PHF10 — The Subunit of PBAF Chromatin Remodeling Complex: Structure and Function Predictions

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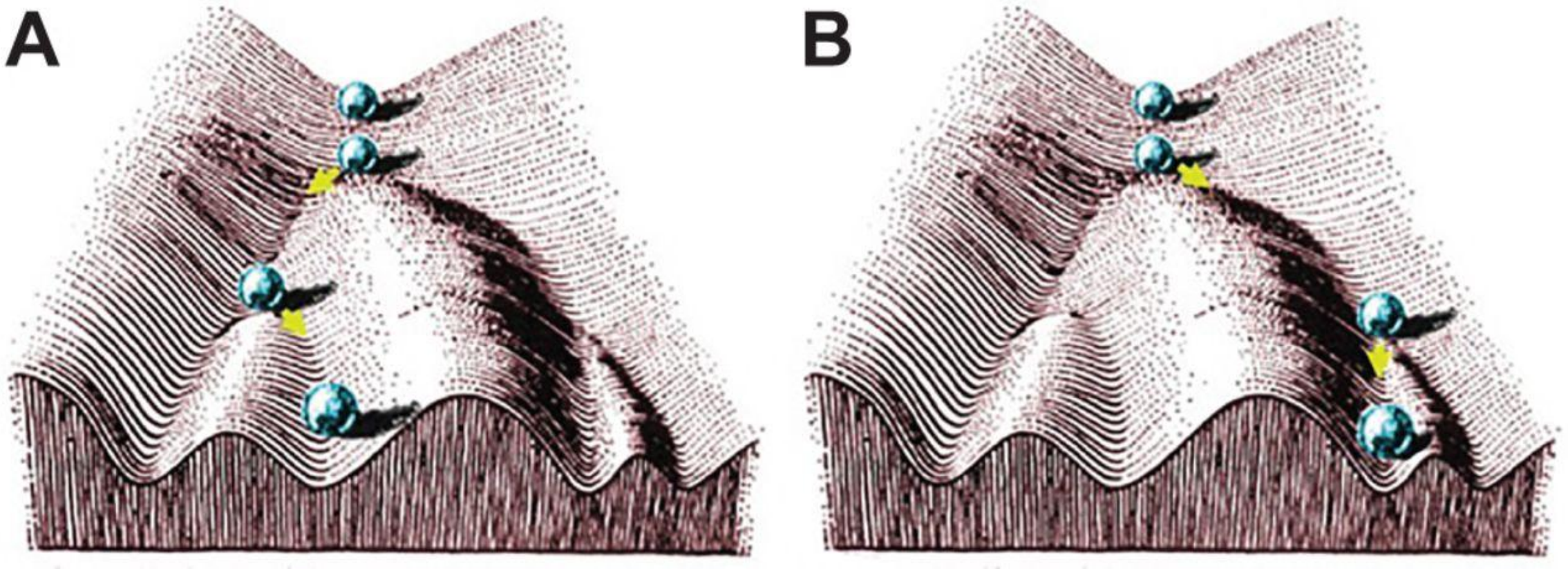
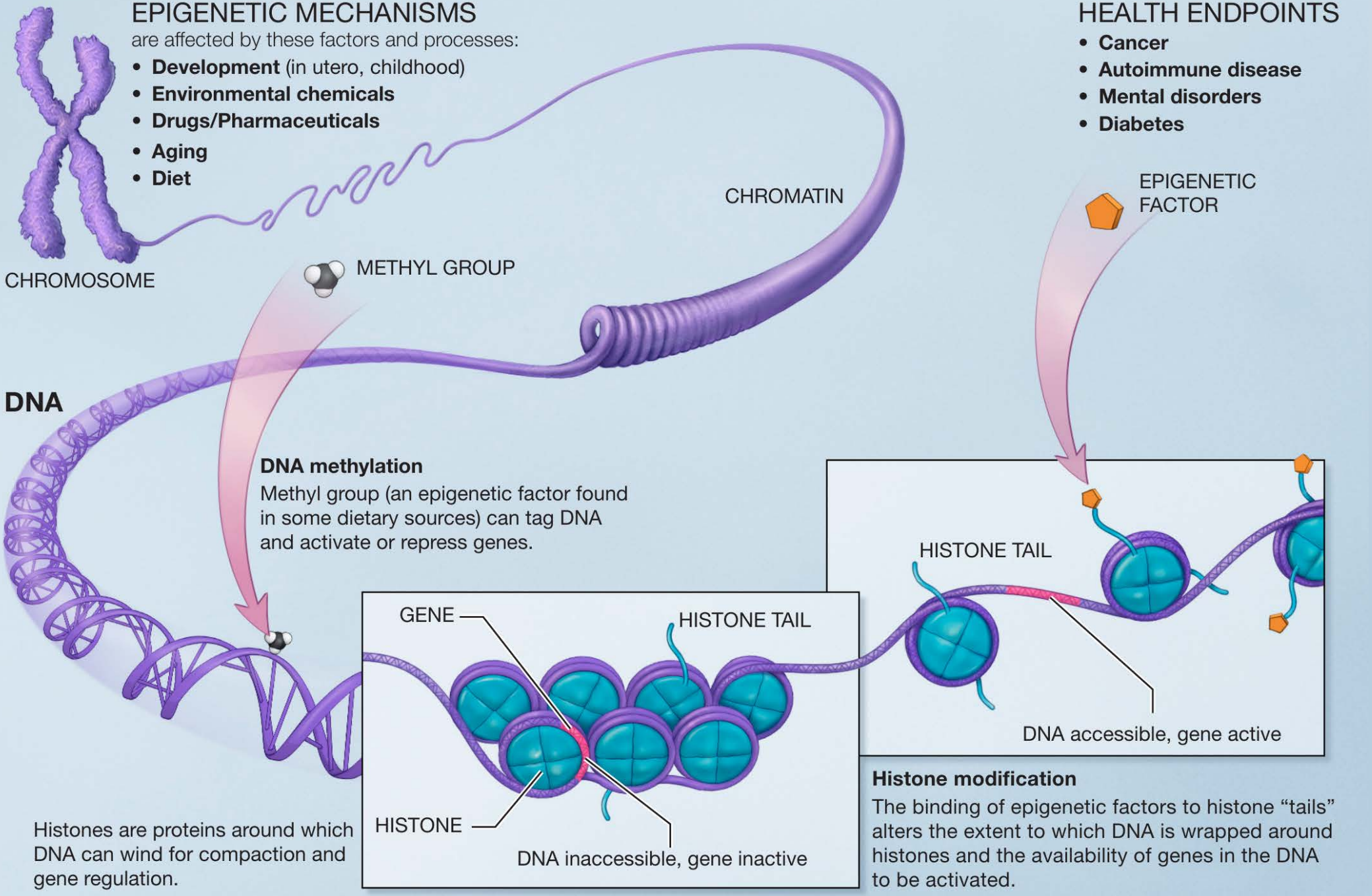
Image: Oryzon

Waddington's developmental landscape



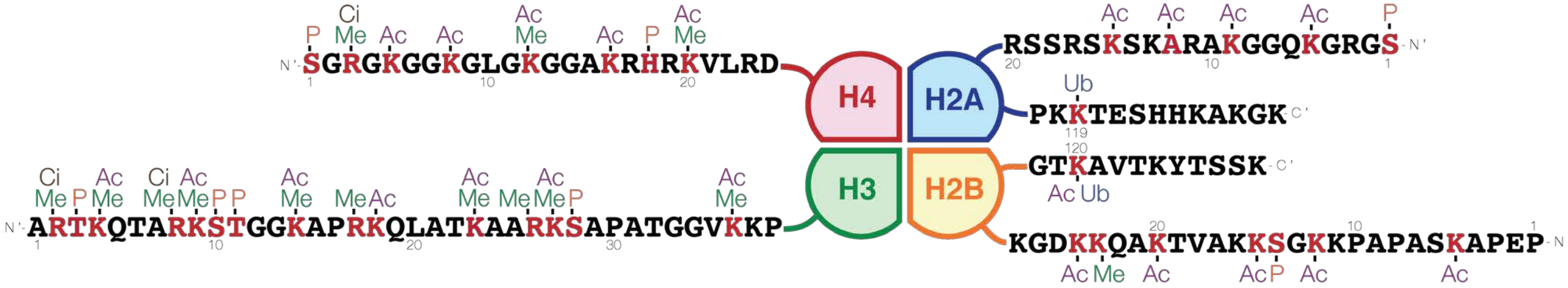
- Hypothesis of "epigenetic" changes, genome methylation: N. Koltsov (1915)
- "Epigenetics": C. Waddington (1942)
- Gene nature was not known at those times



Genetics proposes but epigenetics disposes

Image: Wikipedia

Covalent histone modifications (the “histone code”)



Me Methylation Ac Acetylation Ci Citrullination

Ub Ubiquitination P Phosphorylation

Type of modification	Histone							
	H3K4	H3K9	H3K14	H3K27	H3K79	H3K122	H4K20	H2BK5
mono-methylation	activation[8]	activation[9]		activation[9]	activation[9][10]		activation[9]	activation[9]
di-methylation		repression[4]		repression[4]	activation[10]			
tri-methylation	activation[11]	repression[9]		repression[9]	activation,[10] repression[9]			repression[4]
acetylation		activation[11]	activation[11]	activation[12]		activation[13]		

Image: Wikipedia

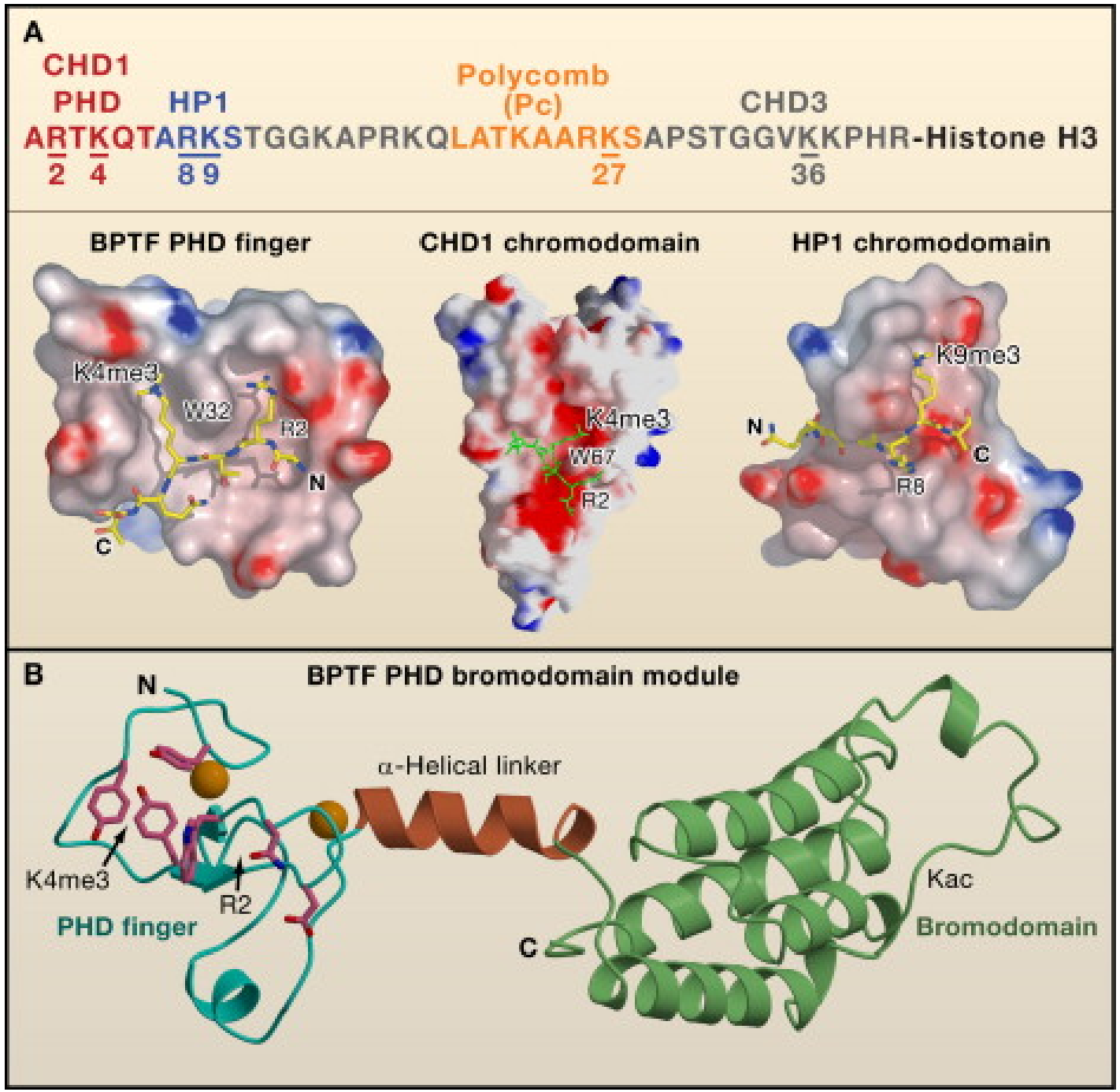


Image: Mellor (2006), *Cell*

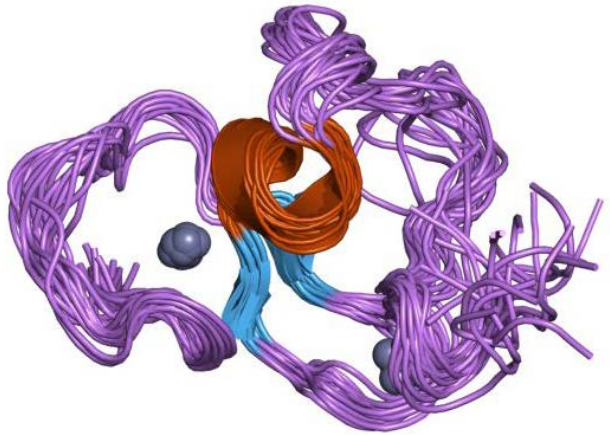
It takes a PHD to read the histone code

Methyl-Lysine Recognition by the PHD Finger and Chromodomains

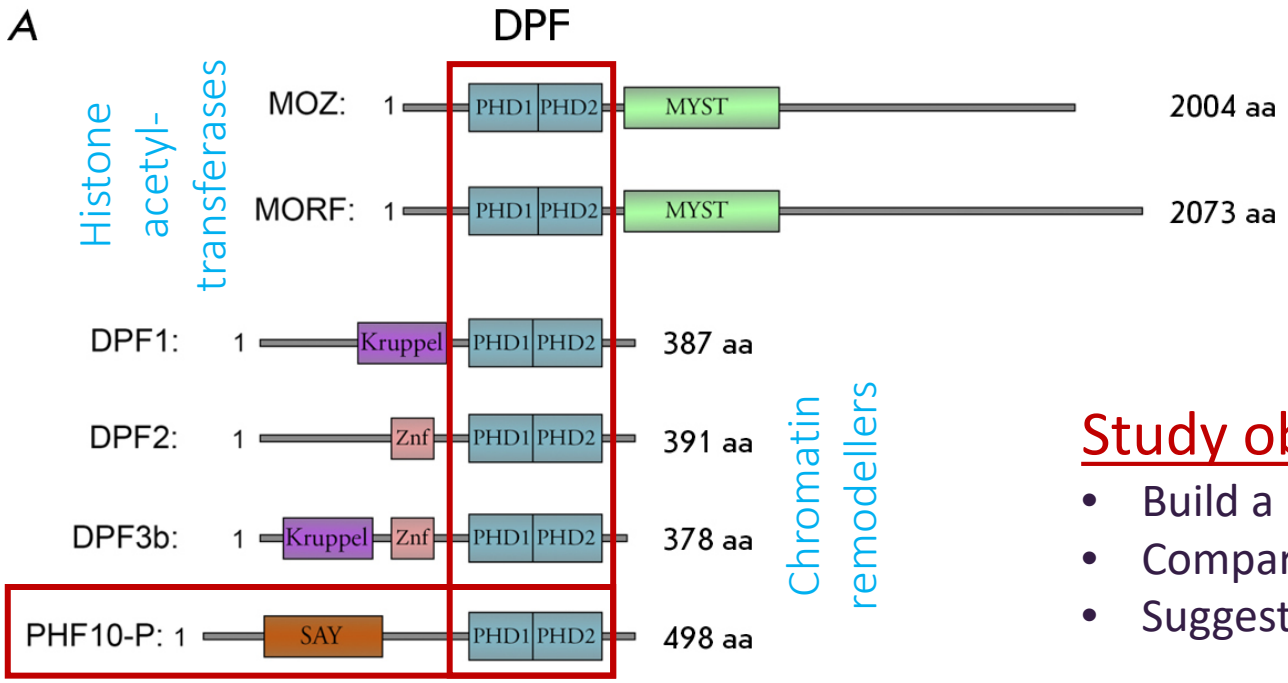
PHD = Plant homeodomain

>100 human proteins

PHD finger: Cys_4-His-Cys_3 motif + $2Zn^{2+}$



DPF: for when a single PhD is just not enough



Study objectives:

- Build a homology model of PHF10's DPF domain
- Compare to other proteins' DPF domains
- Suggest PHF10's affinity to histone modifications

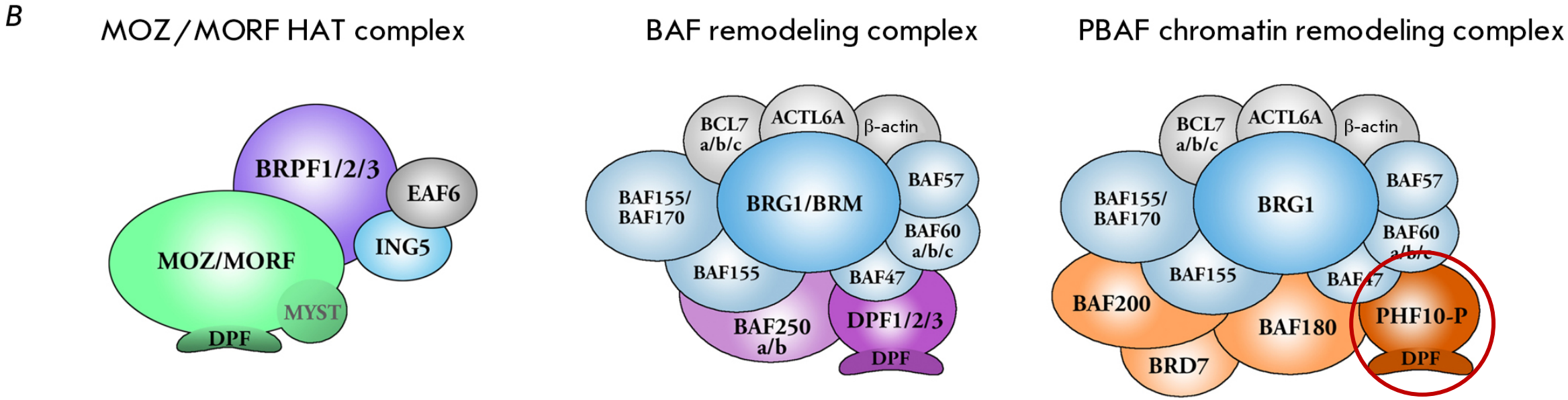
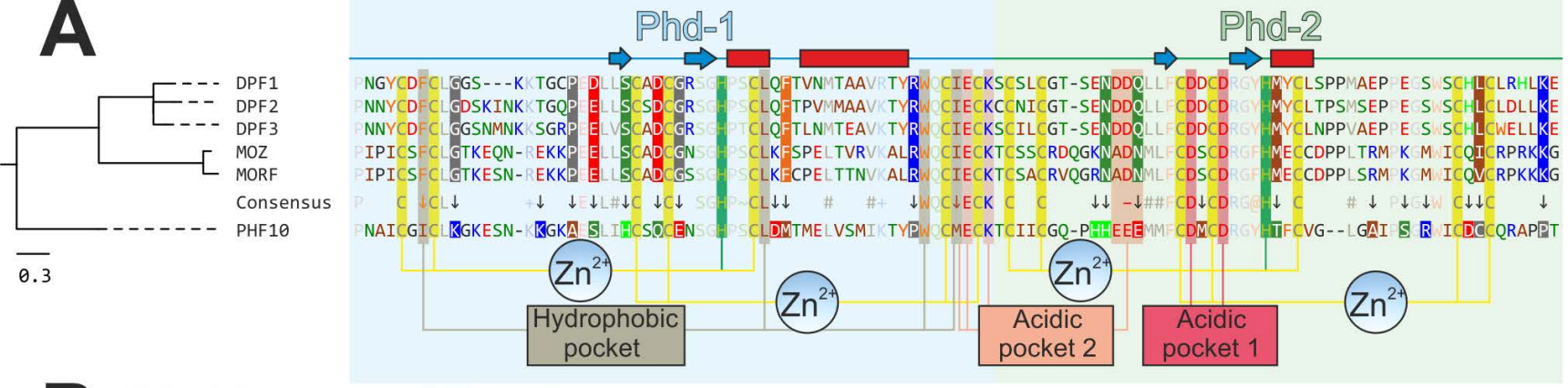
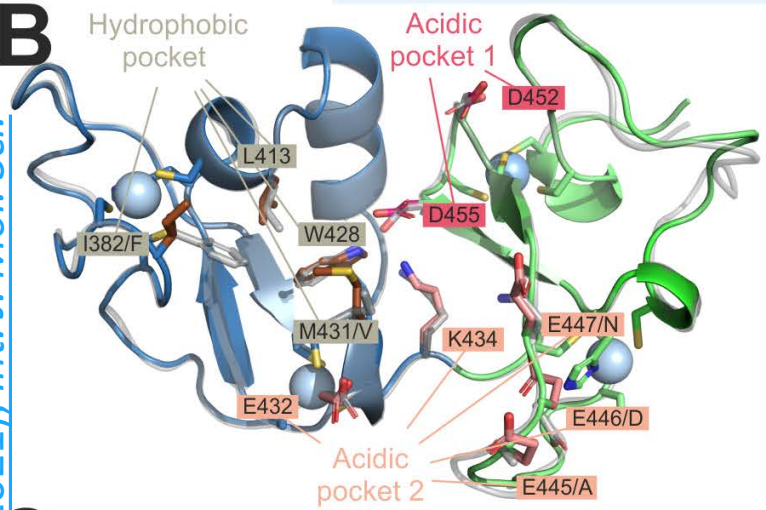
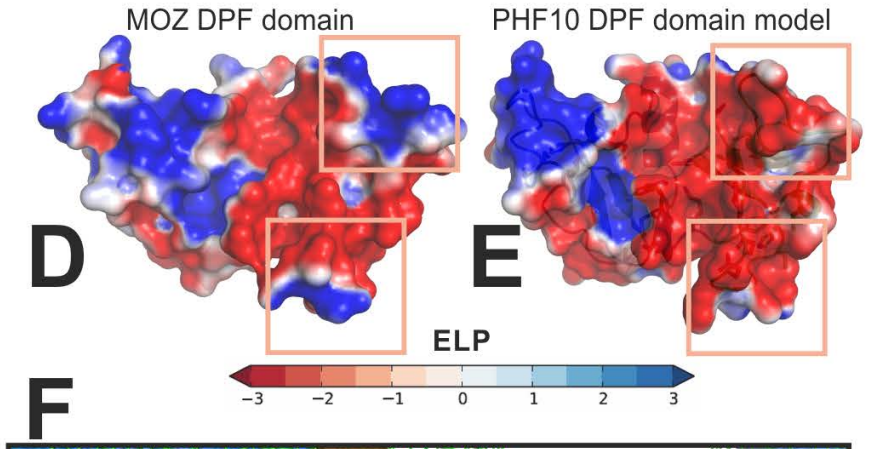
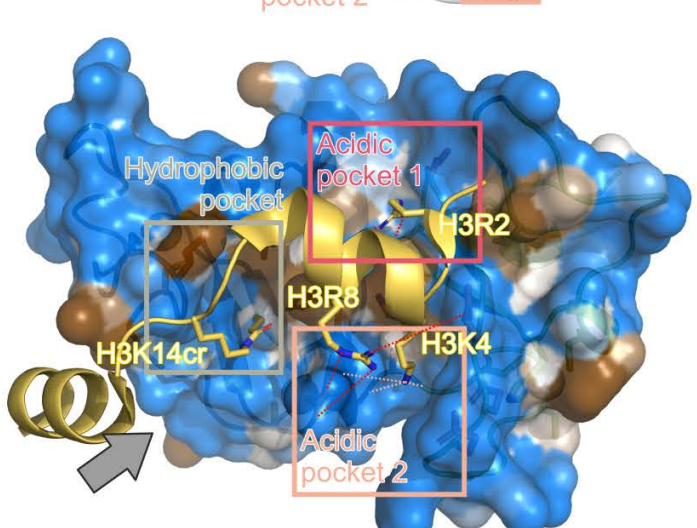


Image: Soshnikova *et al.* (2020), *Acta Naturae*









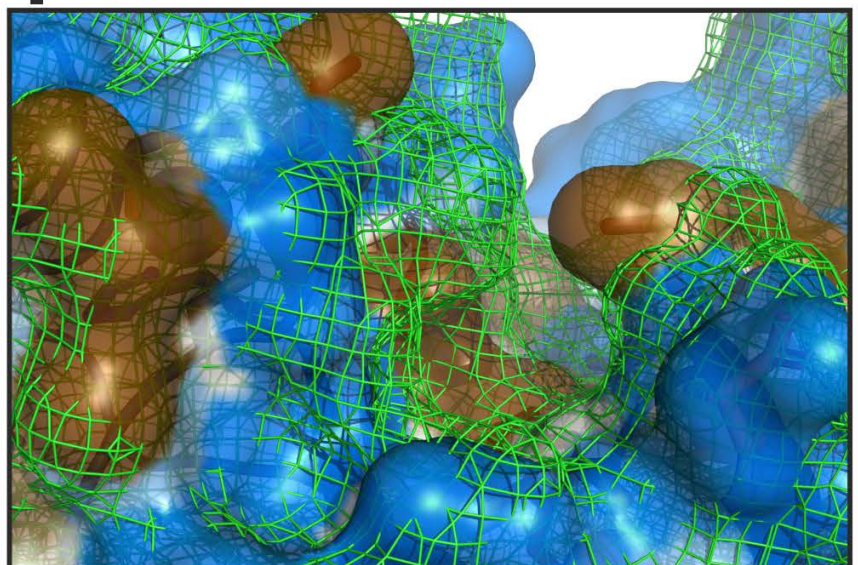


Image: Chugunov et al. (2021), *Int. J. Mol. Sci.*

Homology model of PHF10 DPF domain

- PHF10 DPF domain is homologous, yet most unlike
- MOZ (47% id) is a template
- Two PHD domains, four Zn^{2+}
  - $CCHC/C_4$
- Acidic pocket 1: 100% conserved, anchors histone tails H3R2, H4R17
- Acidic pocket 2:
  - Anchors H3R8
  - Binds unmethylated H3K4 and H4K20, rejecting Kme3 states *via* forming h-bonding "niches" to [I/M]ECK bb's
  - **PHF10:** more acidic (HHEEE pattern), presumably less tolerable to lysine methylation, e.g. rejects H3K4me3
- Hydrophobic pocket binds modified lysines: H3K14ac/cr/bu, H3K9ac/me, H4K5/8/12/16ac
  - **PHF10:** the trench is shifted, presumed affinity to bulkier H3K14/H4K16bu/cr

PHF10 is evolutionary conserved and different from other DPF-containing proteins

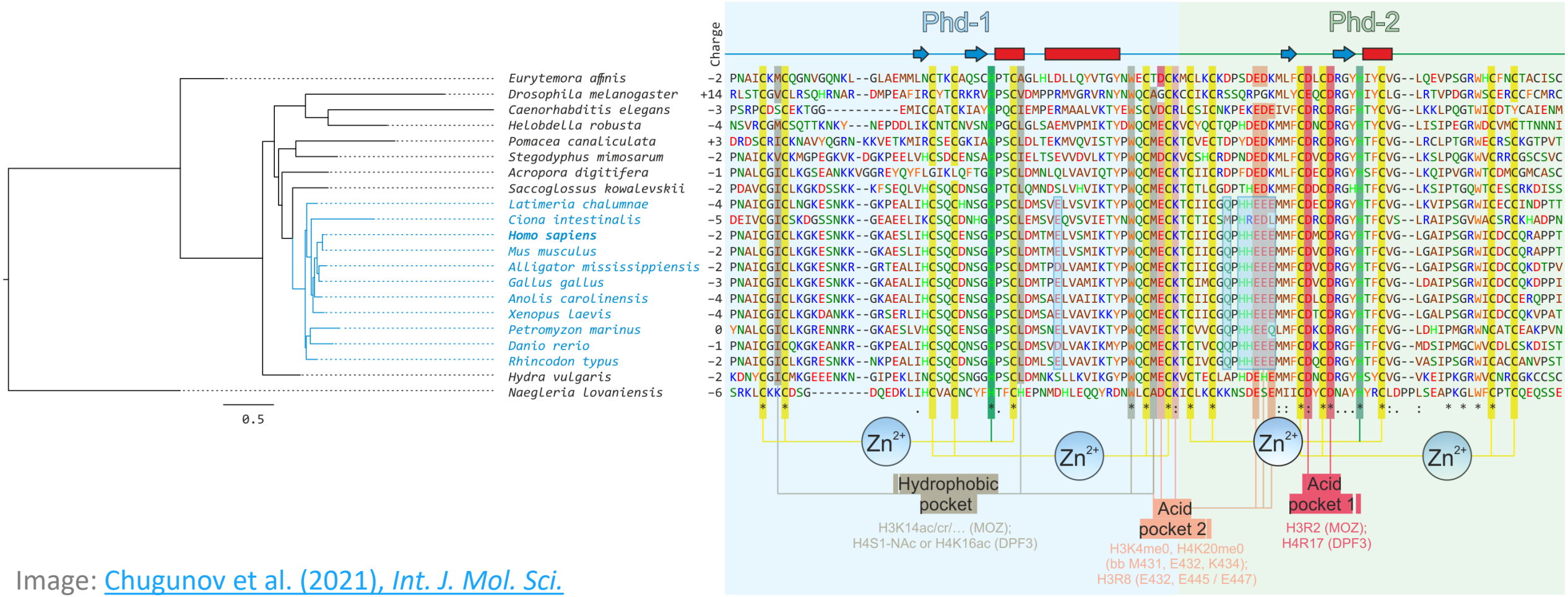
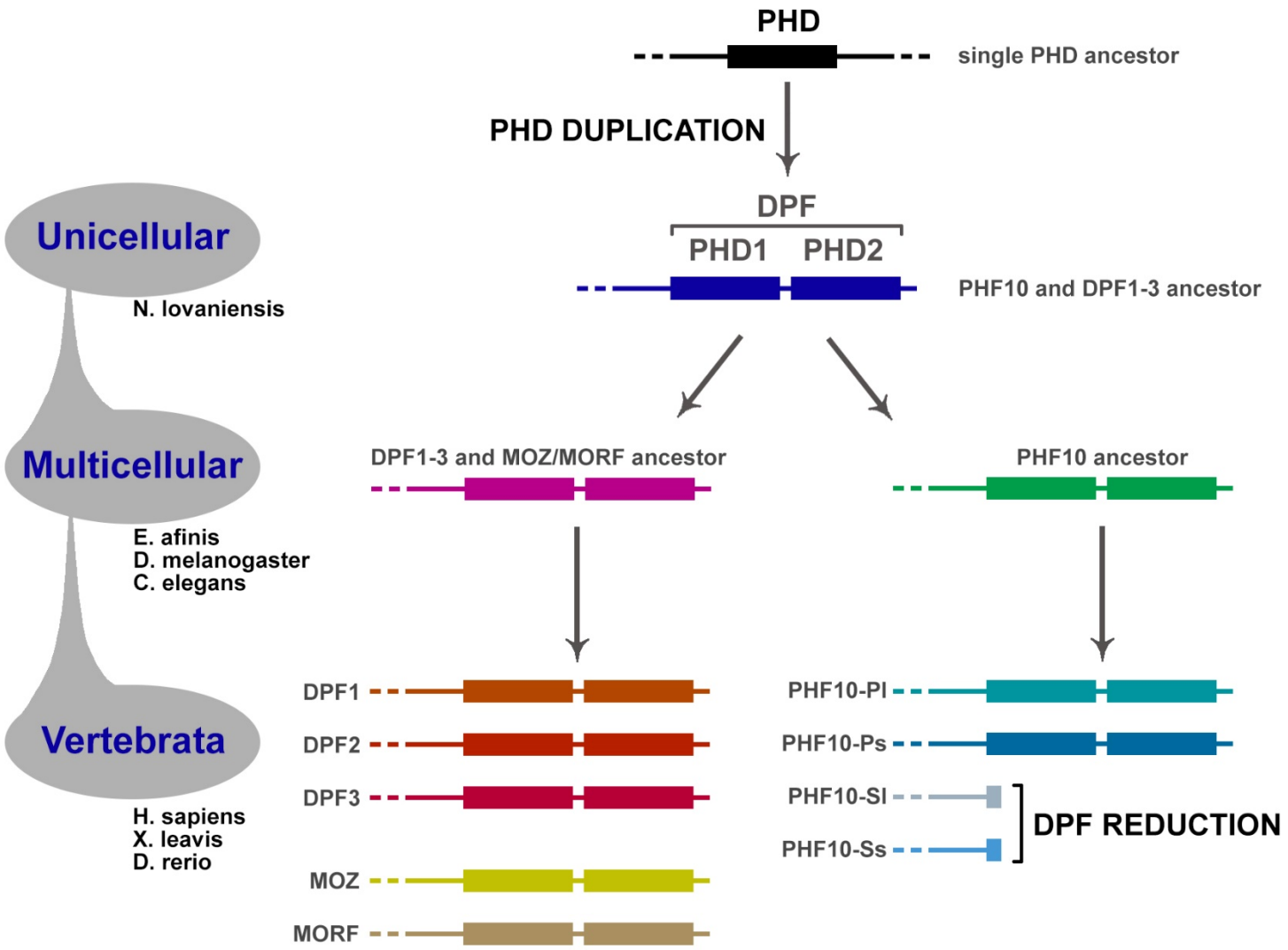


Image: [Chugunov et al. (2021), *Int. J. Mol. Sci.*]

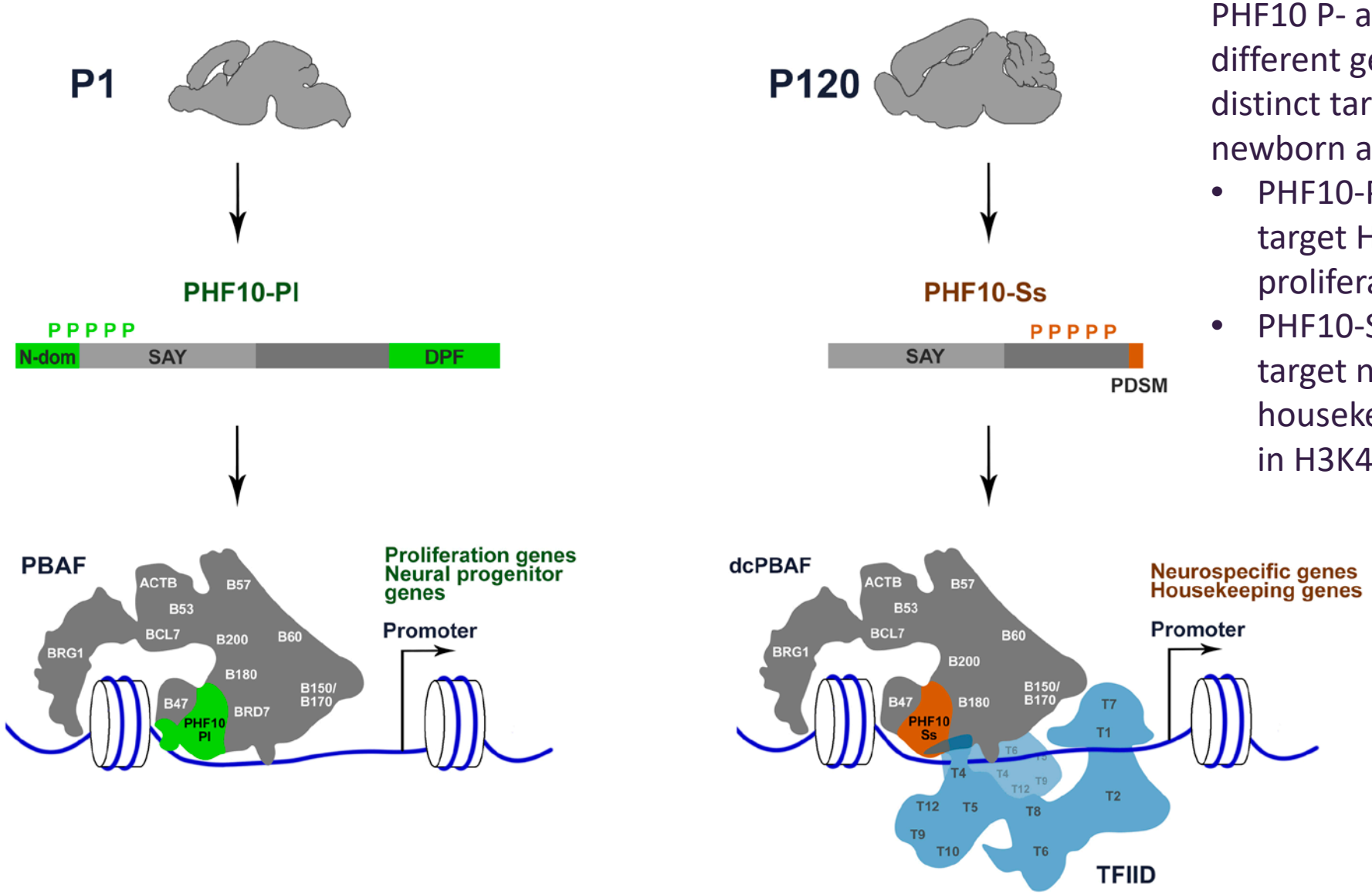
Evolution of DPF-containing proteins



- PHF10 is an ancient DPF-containing protein
- It has been evolving on its own, gaining distinctive features
- In vertebrates, there are four PHF10 splice-forms:
  - Two PHF10-P with DPF
  - Two PHF10-S with reduced DPF domains
- These forms yield different targeting!

Image: Chugunov et al. (2021), *Int. J. Mol. Sci.*

The roles of PHF10 P- and S-forms



PHF10 P- and S-isoforms regulate different gene pools due to distinct targeting, as shown in newborn and adult mice brains:

- PHF10-P (with DPF domain) target H3K14ac-rich proliferating genes
- PHF10-S (without DPF domain) target neurospecific and housekeeping genes, enriched in H3K4me3

Image: N. Soshnikova, personal communication

Conclusion

- PHF10 has started its own evolution (separated from other DPF-proteins) as early as in first multicellular organisms. In vertebrates, it multiplied into four splice forms (two reduced “targeting” DPF domain)

- Homology model of PHF10 DPF domain reveals common and unique features of this protein. Predicted binding pockets for histone modifications:
  - Acidic pocket 1: anchoring by H3R2, H4R17
  - Acidic pocket 2: binding unmodified H3K4 and H4K20, rejecting methylated Kme3
  - Hydrophobic pocket: recognizes hydrophobic lysine modifications, e.g. H3K14/H4K16bu/cr

- Following these 👆 specificities, respective chromatin remodelers should behave differently:
  - PBAF (contains PHF10-P: with DPF domain) remodel gene promotors at the activation
  - dcPBAF (PHF10-S: without DPF domain) remodel constantly active genes — enriched with H3K4me3

Thanks for your attention!

ИБХ