence of noncoding DNA that is evolutionarily conserved. HCNEs can be important sites of evolutionary divergence as mutations in these regions may alter the regulation of conserved genes, producing species-specific patterns of gene expression.

Meissner et al. 2008 Nature

Note:
- Olig1/2 have a bivalent status in mouse embryonic stem (ES) cells → bivalent (H3K27me3/H3K4me3) → not expressed

- Olig1/2 are monovalent active: no H3K27me3 but H3K4me3 → expression in NPCs

DNMT3L links histone methylation to DNA methylation



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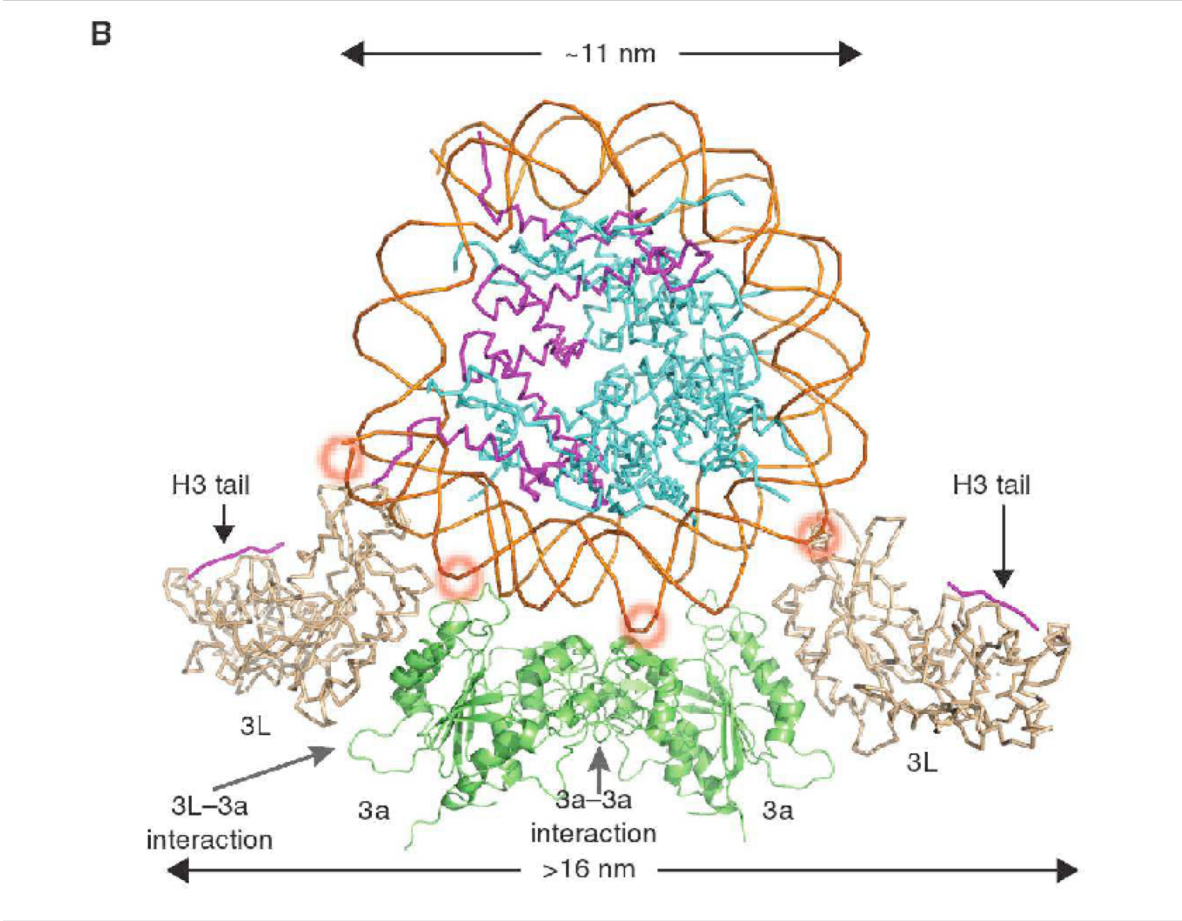
H3K4me0: DNA METHYLATION IN CpG ISLANDS

H3K4me1,2,3: NO DNA METHYLATION IN CpG ISLANDS

De novo DNA methyl-transferases translate patterns of H3K4methylation into heritable patterns of gene expression

HOW???

DNMT3L links histone H3K4 methylation to DNA methylation



DNMT3L/ab ADD domain binds with high affinity to un-methylated Histone H3 tails

DNMT3L/ab in tetramer binds unmethylated histone H3 → CpG methyaltion by DNMT3a/DNMT3b

Mutated DNMT3L does not bind to unmethylated H3K4→ no DNA methyaltion at CpG islands!!

De novo DNA methyl-transferases
translate patterns of H3K4methylation
into heritable patterns of gene expression

H3K4 HKMTs have an important role in defining CpG methylation levels