L1.1.1

Transcriptional regulation, by M. Levine

The first level of control is **TRANSCRIPTION**

Michael Levine review deals with this specific issue that is the first and fundamental level of regulation

Textbook G

Leading Edge
Review

Cell

Looping Back to Leap Forward: Transcription Enters a New Era

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http://dx.doi.org/10.1016/j.cell.2014.02.009

Abstract

Comparative genome analyses reveal that organismal complexity scales not with gene number but with gene regulation. Recent efforts indicate that the human genome likely contains hundreds of thousands of enhancers, with a typical gene embedded in a milieu of tens of enhancers. Proliferation of *cis*-regulatory DNAs is accompanied by increased complexity and functional diversification of transcriptional machineries recognizing distal enhancers and core promoters and by the high-order spatial organization of genetic elements. We review progress in unraveling one of the outstanding mysteries of modern biology: the dynamic communication of remote enhancers with target promoters in the specification of cellular identity.

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https://en.wikipedia.org/wiki/List_of_sequenced_eukaryotic_genomes

https://www.ncbi.nlm.nih.gov/genome/

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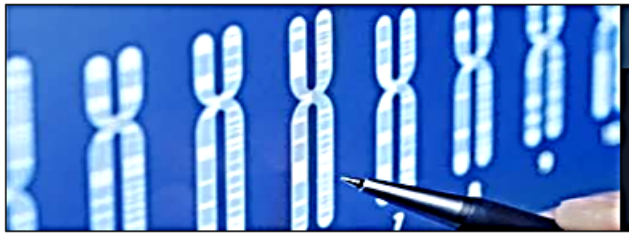

Genome

This resource organizes information on genomes including sequences, maps, chromosomes, assemblies, and annotations.

Using Genome

- Help
- Browse by Organism
- Download / FTP
- Download FAQ
- Submit a genome

Custom resources

- Human Genome
- Microbes
- Organelles
- Viruses
- Prokaryotic reference genomes

Other Resources

- Assembly
- BioProject
- BioSample
- Map Viewer
- Protein Clusters

Genome Tools

- BLAST the Human Genome
- Microbial Nucleotide BLAST

Genome Annotation and Analysis

- Eukaryotic Genome Annotation
- Prokaryotic Genome Annotation
- PASC (Pairwise Sequence Comparison)

External Resources

- GOLD - Genomes Online Database
- Ensembl Genome Browser
- Bacteria Genomes at Sanger
- Large-Scale Genome Sequencing (NHGRI)

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Let’s go to figures

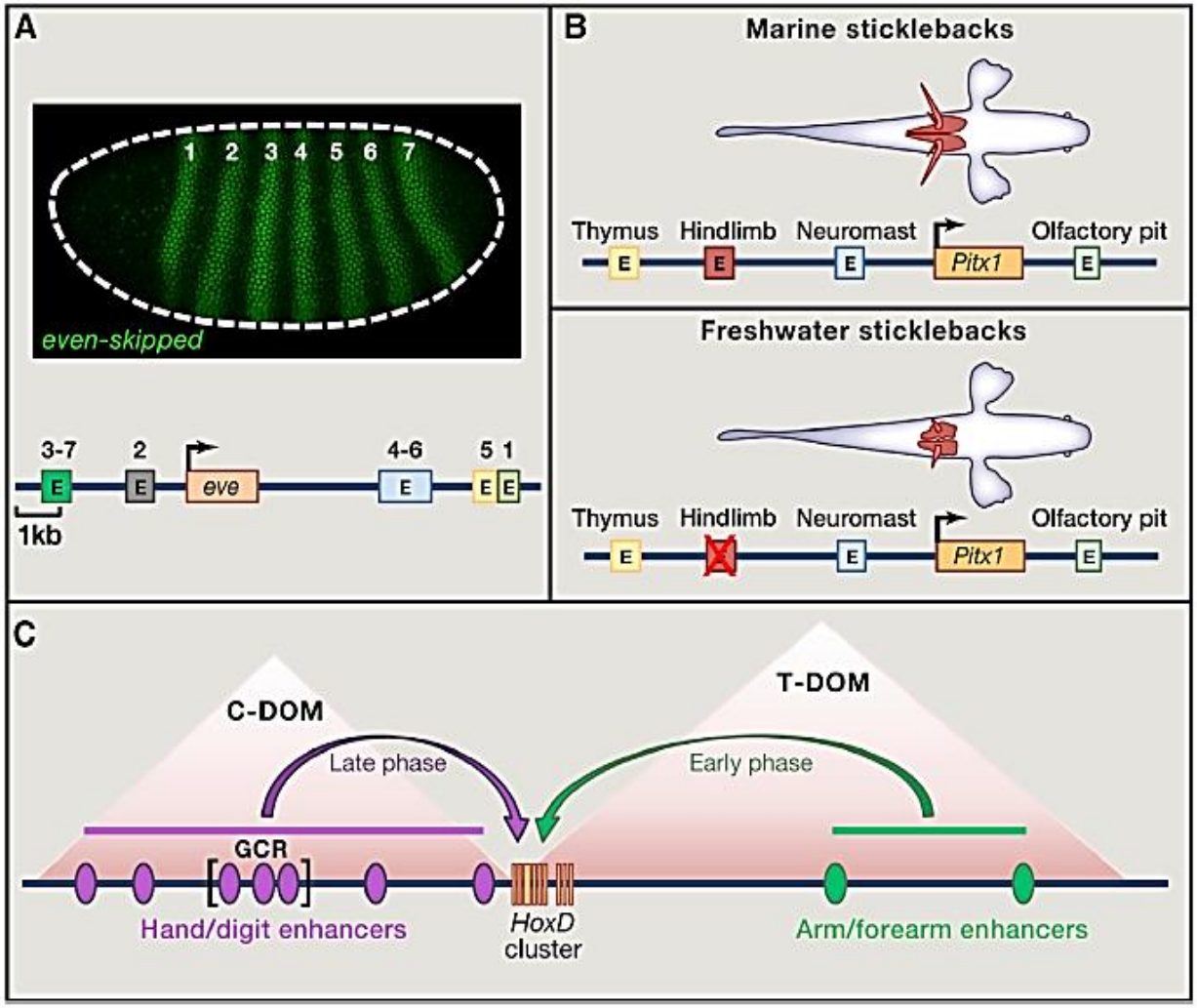

Figure 1. Organization of *cis*-Regulatory DNAs in Metazoan Genomes

Metazoan genes are regulated by multiple enhancers.

(A) Organization of the *even-skipped* (*eve*) locus in the *Drosophila* genome. The *eve* gene is just 3 kb in length but is regulated by individual stripe enhancers (E) located in both 5′ and 3′ flanking regions. The *eve* stripe enhancers function in an additive fashion to produce seven stripes of gene expression in the early *Drosophila* embryo (micrograph by Mike Perry and Michael Levine, personal communication).

(B) Evolution of pelvic fins in stickleback fish. The *Pitx1* gene is regulated in different tissues by a series of enhancers located in both 5′ and 3′ flanking regions. Deletion of the hindlimb enhancer results in reduced development of the pelvic fins (red) in freshwater populations (adapted from Shapiro et al. [2004]).

(C) Organization of the *Hoxd* complex in mice. The complex is regulated by a series of flanking enhancers (purple and green ovals) located in two neighboring TADs. The telomeric TAD (T-DOM) regulates linked *Hoxd* genes in the developing arm and forearm, whereas the centromeric TAD (C-DOM) regulates expression in the hand and the digits (adapted from Andrey et al. [2013]).

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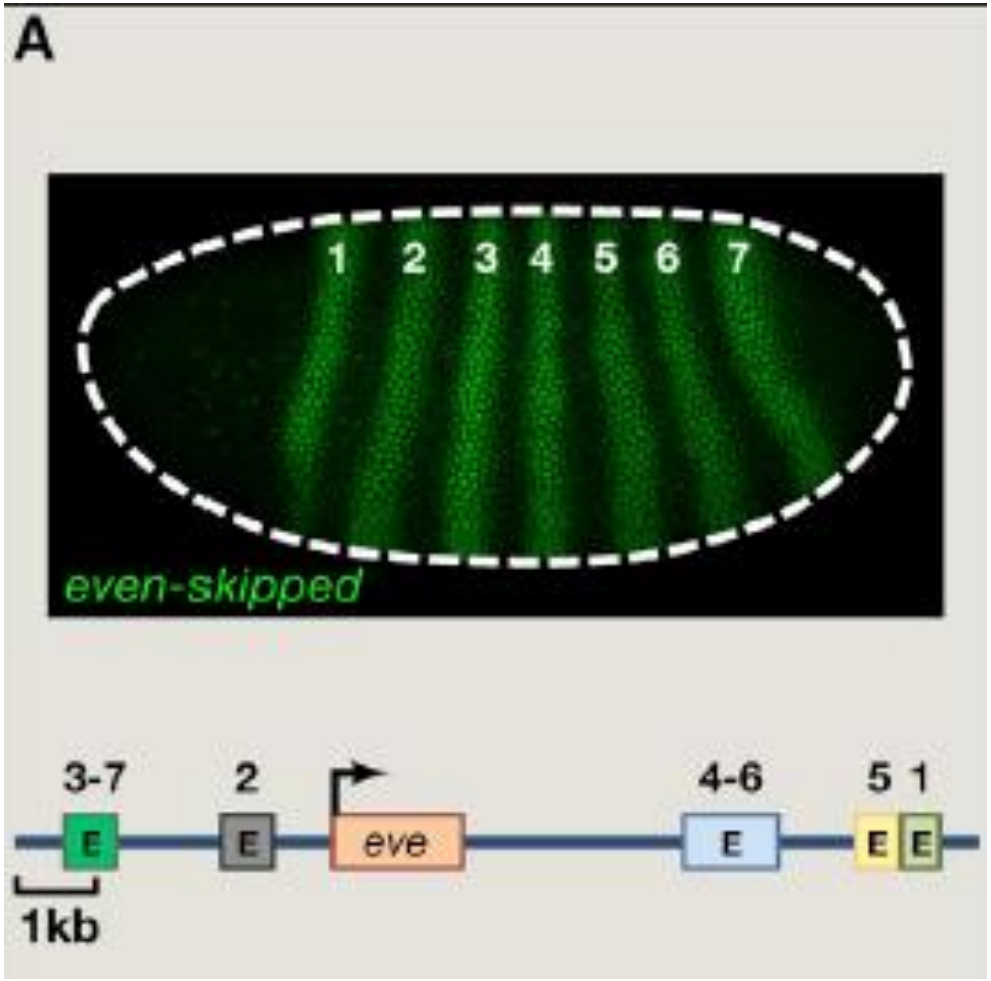
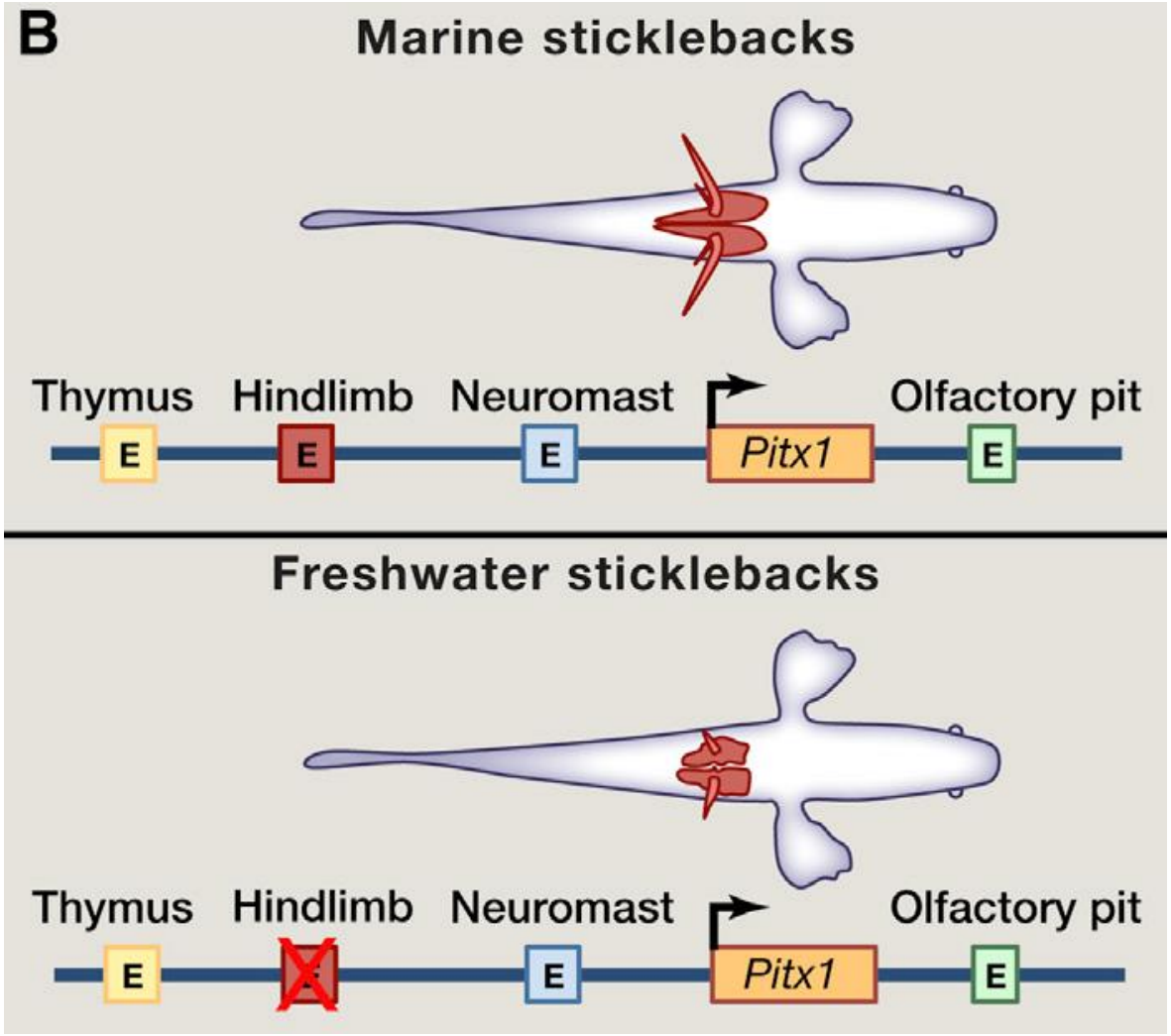


Organization of the even-skipped (eve) locus in the Drosophila genome. The eve gene is just 3 kb in length but is regulated by individual stripe enhancers (E) located in both 5’ and 3’ flanking regions. The eve stripe enhancers function in an additive fashion to produce seven stripes of gene expression in the early Drosophila embryo



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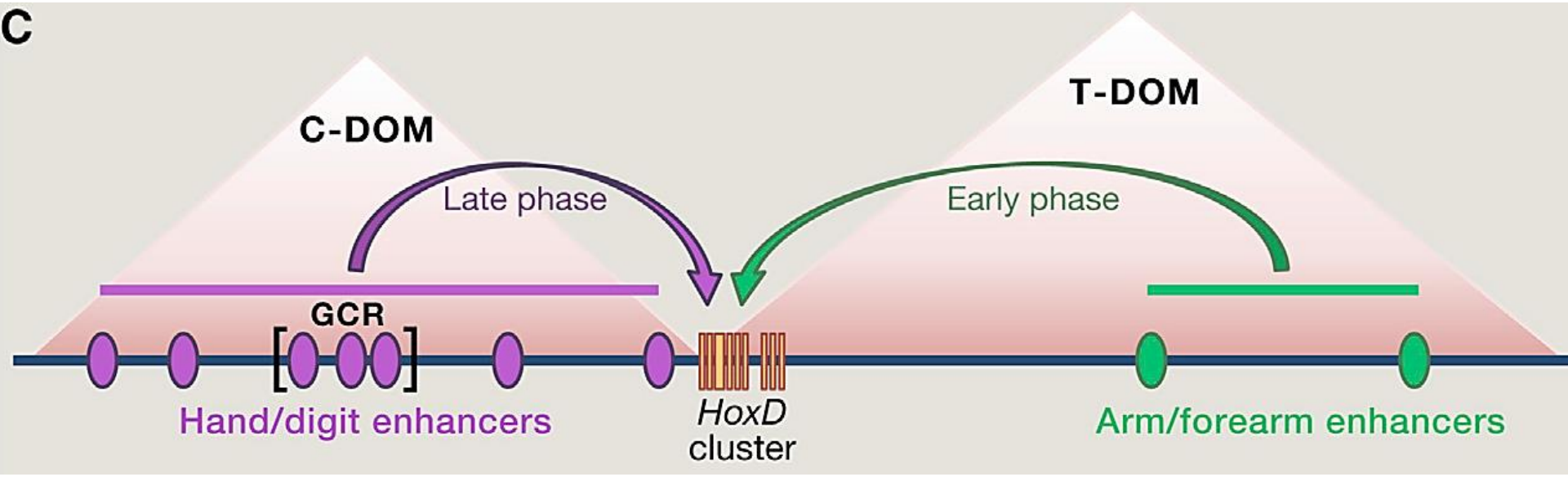


Organization of the Hoxd complex in mice. The complex is regulated by a series of flanking enhancers (purple and green ovals) located in two neighboring TADs. The telomeric TAD (T-DOM) regulates linked Hoxd genes in the developing arm and forearm, whereas the centromeric TAD (C-DOM) regulates expression in the hand and the digits

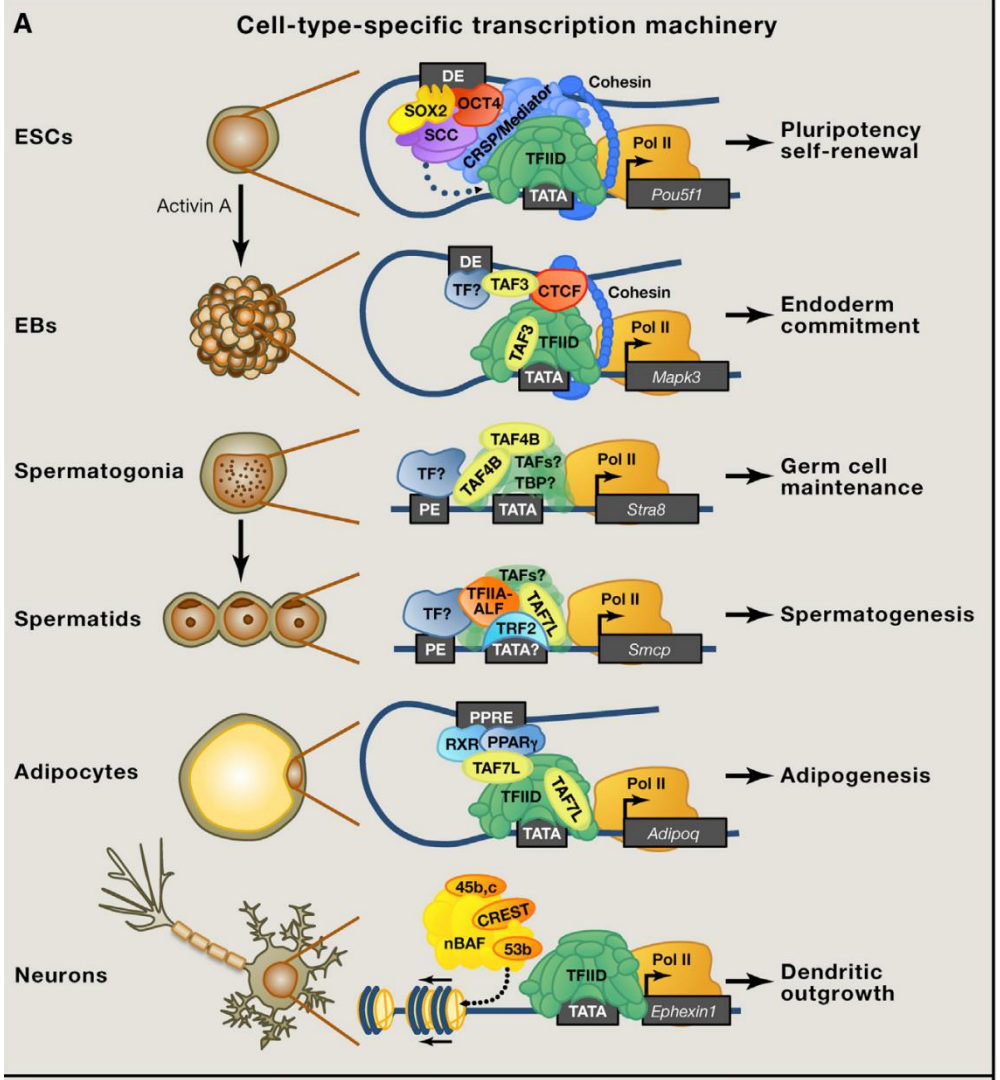
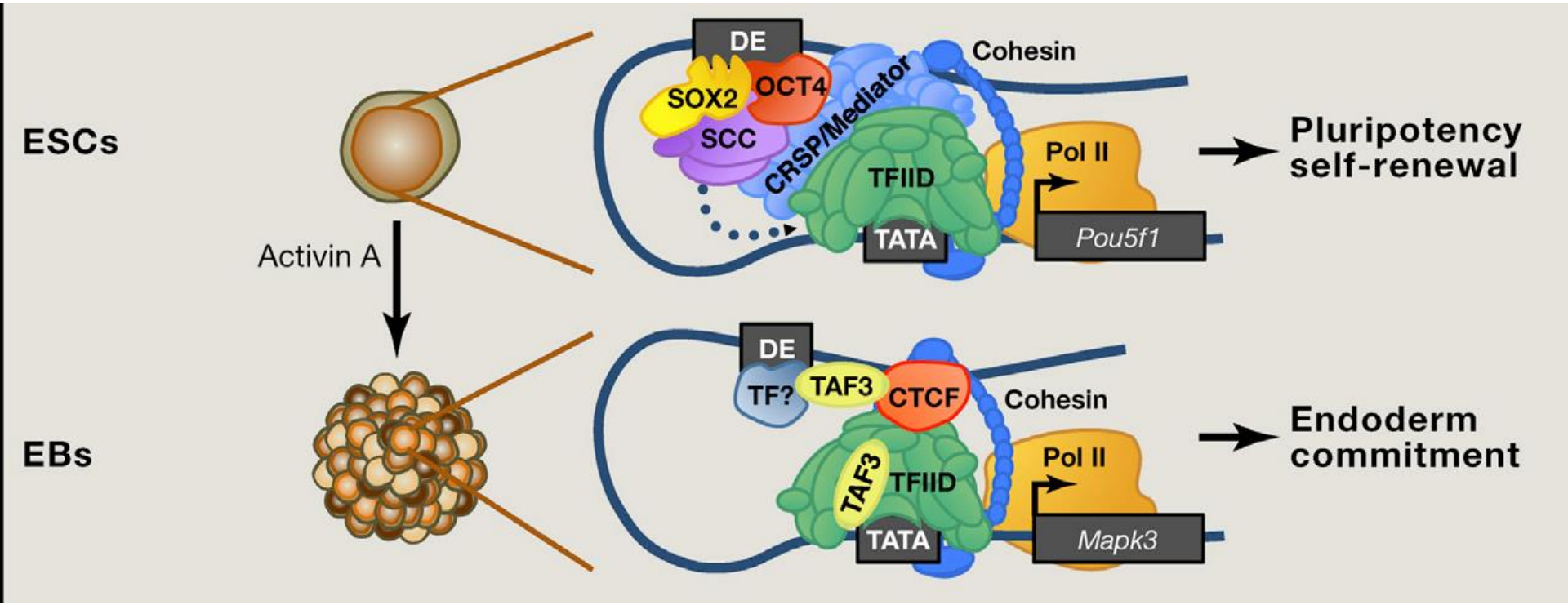


Figure 2. Specialized Transcription Machineries

(A) A diversified set of PICs, coactivators, and chromatin remodelers orchestrates cell-specific transcription programs.

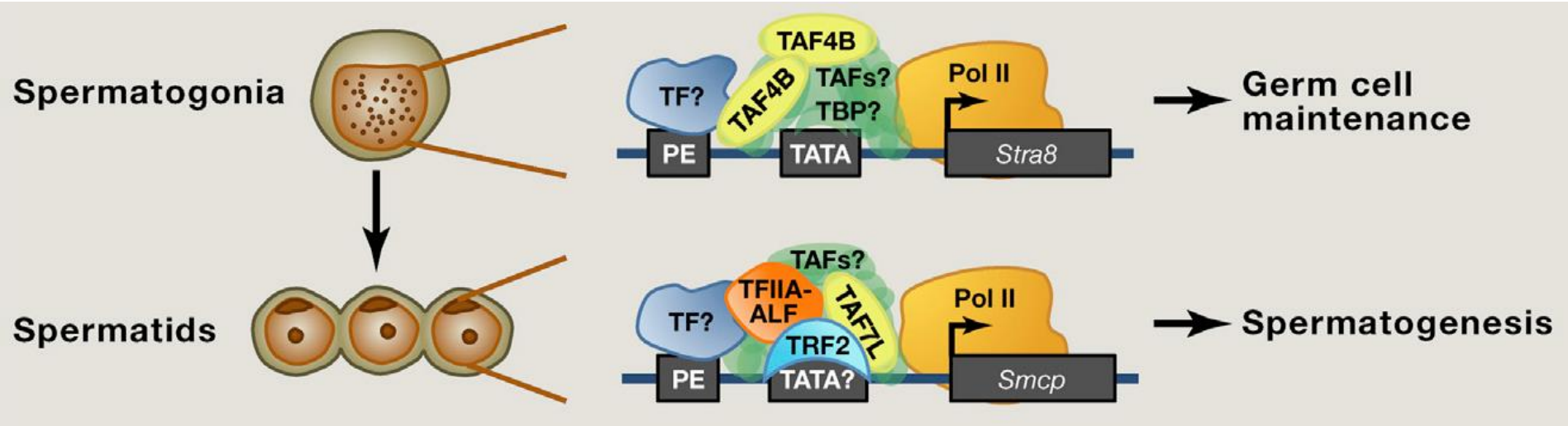


In embryonic stem cells (ESCs), the XPC trimeric complex works as an OCT4/SOX2 stem cell coactivator (SCC) at distal enhancer sites (DE) to sustain the expression of pluripotency and self-renewal genes.
Upon formation of embryoid bodies (EBs), TBP-associated factor TAF3 is required for endodermal lineage differentiation, mediating DNA looping between DEs and core promoters (TATA) of endoderm specification genes in concert with CTCF.

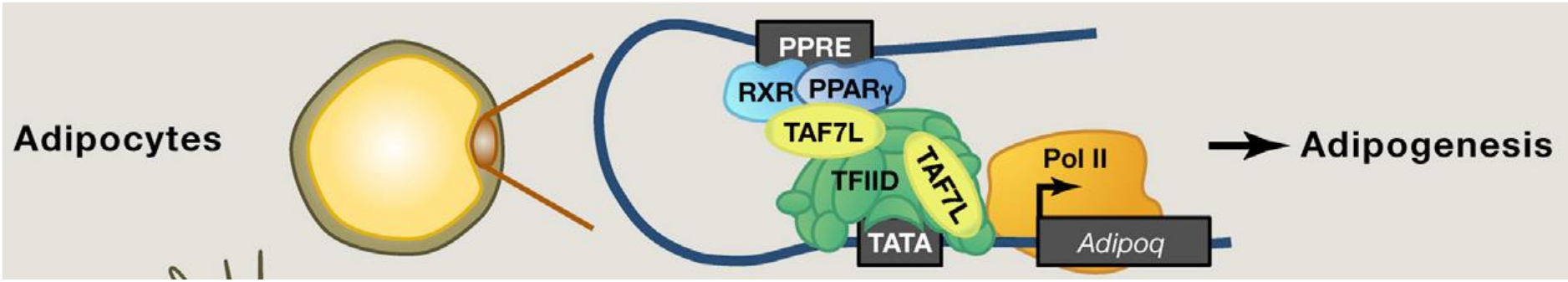
Pre-initiation complex (PIC)

Mediator

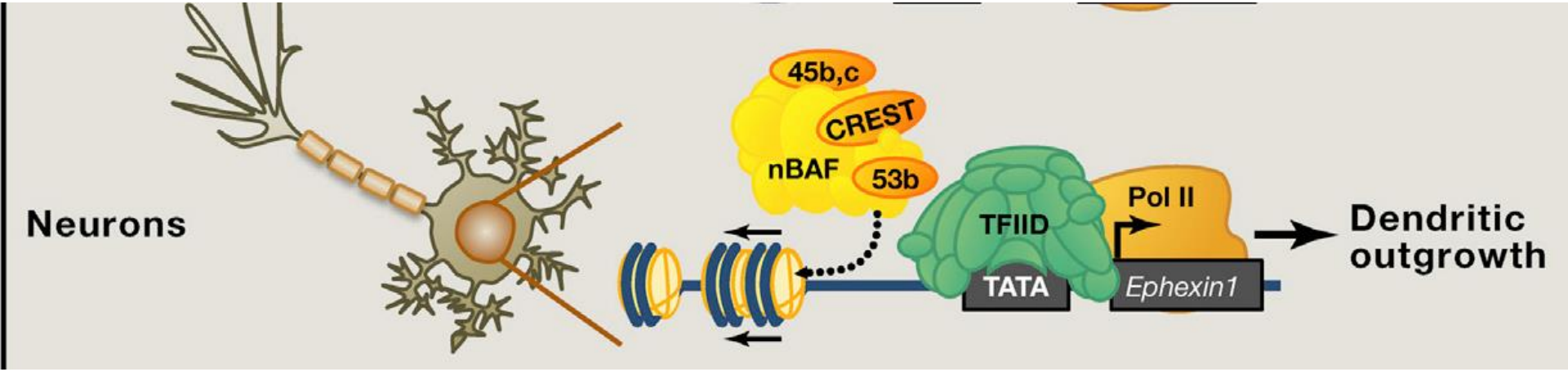
PIC-Mediator



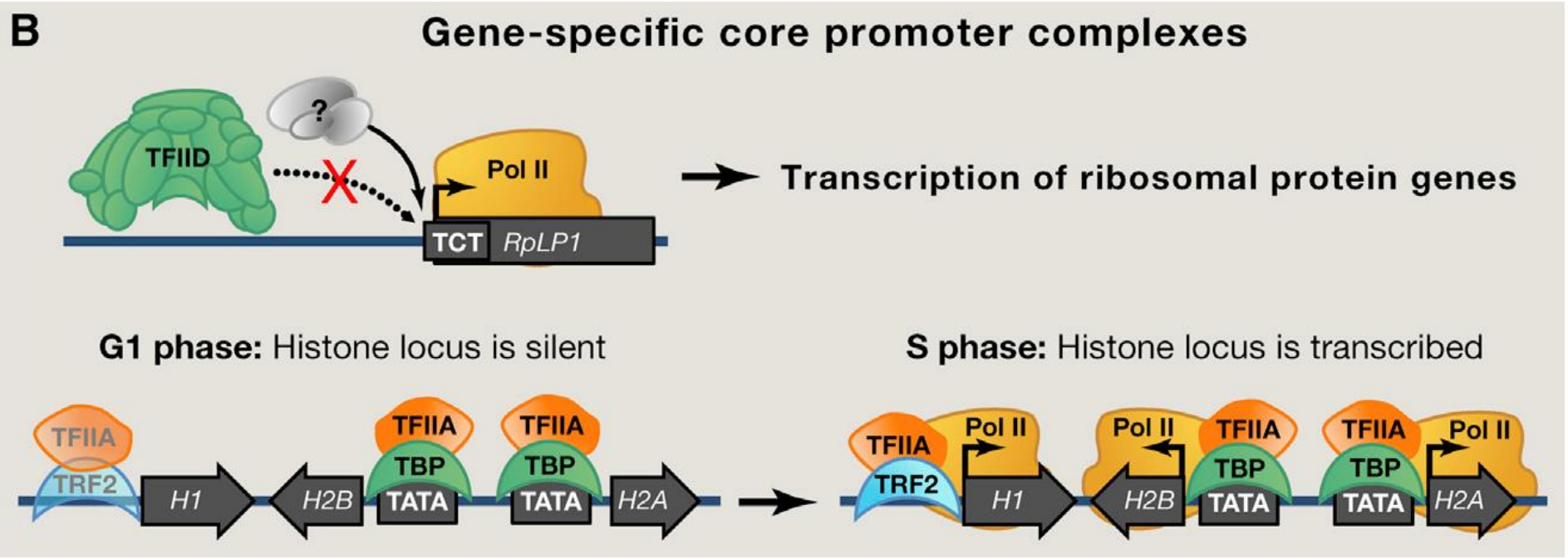
In testis, TAF4B directs a transcription program required to preserve the germ-cell compartment; farther down the differentiation path, in round spermatids, TAF4B is replaced by a core-promoter complex composed of the TAF7 homolog TAF7L, TBP related factor TRF2 and TFIIA, which promotes spermatogenesis instead.



TAF7L also regulates adipogenesis by associating with TBP as a component of TFIID at promoters and with PPARg-RXR as a cofactor at enhancers on adipocyte-specific genes



In neurons, a specialized BAF chromatin-remodeling complex exists (nBAF) that includes neural specific subunits (BAF53b, BAF45b, BAF45c, and CREST) and facilitates transcription of genes involved in dendrite outgrowth.



A yet-uncharacterized, TFIID-independent PIC assembles at the TCT motif (polypyrimidine initiator) encompassing the transcription start site of ribosomal protein genes in Drosophila cells. In Drosophila S2 cells, noncanonical PICs made of TRF2/TFIIA and TBP/TFIIA are responsible for the cell-cycle-restricted expression of H1 and H2B/A histone genes, respectively. TBP/TFIIA, and possibly TRF2/TFIIA, are preloaded on the histone locus in the G1-phase of the cell cycle but only activate transcription when cells enter S phase.

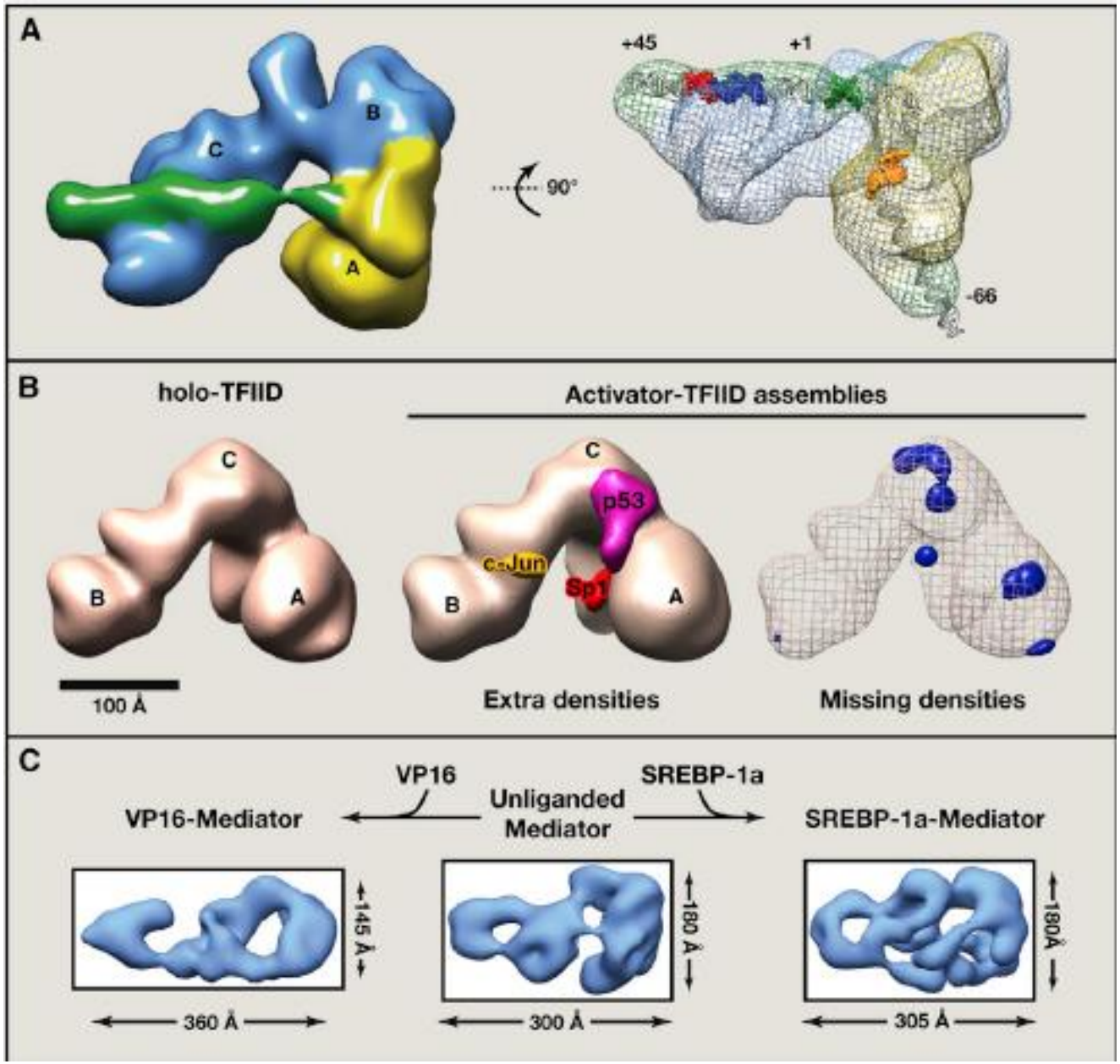
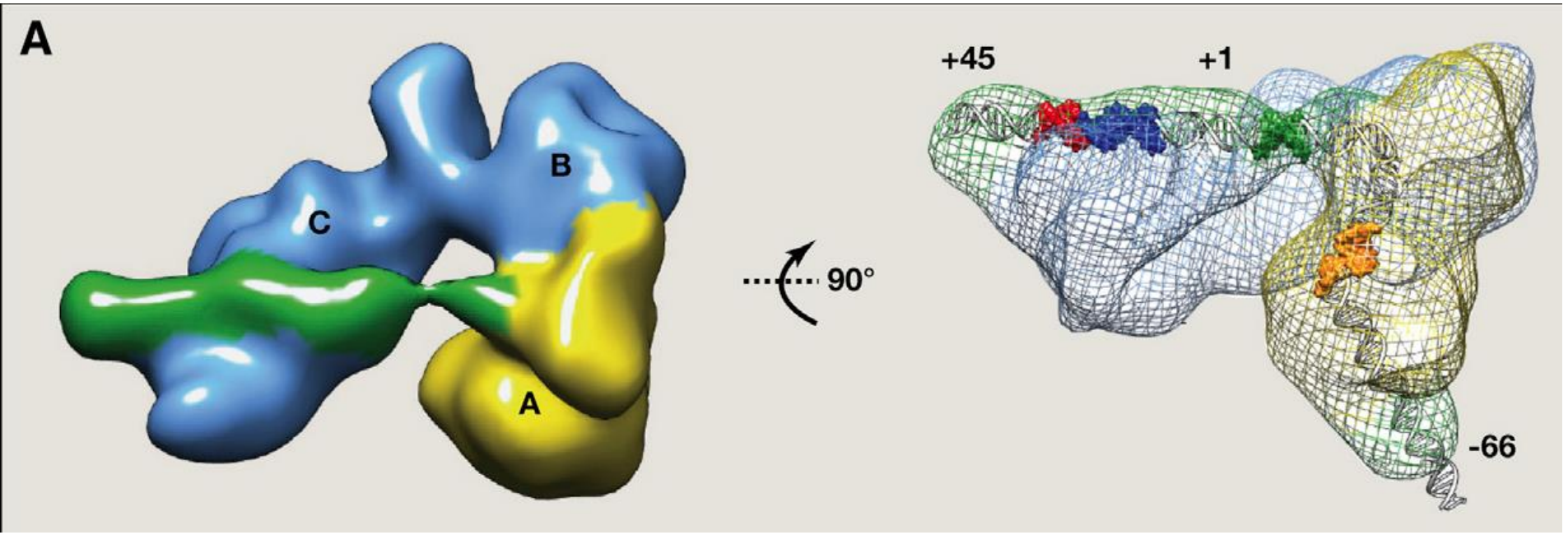
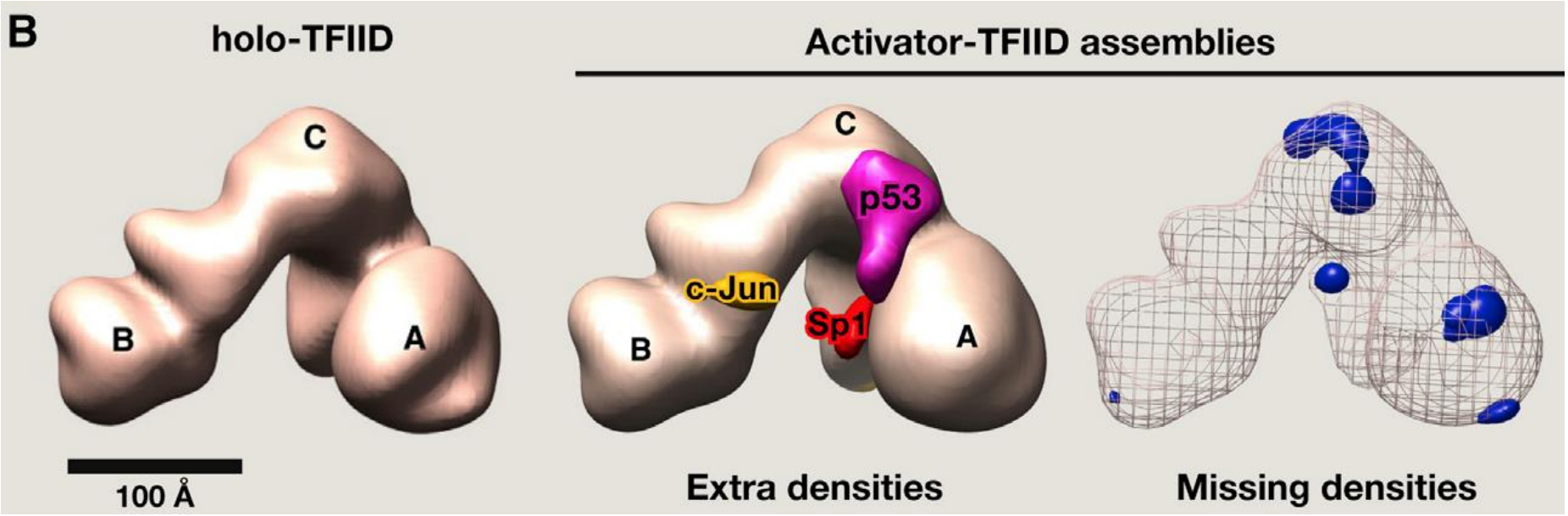


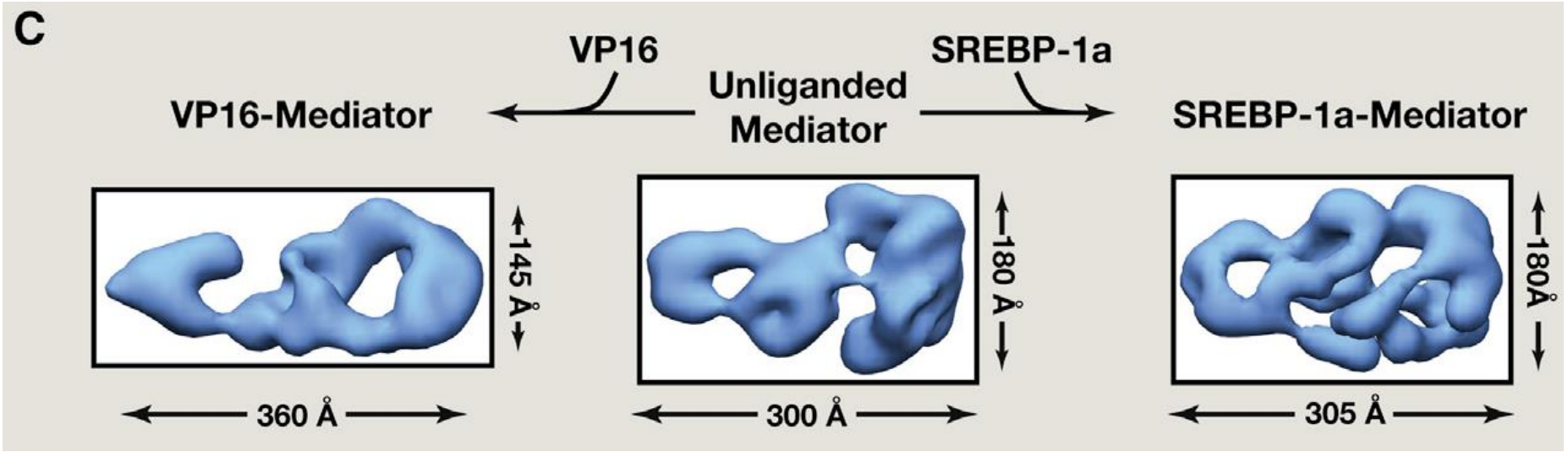
Figure 3. Structural Dynamics of Transcription Machineries



Binding of PIC components to promoter induces dramatic turns of the DNA template, as revealed by EM structure of human TFIID and TFIIA bound to a super-core promoter



Different activators (P53, c-JUN, SP1) target distinct sites and induce localized, as well as common, conformational changes within TFIID, as evaluated by EM structural studies (adapted from Liu et al. [2009]).



ARC/CRSP mediator undergoes dramatic and distinct conformational changes when bound to VP16 versus SREBP-1a activators, as resolved by EM (adapted from Taatjes et al. [2002]).

test

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